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REVIEW

Pseudopemphigoid as caused by topical drugs and pemphigus disease

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Abstract

Pseudopemphigoid can cause a chronic cicatricial conjunctivitis that is clinically identical to the manifestations seen in mucous membrane pemphigoid, a disorder with a common clinical phenotype and multiple autoimmune links. For the purpose of this review, we will describe pseudopemphigoid as caused by topical drugs, the most common etiology with ocular manifestations, and as caused by the pemphigus disease, a more rare etiology. Specifically, we will discuss the ophthalmological features of drug-induced cicatricial conjunctivitis, pemphigus vulgaris, and paraneoplastic pemphigus. Other etiologies of pseudopemphigoid exist that will not be described in this review including autoimmune or inflammatory conditions such as lichen planus, sarcoidosis, granulomatosis with polyangiitis (Wegener's granulomatosis), erythema multiforme (minor, major, and Stevens-Johnson syndrome), bullous pemphigoid, skin-dominated linear IgA bullous dermatosis, and skin-dominated epidermolysis bullosa acquisita. Prompt diagnosis of the underlying etiology in pseudopemphigoid is paramount to the patient's outcome as certain diseases are associated with a more severe clinical course, increased ocular involvement, and differential response to treatment. A complete

history and ocular examination may find early cicatricial changes in the conjunctiva that are important to note and evaluate to avoid progression to more severe disease manifestations. When such cicatricial changes are noted, proper diagnostic techniques are needed to help elucidate a diagnosis. Lastly, collaboration between ophthalmologists and subspecialists such as dermatologists, pathologists, immunologists, and others involved in the care of the patient is needed to ensure optimal management of disease.

Key words: Pseudopemphigoid; Mucous membrane pemphigoid; Cicatricial conjunctivitis; Pemphigus vulgaris; Paraneoplastic pemphigus; Drug-induced conjunctival cicatrization

Core tip: Pseudopemphigoid in the context of chronic cicatricial conjunctivitis mimicking mucous membrane pemphigoid is a disease with terminology that has continuously evolved since its inception. Recent understanding of the ophthalmological and systemic manifestations of pseudopemphigoid as caused by topical drugs and the pemphigus disease demonstrates that significantly decreased vision and/or increased mortality due to paraneoplastic associations may result. Proper diagnosis and treatment of the underlying disease is therefore critical in order to provide maximal care to the patient.

Huang LC, Wong JR, Alonso-Llamazares J, Nousari CH, Perez VL, Amescua G, Karp CL, Galor A. Pseudopemphigoid as caused by topical drugs and pemphigus disease. *World J Ophthalmol* 2015; 5(1): 1-15 Available from: URL: http://www.wjgnet.com/2218-6239/full/v5/i1/1.htm DOI: http://dx.doi.org/10.5318/wjo.v5.i1.1

INTRODUCTION

The first use of the term pseudopemphigoid referred to a non-progressive, unilateral cicatricial conjunctivitis that developed in response to certain aggravating topical medications[1]. Pseudopemphigoid was originally named due to its clinical similarity to mucous membrane pemphigoid (MMP) - an autoimmune blistering disease characterized by subepithelial deposition of antigen-antibody complexes at the basement membrane zone. Subepithelial deposition of autoantibody complexes seen in pemphigoid disease differentiates it from pemphigus that is characterized by intraepithelial deposition of autoantibody complexes. If clinical manifestations of pemphigus produce conjunctival cicatrization identical to MMP, then pemphigus may therefore be characterized as "pseudopemphigoid" and the modern terminology of pseudopemphigoid now includes any etiology that mimics MMP in clinical presentation.

The purpose of this review is to elaborate on the epidemiology, clinical features, diagnosis, and treatment options available for patients with pseudopemphigoid. This paper will review the ocular manifestations associated with three etiologies of pseudopemphigoid including the most common cause, drug-induced cicatricial conjunctivitis[2], and two rare causes from the pemphigus family, pemphigus vulgaris and paraneoplastic pemphigus. Pemphigus foliaceus, a third subset of the pemphigus family, does not involve the conjunctiva and will not be discussed in this review.

Pseudopemphigoid may be caused by a variety of other conditions not included in this review article such as sarcoidosis, granulomatosis with polyangiitis (Wegener's granulomatosis), bullous pemphigoid, skin-dominated linear IgA bullous dermatosis, and skin-dominated epidermolysis bullosa acquisita[3]. Additionally, inflammatory and/or autoimmune disease associated cicatricial conjunctivitis characterized by an interface/lichenoid lymphocytic infiltrate such as lichen planus[4], graft *vs* host disease, erythema multiforme spectrum, and discoid lupus erythematosis[5] are not included in this review article.

PSEUDOPEMPHIGOID

How pseudopemphigoid differs from mucous membrane pemphigoid

Historically, pseudopemphigoid referred to a unilateral drug-induced cicatricial reaction identical to MMP that did not progress upon removal of the inciting drug. The term has since evolved and for the purposes of this review, pseudopemphigoid will be characterized according to the criteria proposed by Thorne *et al*[2]: (1) Chronic cicatricial conjunctivitis; (2) A biopsy that rules out MMP; and (3) The existence of an alternate cause for cicatrization.

MMP refers to a group of autoimmune, subepithelial, blistering diseases that predominantly affect the mucous membranes and are notable for linear deposition of autoantibodies (IgG, IgA, or C3) along the epithelial basement membrane zone on biopsy. The primary distinction between MMP and pseudopemphigoid is that MMP consists exclusively of autoimmune blistering diseases with subepidermal deposition of autoantibodies as opposed to pseudopemphigoid that simply mimics MMP in clinical presentation but does not involve subepidermal deposition of autoantibodies.

How pseudopemphigoid mimics mucous membrane pemphigoid

Clinical features: Pseudopemphigoid, similarly to MMP, may produce a chronic cicatricial conjunctivitis in patients characterized by the presence of scarring. The clinical presentation of a patient with cicatricial conjunctivitis includes irritation, burning, a foreign body sensation, photophobia, tearing, dryness, redness or blurry vision and hyperemic conjunctiva, misalignment of eyelashes, cicatricial entropion, and trichiasis[6].

The Foster[7] staging system developed for MMP may be utilized to characterize the severity of chronic cicatricial conjunctivitis secondary to pseudopemphigoid

Table 1 Staging for severity of cicatricial conjunctivitis

Staging for severity of cicatricial conjunctivitis	
Foster Staging[7]	
I	Subepithelial fibrosis, positive rose-bengal staining in conjunctiva, conjunctival "shrinkage" from abnormal connective tissue due to small white striae that form around the superficial vessels in substantia propria
II	Marked foreshortening of inferior conjunctiva described by (1) 0%-25%; (2) 25%-50%; (3) 50%-75%; and (4) 75%-100%
III	Corneal neovascularization, trichiasis, dystichiasis, keratopathy, subepithelial bands of connective tissue resulting in symblepharon (conjunctival adhesions) formation that is described by (1) 0%-25%; (2) 25%-50%; (3) 50%-75%; and (4) 75%-100%
IV	Severe sicca syndrome, keratinization, ankyloblepharon
Mondino Staging[134]	
I	0%-25% loss of inferior conjunctival fornix depth
II	25%-50% loss of inferior conjunctival fornix depth
III	50%-75% loss of inferior conjunctival fornix depth
IV	75%-100% loss of inferior conjunctival fornix depth

Table 2 Conditions associated with cicatricial conjunctivitis

Trauma
Physical trauma
Chemical burn
Thermal burn
Radiation burn
Infection
Trachoma
Membranous conjunctivitis
Allergic
Chronic atopic keratoconjunctivitis
Mucocutaneous disease
Erythema multiforme
Stevens-Johnson Syndrome
Toxic epidermal necrolysis
Immunobullous disorders
Mucous membrane pemphigoid
Bullous pemphigoid
Pemphigus vulgaris
Paraneoplastic pemphigus
Lichen planus
Dermatitis herpetiformis
Systemic lupus erythematosus
Systemic disorders
Rosacea
Sjogren's syndrome
Graft-*vs*-host disease
Sarcoidosis
Ectodermal dysplasia
Erythroderma ichthyosiform congenital
Drug-induced
Systemic
Topical

as well. In Stage Ⅰ, conjunctival inflammation develops with mucous discharge, subepithelial fibrosis, and areas of degenerated cells in the conjunctival epithelium. Abnormal connective tissue and small white striae develop around the superficial vessels of the substantia propria, producing conjunctival "shrinkage." In Stage Ⅱ, inferior conjunctival foreshortening occurs. In Stage Ⅲ, subepithelial bands of connective tissue create symblepharon (conjunctival adhesions), corneal neovascularization, trichiasis (misdirected eyelash growth), dystichiasis (eyelash growth arising from meibomian glands), and keratopathy due to scarring of the conjunctival goblet cells, lacrimal gland ducts, and meibomian gland orifices. In Stage Ⅳ, severe sicca syndrome, keratinization, and ankyloblepharon (lid adhesions) develop (Table 1).

Despite a severe end-stage presentation, early cicatrization secondary to pseudopemphigoid and MMP is often nonspecific and subtle which causes patients to present with disease that is already erosive and scarring[8]. Additionally, more than 65% of patients may have cicatricial conjunctivitis develop without any symptoms[9]. In a prospective study of 163 eyes with cicatricial change, a diagnostic delay of a median 225 d after symptom onset was noted causing 59% of patients to present as Stage Ⅲ at diagnosis[10]. Therefore, it is paramount to have etiologies such as MMP and pseudopemphigoid on the differential diagnosis for any patient who presents with cicatrization to best optimize management.

Diagnosis: The first step to discovering the etiology of chronic cicatricial conjunctivitis involves the history. The patient should be asked about any past medical history of chemical or thermal burns; membranous conjunctivitis caused by infectious organisms such as adenovirus; mucocutaneous disorders such as erythema multiforme (minor, major, and Stevens-Johnson syndrome), Sjogren's syndrome; systemic allergic disease such as chronic atopic conjunctivitis or rosacea; chronic graft-*vs*-host disease following organ transplantation; history of trachoma if from endemic areas; previous eyelid surgery; or previous use of any aggravating topical or systemic medications (Table 2). Additionally, because many etiologies of pseudopemphigoid include systemic autoimmune bullous disease, the physician should inquire about new onset cutaneous or oral mucosal lesions. Most patients presenting with cicatricial conjunctivitis will have a history that makes the diagnosis simple. If inconclusive evidence is found from the history, then other methods of diagnosis are needed including a conjunctival biopsy.

ETIOLOGIES OF PSEUDOPEMPHIGOID

Drug-induced cicatrization

Epidemiology: Drug-induced conjunctival cicatrization (DICC), also known as drug-induced ocular pseudopemphigoid, produces clinical findings identical to MMP in response to varying offending topical and systemic drugs[11]. The incidence of DICC remains unknown, but has been documented to occur most often in patients who require long-term use of glaucoma medications[11]. In a retrospective cohort study of 145 pseudopemphigoid patients, DICC was the most common cause of pseudopemphigoid in this population occurring in 28.3% of patients[2].

Pathophysiology: DICC can develop as a non-progressive, self-limiting "toxic" reaction to an offending topical drug or as a progressive, immunological process that continues

despite cessation of the offending drug[12-14]. Although increased activity of fibroblasts has been implicated as a possible effect on the local immune system, the exact mechanism by which offending topical drugs directly induce cicatricial conjunctivitis remains unknown[15].

When IgG localized to the ocular epithelial basement membrane zone are found, then autoimmune phenomenon are suggested[15,16]. Practolol, an oral beta-blocker, and its derivative metipranolol, a topical beta-blocker that treats glaucoma, have been implicated to induce immunologically mediated DICC[17-20]. This is related to the chemical structure and pharmacologic metabolism in the body - both compounds require deacetylation for metabolic activation, which produces a toxic aniline derivative in practolol and a slightly less toxic phenol derivative in metipranolol[17]. When oxidized, these derivatives become highly reactive and are normally neutralized in the body by the addition of glucuronic acid or sulfate. However, this mechanism is insufficient in patients that have a lower capacity for enzymatic detoxification[17]. When this occurs, proteins can bind these reactive oxidative products to create antigens[17]. Therefore, the toxicity potential of practolol and metipranolol to produce immunologically mediated cicatricial conjunctivitis occurs in patients who are susceptible to these reactions required for metabolic activation of the drug due to its pharmacologic structure. Drug chemical structure has not been implicated in the mechanism of cicatricial conjunctivitis induced by other offending topical drugs and in many cases of DICC, a toxic or immune-mediated reaction cannot be further defined.

Epitope spreading is one possible theory that may elucidate the mechanism behind autoimmune phenomenon as induced by topical drugs. Epitope spreading[21,22] refers to the phenomenon of autoimmune reactivity not only against one protein, but also against other epitopes on the same protein or other proteins in the same tissue. Intramolecular epitope spreading that occurs between different epitopes on the same protein is often used to explain the molecular pathogenesis and severity of disease in bullous pemphigoid[23]. Additionally, epitope spreading may occur due to tissue damage that causes certain antigens to become newly exposed to autoreactive T or B cells, thus producing an autoimmune disease in predisposed individuals[21,24]. This mechanism of epitope spreading can be promoted by injury that exposes previously sequestered antigens, causing activation of antigen presenting cells that attract autoreactive lymphocytes in these individuals[22]. Intermolecular epitope spreading that occurs between two different proteins has been cited to explain the conversion of one autoimmune disease into another. Pemphigus autoimmune disease converting into pemphigoid disease, or conversions between other autoimmune blistering diseases either simultaneously or separated by a few years, is hypothesized to occur when tissue damage exposes protein parts that are normally undetected by the immune system[25,26]. In a similar manner, ocular mucosal injury due to Stevens-Johnson syndrome, Lyell Syndrome, or direct chemical injury from drugs may be implicated to expose normally hidden antigens to processing and presentation by activated T-cells, resulting in the formation of MMP[12,21,24].

Incidences of MMP developing in uninvolved eyes of patients that did not receive the inciting drug may indicate an immunological etiology[12]. On the other hand, instances of unilateral changes histologically and immunologically identical to MMP that occur in only the eye that received an offending drug is considered to be drug-induced[16]. The absence of bilateral ocular involvement, other mucosal or cutaneous manifestations, and disease that is non-progressive after cessation of the offending drug suggests a drug-induced reaction. Therefore, DICC may involve either a toxic mechanism of damage or an autoimmune etiology where inciting topical medications sensitize predisposed individuals to developing a more rapid onset of ocular MMP.

Clinical findings: DICC produces symptoms of cicatrization clinically identical to MMP. Two distinguishing factors that differentiate DICC from MMP include unilaterality of symptoms localized to the eye that received the topical therapy as well as non-progression of disease after cessation of the drug. However, reports of progressive DICC have occurred in the literature[13,14].

A total of 7 studies comprising 63 cases of drug-induced conjunctival cicatrization were found in the literature[1,2,14,16,27-29]. The most commonly used inciting topical drugs and the average duration of utilization before onset of DICC symptoms consisted of: timolol (73% or 46/63) for an average 10.5 years, pilocarpine (51% or 32/63) for an average 9 years, dipivefrin (49% or 31/63) for an average 7 years, latanoprost (13% or 8/63) for an average 8 years, echothiophate iodide (11% or 7/63) for an average 8 years, epinephrine (10% or 6/63) for an average 2 years, acetazolamide (6% or 4/63) for an average 9 years, betaxolol (3% or 2/63) for an average 6 years, idoxuridine (6% or 4/63) for an average 2 years, dichlorphenamide (5% or 3/63) for an average 3 years, and bromonidine (8% or 5/63) and other beta blocker antiglaucomatous medications for an unknown duration of time (48% or 30/63).

Of 7 studies comprising 23 patients with drug-induced conjunctival cicatrization found in the literature, the most common clinical findings included: forniceal foreshortening (57% or 13/23), symblepharon formation (48% or 11/23), trichiasis (48% or 11/23), corneal epithelial defects (35% or 8/23), entropion (30% or 7/23), corneal pannus (30% or 7/23), pseudopterygium formation (4% or 1/23), and corneal perforation (4% or 1/23)[1,14,16,27-30].

Diagnostic studies: There are no specific changes associated with medications that induce cicatrization nor is there a favored location of conjunctival involvement to distinguish DICC from idiopathic MMP[11]. Histopathological features seen on conjunctival biopsy can vary according to whether cicatrization is mild or severe[31]. When histopathological changes are seen, biopsy specimens can be identical to that of MMP and include subepithelial fibrosis, subepithelial infiltration with inflammatory cells,

reduction or loss of goblet cells, and basement membrane thickening[1,12,19,28]. Conjunctival biopsy with the use of direct immunofluorescence (DIF) is often not helpful as the findings are usually absent or nonspecific. However, IgG and complement staining to the epithelial basement membrane zone have been reported[1,15]. Although it is more common for immunofluorescent testing to lack positive findings, patients who present with both DICC and positive basement membrane zone autoantibody deposition should be considered to have MMP[3]. Otherwise, if the patient presents with a unilateral, non-progressive cicatrization of the conjunctiva, lacks other cutaneous or oral mucosal lesions, has a history of topical medication use for a prolonged amount of time, and other causes of conjunctival shrinkage have been excluded, then DICC should be considered.

Treatment: Management of DICC involves withdrawing the causative drug as early as possible and monitoring the patient carefully for the progressive type of disease. As topical intraocular lowering pressure therapies are commonly implicated in the pathogenesis of DICC, therapy involves a dual approach that includes controlling intraocular pressure and treating the signs of cicatrization. The primary management to resolve or inhibit the progression of fibrosis is cessation of intraocular lowering pressure medication[12]. The treatment to control intraocular pressure includes systemic carbonic anhydrase inhibitors followed by early surgical trabeculectomy[14,16]. If there are no other treatment options for the topical preparation suspected to be the offending drug, then re-introducing the medication in an unpreserved preparation may help. The patient should be followed closely for progressive disease and if progression occurs, then one must consider that the patient has developed ocular MMP and begin the patient on therapy.

A total of 7 studies comprising 63 cases of DICC or drug-induced pseudopemphigoid were found in the literature[1,2,14,16,27-29]. Aside from cessation of the inciting drug, management to control signs of cicatrization included medical treatment involving dapsone (10% or 2/21) or steroids (10% or 2/21). Procedural treatments to control sequelae of cicatrization include electrolysis and cryotherapy. Surgical treatments to control sequelae of cicatrization included anterior lamellar repositioning, tarsectomy, mucous membrane grafting, lower lid retractor tightening, lamellar keratoplasty, conjunctival transplant, terminal tarsal rotation procedure, and everting sutures. When switching to a different anti-glaucomatous medication, acetazolamide (14% or 3/21) or methazolamide (14% or 3/21) were utilized. Surgical treatment to manage uncontrolled intraocular pressure included trabeculectomy.

Prognosis: Clinical outcomes after procedural and/or medical treatment included persistence of ocular lesions without progression (48% or 10/21), remission of ocular lesions defined as regression (33% or 7/21), progression of ocular lesions (10% or 2/21), and recurrence of ocular lesions (5% or 1/21). Overall, average follow up time was 25 mo. If cicatrization is non-progressive upon withdrawal of inciting drug, then prognosis is favorable and management should treat the signs of scarring. If cicatrization is progressive upon withdrawal of inciting drug, then management and prognosis should be according to that of MMP.

Pemphigus vulgaris

Epidemiology: Pemphigus vulgaris (PV) is an intraepithelial blistering disease with a reported incidence of 4 to 4.7 cases per one million individuals[32,33]. PV most often affects patients in the fourth to fifth decade of life with equal occurrence in both sexes[34,35]. This differs from MMP that occurs less commonly at an incidence of 1.13 cases per one million individuals and presents in older individuals with a female predominance[8,36-41]. PV affects all races, but a higher predilection is associated with certain HLA subtypes such as the HLA-DRB1*0402 in Ashkenazi Jews and DRB1*1401/04 and DQB1*0503 in patients of European or Asian origin[42-44].

Pathophysiology: PV is an autoimmune disease characterized by suprabasal acantholysis (loss of cell-to-cell adhesions in epidermal cells that occurs just above the basal layer) induced by IgG binding to target antigens desmoglein 1 and 3 of the cadherin family[45-47]. Acantholysis leads to formation of a cleft which subsequently develops into an intraepithelial bulla[48]. This differs from MMP that is characterized by subepithelial lesions due to autoantibodies directed against various target antigens identified in the basement membrane zone.

PV antigens, desmoglein 1 and 3, are part of desmosome complexes that anchor intermediate filaments for adhesion between adjacent cells. These complexes consist of plakoglobin, plakophilin, desmoplakin, and desmosomal cadherins[45]. Desmoglein 1 (160 kDa) is located more superficially just below the stratum corneum whereas desmoglein 3 (130 kDa) is confined to the lower levels just above the basal cell layer[45,48].

Ocular involvement in PV is rare and its low incidence in the literature may be related to the course of disease or due to underreporting. Desmoglein 3 is heavily expressed in the basal layer of conjunctival epithelium along with strong expression of desmocollin 3, and desmoplakin 1 and 2, throughout the conjunctiva[49,50]. The mechanism on why ocular involvement in PV is rare despite the presence of anti-desmoglein 3 autoantibodies in disease is unclear. Suggestions include that the ocular surface is less exposed to trauma than other tissues normally affected by PV[51]; that there is inactivation of desmoglein 3 in ocular epithelium that is readily compensated by other desmosomal proteins thereby leaving only a minority of patients susceptible to disease if compensation cannot be attained[49]; or that conjunctival involvement in PV is simply underreported.

Clinical findings: PV is characterized by the development of large, flaccid cutaneous blisters and mucosal surface

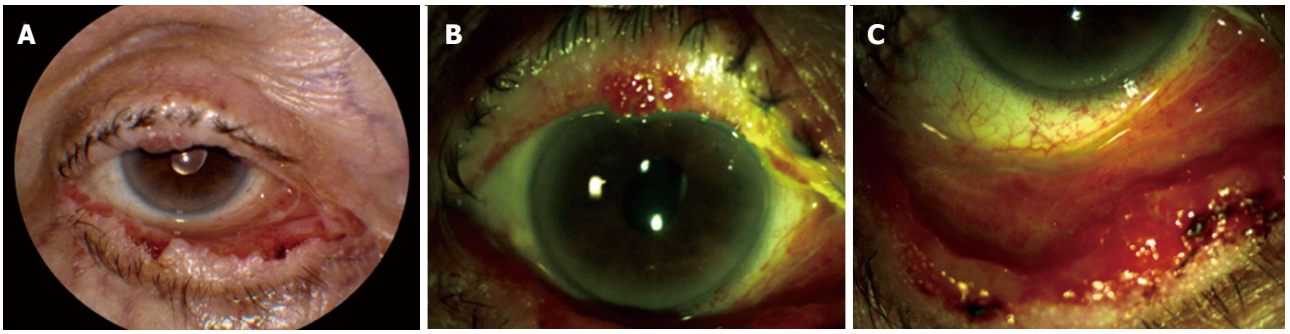

Figure 1 Clinical manifestations of ocular pemphigus vulgaris. A: Lid margin erosions of the medial aspect on the lower lid and blisters of the upper lid; B: Higher magnification of eyelid demonstrating erosions and crusting of the upper eyelid with superficial blisters; C: Conjunctival hyperemia, crusting from lid margin erosions, and mucoid discharge.

involvement including the oral mucosa, conjunctiva, esophagus, larynx, and genitalia. Cutaneous lesions are fragile blisters that bleed easily and are characteristic for demonstrating Nikolsky's sign (rubbing of the perilesional skin with slight pressure produces exfoliation of the outer layer) and the indirect Nikolsky sign (moving an intact blister laterally and enlarging it with pressure)[52].

Mucosal involvement is the most common manifestation of PV and painful, chronic erosions of mucus membranes are often the initial presentation[39,53,54]. Ocular involvement in PV is rare and typically benign - ocular lesions do not usually progress to scarring and patients often fully recover without sequelae[51,55]. If ocular involvement occurs, it typically induces bilateral conjunctivitis without fibrosis (Figure 1)[56]. Lid margin erosions in the medial aspect of the lower eyelid can be characteristic of ocular pemphigus vulgaris (OPV)[57]. This differs from MMP that most commonly presents ophthalmologically with signs of overt cicatrization including symblepharon, trichiasis, punctate keratitis, and entropion[10].

A total of 10 studies comprising 36 OPV patients were found in the literature[34,49,51,55,58-63]. The most common ocular symptoms included the following: conjunctival hyperemia (49% or 17/35), conjunctivitis (46% or 16/35), conjunctival ulceration (14% or 5/35), lid margin erosions (14% or 5/35), corneal erosions (6% or 2/35), erosions of the medial canthus (3% or 1/35), and pseudomembrane formation (3% or 1/35). Concomitant systemic manifestations most commonly included oral involvement (80% or 28/35) followed by cutaneous lesions (54% or 19/35). The initial presentation of disease included ocular involvement in 41% (14/34) of cases.

Despite the seemingly benign nature of OPV, other studies suggest that ocular involvement in PV may be a sign of severe or recurrent disease that can occur in conjunction with exacerbation of systemic disease or in patients who have previously failed conventional immunosuppressive therapy[34,51,58]. Although fibrosis is very uncommon in PV, a subset of patients characterized by ocular involvement as the first manifestation of disease can produce a progressive cicatricial conjunctivitis in a similar manner to MMP[35].

In the largest series in the literature regarding OPV patients, Chirinos-Saldaña *et al*[35] described 15 patients whose presentation included the following: conjunctival hyperemia (100% or 15/15), cicatrization (100% or 15/15), subconjunctival scarring (100% or 15/15), conjunctival cul-de-sac shortening (73% or 11/15), symblepharon formation (40% or 6/15), eyelid involvement including trichiasis or entropion (33% or 5/15), corneal perforation (27% or 4/15), and ankyloblepharon formation (7% or 1/15). Concomitant systemic manifestations included oral (20% or 3/15) and cutaneous involvement (7% or 1/15). The initial presentation of disease included ocular involvement in 100% (15/15) of cases. These results, alongside other reports in the literature involving progressive keratolysis with secondary corneal perforation[64,65], have led authors to conclude that a subset of patients exist with atypical pemphigus characterized by severe ocular involvement as the primary manifestation of disease[35]. Although all patients in this series had immunopathological diagnoses of PV, additional serology studies and/or secondary confirmatory biopsies were not performed to determine the coexistence of MMP. Dual diagnoses of MMP and PV have been previously reported in the literature[66,67] and therefore remain a possibility in this series.

Diagnostic studies: Histopathological studies utilizing hematoxylineosin staining of conjunctival biopsies in OPV demonstrate suprabasal and intraepithelial acantholysis that is characteristic of the pemphigus disease with splitting that occurs above the basal layer[51,61]. This differentiates OPV from MMP where most changes occur at the basement membrane zone with subepithelial conjunctival shrinkage; inflammatory infiltrate involving lymphocytes, macrophages, and plasma cells; and squamous metaplasia progressing to parakeratosis and keratinization of conjunctival epithelium[56,68].

The initial laboratory method to diagnose PV includes a conjunctival biopsy with subsequent DIF to IgG deposits in the intercellular space (Figure 2). This demonstrates antibodies directed against pemphigus antigens including desmosomal proteins desmoglein 3 and 1. This differs from MMP that demonstrates IgG deposits in the subepithelial space with antibodies directed against a variety of antigens not including desmoglein 3 and 1.

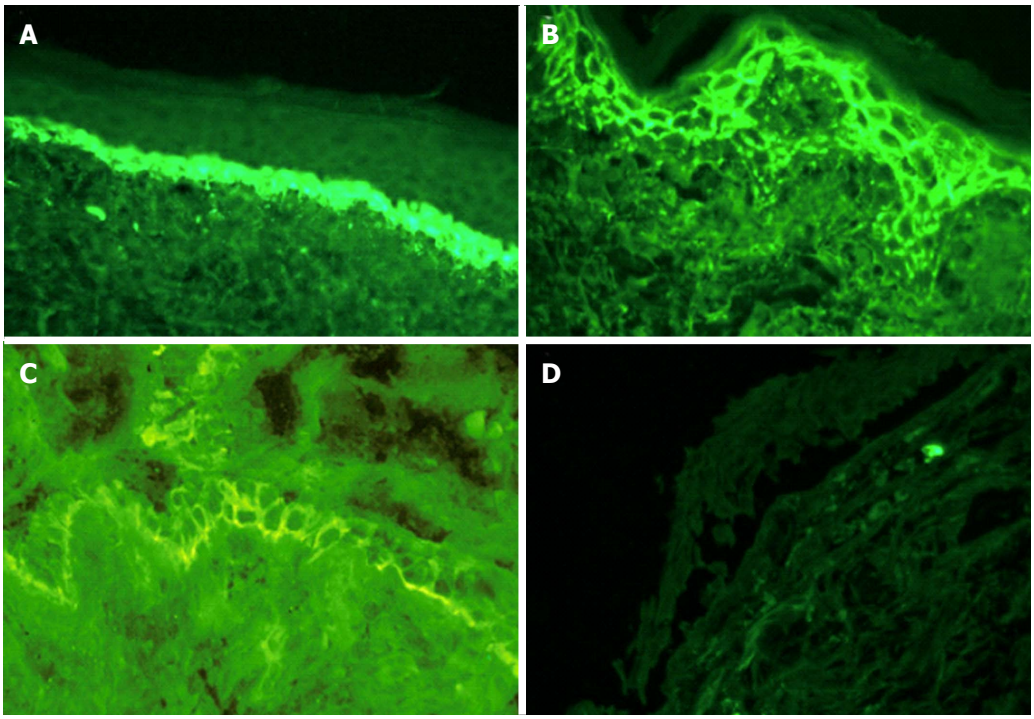

Figure 2 Direct immunofluorescence studies of conjunctival biopsies. A: Conjunctival mucous membrane pemphigoid showing thick linear IgG along the lamina propria in a background of squamous metaplasia; B: Conjunctival pemphigus vulgaris showing linear IgG deposition on desmosomal areas of epithelial cell surfaces displaying a classic "chicken-wire" pattern; C: Conjunctival paraneoplastic pemphigus (PNP) showing linear IgG along the lamina propria with a hemidesmosomal pemphigoid-like in conjunction with a desmosomal pemphigus vulgaris-type epithelial cell surface "chicken-wire" type pattern. The pattern in PNP is due to the presence of IgG autoantibodies against hemidesmosomal antigens (plakin proteins: BP230/BPAG1 and plectin) as well as desmosomal antigens (plakin proteins: desmoplakin, envoplakin, periplakin, and desmogleins 3 and 1); D: Conjunctival pseudopemphigoid (most likely drug-induced) showing negative IgG deposition along the lamina propria in a background of subepithelial clefting, mild submucosal fibrosis, and incipient epithelial metaplasia.

Indirect immunofluorescence (IIF) is utilized to detect a titer of circulating autoantibodies through serologic assays. IIF in PV will have serum positive for anti-intercellular substance antibodies in greater than 80%-90% of untreated cases which can be correlated with disease activity[68,69]. This differs from MMP where circulating antibodies are found less commonly than in PV, but may also be utilized to monitor disease activity[3,15,70].

Direct immunoelectron microscopy (IEM) detects peroxidase-labeled antibodies attached to autoantigens in tissue that react with various agents to form electron-dense material[71]. Indirect IEM localizes pemphigus-associated antigens to the extracellular hemidesmosomes in the upper portion of the lamina lucida. This differs from MMP where IEM localizes immune deposits to the lower lamina lucida and lamina densa[56].

The detection of target antigen in OPV can be accomplished through immunoblotting and immunoprecipitation techniques, which identify unknown target antigens bound to autoantibodies. Although immunoprecipitation is less available and more difficult to perform, it is more sensitive than immunoblotting because it utilizes native protein as opposed to denatured protein substrates[52]. A standardized enzyme-linked immunosorbent assay can be utilized to measure autoantibody titers to both desmoglein 3 and desmoglein 1 with higher sensitivity compared to IIF[72]. This differs from MMP that demonstrates immunoprecipitation of various target antigens not including desmoglein 3 and 1.

Treatment: Before the availability of immunosuppressive therapy, mortality for PV reached up to 90% but has now dropped to 3.3% with the use of corticosteroids, cytotoxic drugs, and other biologic agents with immunomodulatory effects[68,73]. Ocular lesions appear to be more responsive to treatment compared to other sites of mucosal involvement[51].

First line therapy for PV includes corticosteroids. Corticosteroids may be used alone or in conjunction with corticosteroid-sparing immunosuppressive agents to allow gradual weaning of steroids to decreased doses or alternate-day therapeutic regimens[60,74,75]. Side effects of corticosteroid treatment most commonly seen include weight gain, cushingoid features, infection, gastrointestinal bleeding, hypertension, hyperglycemia, osteoporosis, and acne[73]. To avoid the occurrence of these side effects, corticosteroids may be used concurrently with sulfone derivatives, immunosuppressive agents, antimetabolites, alkylating agents, and biologic agents.

A total of 10 studies encompassing 39 OPV patients and treatments with multi-drug systemic regimens were found in the literature[34,35,49,55,58-63]. These regimens most commonly consisted of: systemic steroids (82% or 32/39), dapsone (18% or 7/39), azathioprine (13% or 5/39), cyclophosphamide (13% or 5/39), mycophenolate mofetil (10% or 4/39), methotrexate (10% or 4/39), and

rituximab (5% or 2/39). Additionally, adjunctive topical drops were utilized in 40% (4/10) studies, of which the most commonly used were topical steroids (8% or 3/39) followed by topical diclofenac, naphazolin, zinc sulphate, chloramphenicol, cyclosporine, and tacrolimus (each 3% or 1/39). Surgical procedures for treatment consisted of penetrating keratoplasty (8% or 3/39) and manual removal of pseudomembranes (3% or 1/39). Overall, the average duration of treatment was 42.1 d.

Prognosis: Factors associated with worse prognosis in PV include ethnicities such as Indo-Asian and Jewish origin, younger age of onset, higher initial intercellular antibody titer, and higher initial desmoglein 3 titer[76,77]. If left untreated, the spread of erosions and bullae leads to severe infection and eventually death with 50% mortality at 2 years and almost 100% mortality at 5 years[78]. If treated, cutaneous lesions heal with re-epithelialization leaving residual hyperpigmentation without scarring.

Of 10 studies encompassing 39 OPV patients treated with multi-drug systemic regimens, outcomes of treatment included remission defined as regression of ocular lesions (54% or 21/39), remission of ocular lesions with persistence of other systemic manifestation of disease (13% or 5/39), persistence of ocular lesions without progression (8% or 3/39), progression of ocular lesions (18% or 7/39), and recurrence of ocular lesions (8% or 3/39). Overall, average follow-up time was 26.6 mo[34,35,49,55,58-63].

Paraneoplastic pemphigus

Epidemiology: Paraneoplastic pemphigus (PNP), also known as paraneoplastic autoimmune multiorgan syndrome, is a rare intraepithelial blistering disease that occurs less commonly than MMP. PNP occurs at an unknown incidence although approximately 250 cases have been reported in the literature[79]. PNP typically affects patients aged 45-70 years old although cases have occurred in children[80] and males appear to be more commonly affected compared to females[81]. The disease affects all races, but a higher predilection is associated with certain HLA subtypes such as the DRB1*03 allele in Caucasian patients and HLA Cw*14 in Chinese patients[82,83]. Additionally, PNP is strongly associated with underlying malignancy, more often lymphoproliferative neoplasms (chronic lymphocytic leukemia and non-Hodgkin Lymphoma), and the type of malignancy may be related to the ethnic background of the patient. A high prevalence of PNP associated with Castleman's disease and follicular dendritic cell sarcomas in Chinese and Korean patients has been documented[84].

Pathophysiology: PNP is an intraepithelial blistering disease characterized by autoantibodies that bind desmoglein 3, similarly to the pathogenic mechanism seen in PV. However, in PNP, the autoantibodies bind to epitopes distributed throughout the extracellular domain of desmoglein 3 as opposed to solely the N-terminal extracellular domain in PV[85]. Additionally, PNP has multiple other target antigens including the plakin protein family that connects cytoskeletal networks. These target antigens include desmoplakin I (250 kDa), desmoplakin Ⅱ (210 kDa), bullous pemphigoid antigen 1 (BPAG1, 230 kDa), envoplakin (210 kDa), periplakin (190 kDa), plectin (500 kDa), desmocollin 2 (105 kDa), desmocollin 3, α2-macroglobulin-like-1 (A2LM1, 170 kDa), desmoglein 1 (160 kDa), and desmoglein 3 (130 kDa)[85-93]. This differs from MMP that is characterized by subepithelial lesions due to autoantibodies directed against various target antigens not including the plakin protein family.

Clinical features: PNP is a systemic autoimmune disease that occurs mostly in the setting of lymphoproliferative malignancies. PNP manifests as persistent painful erosions of mucous membranes and chronic cicatricial conjunctivitis clinically identical to MMP. Anhalt *et al*[94] termed paraneoplastic pemphigus to refer to a distinct clinical, histopathologic, and immunopathologic condition that included 5 criteria, of which Camisa *et al*[95] later revised these into major and minor criteria (Table 3)[69,94,95].

The distinguishing clinical manifestations that differentiate PNP include a painful and intractable ulcerating stomatitis that extends to the vermillion surface of the lips[45,96,97] and tense bullae that develop on the palms and/or soles[98]. Cutaneous manifestations of PNP are widely variable and can include superficial vesicles and flaccid blisters (pemphigus-like); scaly erythematous papules with or without tense blisters (bullous pemphigoid-like); polymorphic lesions (erythema multiforme-like); disseminated red scaly papules (graft *vs* host disease-like); or small violaceous papules with predominant mucosal membrane involvement (lichen planus-like)[99].

A total of 12 studies comprising 23 PNP patients with ocular involvement were found in the literature[84,94,100-109]. The most common ocular symptoms included the following: conjunctival erosions (68% or 15/22), conjunctivitis (45% or 10/22), pseudomembrane formation (27% or 6/22), conjunctival scarring (23% or 5/22), symblepharon formation (18% or 4/22), conjunctival shrinkage (14% or 3/22), forniceal foreshortening (9% or 2/22), corneal epithelial defect (5% or 1/22), and corneal perforation (5% or 1/22). Concomitant systemic manifestations included oral involvement (100% or 23/23) and cutaneous involvement (96% or 22/23). The most common initial presentation of disease was oral involvement (94% or 17/18) followed by ocular (17% or 3/18) and cutaneous (11% or 2/18) lesions.

Additionally, PNP is associated with malignant neoplasms. PNP may be the initial manifestation of a previously undetected malignancy in up to 33% of cases[81,102,110] or PNP may arise years after a patient has already undergone treatment for a previously known malignancy[111]. Of 12 studies comprising 23 PNP patients with ocular involvement, associated malignancies included the following: non-Hodgkin lymphoma (43% or 10/23), Castleman's disease (22% or 5/23), follicular dendritic cell sarcoma (22% or 5/23), peripheral T cell lymphoma (4% or 1/23), thymoma (4% or 1/23), and squamous cell lung carcinoma (4% or 1/23)[84,94,100-109]. Others have reported

Table 3 Diagnostic criteria for paraneoplastic pemphigus

Diagnostic criteria for paraneoplastic pemphigus	
Anhalt *et al*[94]	**Camisa *et al*[95]**
Painful mucosal and polymorphous skin erosions that involves the trunk, extremities, palms, and soles of a patient with a neoplasm	Major criteria
Histological changes including intraepidermal acantholysis, keratinocyte necrosis, and vacuolar interface dermatitis)	Polymorphous mucocutaneous eruption
Direct immunofluorescence findings of IgG and complement localized to the intercellular regions of the epithelium in a linear or granular fashion at the basement membrane zone	Concurrent internal neoplasia
Circulating autoantibodies that bind to stratified squamous epithelium as well as simple, columnar, and transitional epithelium	Specific serum immunoprecipitation pattern
Immunoprecipitation studies that demonstrate the presence of autoantibodies directed against a complex of five proteins of 250, 230, 210, 190, and 170 kDa	Minor criteria
	Histology demonstrating acantholysis
	Direct immunofluorescence demonstrating intercellular and basement membrane staining
	Indirect immunofluorescence staining with rat murine epithelium
	Diagnosis: All three major or two major and two minor required to diagnosis paraneoplastic pemphigus

the occurrence of chronic lymphocytic leukemia in up to 18%-29% of cases[97,108] as well as adenocarcinoma of various solid organs including the pancreas, colon, breast, prostate, and liver and squamous cell carcinoma of the tongue, cervix, and kidney[107,108,112-116].

Diagnostic studies: Histopathological studies utilizing hematoxylin-eosin staining in conjunctival biopsies from patients with PNP include the characteristic feature of pemphigus - vacuolization of basal cells and suprabasilar intraepithelial acantholysis[109]. Specimens taken from cutaneous biopsy may be widely variable and reflect the clinical polymorphisms present in this disease. Histopathologic features that are unique to PNP and are not found in other pemphigus subsets include vacuolar degeneration of basal keratinocytes with lichenoid or lymphohistiocytic infiltration as well as apoptotic keratinocytes located throughout the epidermis[84,94]. These changes differentiate PNP from MMP where changes occur exclusively at the basement membrane zone with subepithelial conjunctival shrinkage; inflammatory infiltrate involving lymphocytes, macrophages, and plasma cells; and squamous metaplasia progressing to parakeratosis and keratinization of conjunctival epithelium[56,68].

DIF studies show IgG and complement (C3) distributed both intercellularly and at the basement membrane zone in a linear or granular distribution[98]. This differentiates PNP from other types of pemphigus where only intercellular deposits are found and from MMP where only subepithelial deposits are found. Histological examination of biopsy parallels the clinical phenotype categorization and may demonstrate suprabasal acantholysis; keratinocytic dyskeratosis, apoptosis, and necrosis; vacuolization of the basal layer; or a lichenoid appearance seen along the dermal-epidermal junction[117,118].

IIF in PNP demonstrates autoantibodies binding to a variety of epithelium including simple columnar, transitional, respiratory, gastrointestinal, and myocardium[88]. This differentiates PNP from PV where autoantibodies against desmoglein 3 are restricted to stratified squamous epithelial tissues and from MMP where autoantibodies are found only in the epidermal basement membrane zone.

Additionally, IIF using murine bladder and tongue or monkey esophagus distinguishes PNP because these tissues express desmoplakin 1 without desmoglein 3[81,119]. When IIF results are indeterminate, western blotting and immunoprecipitation may provide more sensitive techniques. Detection of autoantibodies to envoplakin and periplakin is most specific followed by desmoplakin I and Ⅱ[79].

Utilization of IEM enables visualization of autoantibodies binding to desmosomes, hemidesmosomes, and spreading along the keratinocyte cell surface including the lamina lucida[120,121].

Immunoprecipitation demonstrating polyclonal autoantibodies that target a complex of plakin proteins is best for diagnosis and is a major criterion for diagnosis of PNP[95,122]. The combination of rat bladder IIF and immunoblotting has equally sensitive results that are highly specific; this can be utilized as an alternative approach to immunoprecipitation for serologic diagnosis[122].

Treatment: Treatment for PNP is directed towards relieving symptoms of PNP as well as treating the underlying neoplasm. Resection of benign neoplasms may lead to improvement or remission of cutaneous lesions in 6-11 wk[86,105,118]. However, the disease often progresses despite surgical excision and chemotherapy[118]. Aside from treating the associated neoplasm, management of PNP includes corticosteroids and adjunctive corticosteroid-sparing agents to decrease the incidence of side effects. Concurrent use of corticosteroids with sulfone derivatives, immunosuppressive agents, antimetabolites, alkylating agents, and biologic agents may occur although PNP is much less responsive to therapy compared to other forms of pemphigus[123]. In general, skin lesions are usually more responsive whereas mucosal lesions are highly refractory to treatment and recover more slowly[57,86,124].

A total of 12 studies encompassing 23 PNP patients with ocular involvement were found in the literature[84,94,100-109]. Treatment regimens most commonly consisted of: systemic steroids (81% or 13/16), rituximab (31% or 5/16), cyclophosphamide (31% or 5/16), cyclosporine (25% or 4/16), azathioprine (25% or 4/16), IVIG (25% or 4/16), vincristine (25% or 4/16), chlorambucil (19% or 3/16), and fludarabine, doxorubicin, bleomycin, double filtration

Table 4 Overview of mucous membrane pemphigoid and pseudopemphigoid as caused by the pemphigus disease

	MMP	Pseudopemphigoid	
		PNP	OPV
Location	Subepidermal	Intraepidermal	Intraepidermal
DIF	IgG/IgA/IgM/C3	IgG/C3	IgG/C3
IIF on salt-split skin	Dermal, epidermal, or combined depending on antigen	Not applicable	Not applicable
IEM: ultrastructural location of antigen	Lamina lucida Lamina densa Sublamina densa (anchoring fibrils)	Hemidesmosomes Desmosomal plaques Lamina lucida	Desmosomes
Immunoblot: determination of antigen	Bullous pemphigoid antigen 1 (Bullous Pemphigoid 230) Bullous pemphigoid antigen 2 (Bullous Pemphigoid 180, type XVII collagen) Type VII collagen (290 kDa) Laminin332, epiligrin, or laminin 5 α3β3γ2 (165, 145, 140, 105 kDa) Laminin 6 (α3) Integrin beta 4 45 kDa epithelial protein 130 kDa epithelial protein 140 kDa epithelial protein 205 kDa epithelial protein 168 kDa epithelial protein Uncein LAD-1 (97/120 kDa)	Plakin protein family: Desmoplakin I (250 kDa) Bullous pemphigoid antigen 1 (230 kDa) Desmoplakin Ⅱ and envoplakin (210 kDa) Periplakin (190 kDa) Plectin (500 kDa) Desmocollin 2 (105 kDa) Desmocollin 3 α2-macroglobulin-like-1 (A2LM1, 170 kDa) Desmoglein 1 (160 kDa) Desmoglein 3 (130 kDa)	Desmoglein 1 (160 kDa) Desmoglein 3 (130 kDa)
Increased malignancy	Yes - solid malignancies (laminin 332 subtype)	Yes - lymphoproliferative malignancies	--

MMP: Mucous membrane pemphigoid; PNP: Paraneoplastic pemphigus; OPV: Ocular pemphigus vulgaris; DIF: Direct immunofluorescence; IIF: Indirect immunofluorescence; IEM: Immunoelectron microscopy; LAD-1: Linear IgA bullous dermatosis autoantigen 1.

membrane plasmapheresis, methotrexate, and daclizumab (each 6% or 1/16). Additionally, adjunctive topical drops were utilized in 27% (3/11) of studies, of which the most commonly used were topical steroids (13% or 2/16) followed by topical tacrolimus (6% or 1/16). Surgical procedures consisting of resection of primary tumor occurred in 48% (11/23) of cases. Discontinuation of treatment due to side effects occurred in 13% of cases (3/23) and included plasmapheresis secondary to hypogammaglobulinemia and hypoalbuminemia; cyclosporine secondary to renal dysfunction; and cyclophosphamide, vincristine, prednisone, and rituximab regimen secondary to chemotherapy related side effects.

Prognosis: Of 12 studies encompassing 23 PNP patients with ocular involvement treated medically and/or surgically, outcomes included remission defined as regression of ocular lesions (30% or 7/23), remission of ocular lesions but persistence of other systemic manifestations (9% or 2/23), persistence of ocular lesions without progression (22% or 5/23), progression of ocular lesions (22%, 5/23), and recurrence of ocular lesions (4% or 1/23). Prognosis including death as final outcome occurred in 61% of cases (14/23) at an average 26 mo after onset of symptoms due to PNP[84,94,100-109]. Although reports of long-term survival have been described in the literature[104,125-128], others indicate that mortality rates may reach up to 90% with a mean survival of less than 1 year[128-130].

Death most commonly occurs secondary to malignancy, sepsis, or respiratory failure due to pulmonary involvement producing bronchiolitis obliterans[131,132]. Pulmonary involvement may occur and can continue to progress despite treatment with immunosuppressants, resection of malignancy, and improvement of other mucocutaneous symptoms[133]. Factors associated with worse prognosis in PNP include presence of erythema multiforme-like lesions, keratinocyte necrosis on biopsy specimens, and non-Hodgkin lymphoma patients with an increased risk of infection due to systemic chemotherapy and corticosteroids[128].

CONCLUSION

Pseudopemphigoid as caused by topical drugs and pemphigus disease may produce a chronic cicatricial conjunctivitis that can present clinically identical to MMP. In these cases, a vigilant history and examination combined with thorough diagnostic methods are needed to differentiate these diseases (Table 4). Distinguishing between the different causes of pseudopemphigoid that includes but is not limited to drug-induced cicatricial conjunctivitis, pemphigus vulgaris, and paraneoplastic pemphigus is paramount as there may be a poorer prognosis or a more severe clinical course unresponsive to medical management. Collaboration of the ophthalmologist with subspecialists such as the dermatologist, immunologist, and others involved in care of the patient is critical to prevent progression of the disease.

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MINIREVIEWS

Cranial neuropathies in sarcoidosis

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Abstract

Sarcoidosis is a multisystem, chronic inflammatory disease that is characterized by the development of non-caseating granulomas in multiple body tissues and organ systems. Neurological complications of systemic sarcoidosis include peripheral and cranial neuropathies, myopathies, seizures, gait dysfunction, and cognitive decline. Because sarcoidosis has a predilection to involve the basilar meninges, cranial neuropathy is the most prevalent neurological deficit seen when the nervous system is involved. Sarcoidosis cranial neuropathy may occur at different stages of the disease and even as the initial clinical manifestation of central nervous system involvement. Attributing a cranial neuropathy to sarcoidosis can be challenging, particularly in the setting of normal imaging studies. In this review, cranial neuropathies in sarcoidosis are discussed in detail.

Key words: Sarcoidosis; Neurosarcoidosis; Cranial neuropathy; Central nervous system

Core tip: Sarcoidosis is a multisystem, chronic inflammatory disease that is characterized by the development of non-caseating granulomas in multiple body tissues and organ systems. Neurological complications occur in 5%-15% of the cases. Because sarcoidosis has a predilection to involve the basilar meninges, cranial neuropathy is the most prevalent neurological deficit seen when the nervous system is involved. Several review papers on neurosarcoidosis have been published, but none has elaborated on cranial neuropathies. In this review, cranial neuropathies in sarcoidosis are discussed in detail, with elaboration on each cranial nerve individually and a representation of case reports from the literature.

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INTRODUCTION

Sarcoidosis is a multisystem, chronic inflammatory disease that is characterized by development of non-caseating granulomas in multiple body tissues and organ systems. Sarcoidosis affects more women than men and more adults than children. In the United States, the disease affects more African Americans than Caucasians. Neurological complications occur in 5%-15% of individuals diagnosed with systemic sarcoidosis[1-4], imaging studies reveal neurological disease in 10% of all patients[5], and postmortem

Table 1 Frequencies of clinical signs and symptoms associated with neurosarcoidosis

Symptoms	%
Cranial nerve palsies	50-75
Overall parenchymal disease	50
Headache	30
Meningeal signs	10-20
Endocrinopathies	10-15
Hydrocephalus	10
Mass lesion(s)	5-10
Seizures	5-10
Encephalopathy/vasculopathy	5-10

Source: Stern *et al*[39].

Table 2 Frequencies of occurrence of cranial neuropathies in sarcoidosis

Cranial nerve	Frequency of occurrence
CN-I	Rare
CN-II	5% of all patients with sarcoidosis
CN-Ⅲ, -IV, -VI	Rare
CN-V	Rare
CN-Ⅶ	25%-50% of all patients with sarcoidosis
CN-Ⅷ	1%-7% of all patients with sarcoidosis
CN-IX, -X, -XI	Common
CN-XI	Rare
CN-XII	Rare

CN: Cranial nerve.

studies report that ante-mortem diagnosis is made in only half of the cases with nervous system involvement[6]. The exact site of involvement and pathogenesis are difficult to establish, as biopsy and autopsy material is not commonly obtained. Neurological manifestations of sarcoidosis include peripheral and cranial neuropathies, myopathies, seizures, gait dysfunction, and cognitive decline. The presenting symptoms of intracranial sarcoidosis are typically related to meningeal, cranial nerve, hypothalamus, and pituitary involvement[7-9]. Common imaging findings include hydrocephalus, mass lesion(s), and leptomeningeal enhancement.

Because sarcoidosis has a predilection to involve the basilar meninges, cranial neuropathy is the most prevalent neurological deficit seen when the nervous system is involved[10], and has been reported in as many as 50%-75% of patients with neurosarcoidosis[7]. Table 1 outlines the frequency of some of the most common neurological signs and symptoms associated with neurosarcoidosis. Granulomatous basal meningitis, direct infiltration of cranial nerve(s), and increased intracranial pressure are all potential mechanisms causing cranial neuropathies. Attributing a cranial neuropathy to sarcoidosis can be challenging, especially in the event of normal brain imaging and the often poor correlation between abnormal imaging and clinical findings. For example, in 13 patients with central nervous system (CNS) sarcoidosis and cranial neuropathies, only 9 had correlating brain imaging findings[11]. Several explanations of negative brain imaging in patients with cranial neuropathies related to sarcoidosis have been proposed, including extra-cranial nerve involvement, minimal infiltration of the involved cranial nerve by the disease, and small size granulomas.

Cranial neuropathy of neurosarcoidosis can involve one or multiple cranial nerves simultaneously. Table 2 shows the frequency of occurrence of cranial nerve involvement. Cranial nerves can be affected by direct infiltration of the nerve at any anatomical location, extra- or intra-cranially, or by other processes such as increased intracranial pressure and mass lesions.

THE PATHOGENESIS OF NEUROSARCOIDOSIS

Several mechanisms have been proposed to explain the pathogenesis of sarcoidosis, but none are conclusive. Several studies suggest a particular role of T-lymphocytes, triggered by an antigen of an unknown origin, in amplifying a local cellular immune response that is crucial for the development of sarcoidosis[12,13]. Non-necrotizing granulomas of sarcoidosis are composed of epithelioid macrophages, lymphocytes, and monocytes, and the consequential inflammation is often perivascular. Thickening of the vascular intima and media, along with fibrosis, may lead to ischemic injury.

CNS sarcoidosis has a predilection to involve the leptomeninges, with a granulomatous inflammatory exudate that infiltrates brain parenchyma through the Virchow-Robin spaces[14,15]. This pattern of infiltration may explain the predilection of neurosarcoidosis to the base of the brain where the Virchow-Robin spaces are particularly large and, consequently, the high incidence of cranial neuropathies[16-18].

OLFACTORY NERVE, OR CRANIAL NERVE-I

Involvement of the olfactory nerve, cranial nerve- I (CN- I), in sarcoidosis is considered rare[19]. Clinical signs and symptoms include anosmia and hyposmia. Isolated involvement of CN- I in patients with neurosarcoidosis is rare, and anosmia is an extremely infrequent isolated clinical presentation[20]. In a series published by Delaney[2], 17% of patients with neurosarcoidosis had anosmia, whereas Colover *et al*[20] reported this symptom in only 2 of 118 cases (< 0.2%). CN- I can be affected by direct infiltration of the nasal mucosa, intracranial disease, basal granulomatous meningitis, or a combination of these mechanisms. Kieff *et al*[21] reported a case of a 51-year-old man who presented with a 6-wk history of anosmia and visual difficulty. Magnetic resonance imaging (MRI) of the brain showed an enhancing subfrontal, extra-axial mass with accompanying edema. Tissue biopsy demonstrated non-caseating granulomas, consistent with the diagnosis of neurosarcoidosis.

OPTIC NERVE, OR CRANIAL NERVE-Ⅱ

Following the facial nerve, the optic nerve, or cranial nerve-Ⅱ (CN-Ⅱ), is the second most commonly involved

nerve in patients with neurosarcoidosis[7]. Approximately 5% of patients with sarcoidosis experience some type of optic neuropathy during the course of the disease, and about 30% of those will have other signs of neurosarcoidosis. Granulomatous infiltration of the optic nerves, chiasm, or tracts has been reported in autopsy studies[22].

Clinical signs of optic neuropathy occur as a result of increased intracranial pressure and papilledema, intracranial compression leading to optic atrophy, and/or direct invasion of the nerve by the forming granulomas. Optic nerve involvement is associated with papilledema, disc edema, or optic nerve head granulomas. Disc edema is the most common optic nerve abnormality in patients with neurosarcoidosis, with optic atrophy and neuritis being much less frequent[23]. Retrobulbar involvement of the optic nerve may mimic the clinical picture of optic neuritis, with acute loss of vision, with or without optic disc edema[24,25]. Pituitary granulomatous disease may also extend to affect the optic chiasm, with a correlating clinical picture of bi-temporal visual field loss and pituitary dysfunction[26,27]. Infiltration of the optic tract or the visual cortex is much less common.

OCULOMOTOR, TROCHLEAR, AND ABDUCENS NERVES (CN-Ⅲ, -Ⅳ, AND -Ⅵ)

External ophthalmoplegia is an infrequent manifestation of CNS sarcoidosis[2]. Involvement of CN-Ⅲ, -Ⅳ and -Ⅵ is rare[20]. Potential pathological mechanisms leading to ophthalmoplegia include direct invasion of a cranial nerve or extraocular muscles by granuloma, increased intracranial pressure, leptomeningeal disease, or orbital mass effect. Ischemia to the involved cranial nerve as a result of perivasculitis has also been suggested as a mechanism contributing to ophthalmoplegia in a patient with neurosarcoidosis[28]. Overall, the frequency of extraocular muscles and/or innervating cranial nerve involvement in neurosarcoidosis is felt to be under-reported, as biopsy of these structures is rarely performed. Clinical signs and symptoms include double vision, ptosis, pupillary involvement, and ophthalmoplegia.

There are several reports of CN-Ⅲ palsy as a manifestation of CNS sarcoidosis, typically as a result of aseptic meningitis causing multiple cranial neuropathies[29-31]. Ueyama *et al*[30] reported a patient with isolated CN-Ⅲ palsy as an initial manifestation of sarcoidosis. The case was of a 28-year-old man who presented with sudden onset of complete CN-Ⅲ palsy. A conventional cerebral angiogram was unremarkable. Cerebrospinal fluid analysis revealed elevated lymphocytes and protein, but negative cytologic analysis. Brain MRI showed enhanced thickening of CN-Ⅱ at the level of the ponto-midbrain junction. A chest radiograph revealed bilateral hilar lymphadenopathy, and lymph node biopsy showed non-caseating granulomas confirming sarcoidosis[30]. Velazquez *et al*[31] reported a case of a 53-year-old woman who presented with bilateral CN-Ⅲ palsy and was subsequently found to have biopsy-proven sarcoidosis. The majority of other cases reported on CN-Ⅲ palsy related to sarcoidosis were associated with multiple cranial neuropathies[11,28].

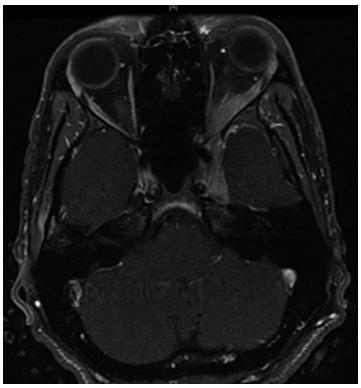

Figure 1 Brain magnetic resonance imaging with gadolinium showing diffuse thickening and enhancement of the dura involving the left cavernous sinus, with mild mass effect on the left temporal lobe, and soft tissue enhancement extending anteriorly through the foramen rotundum and left orbital apex.

As stated previously, involvement of CN-Ⅳ or -Ⅵ is rare[2,20]. In the series published by Wiederholt *et al*[19], 18 of 807 patients with sarcoidosis had cranial nerve lesions. No trochlear or abducens nerve involvement was reported, whether in isolation or in combination with other cranial neuropathies.

We evaluated a 23-year-old African American man who presented to our institution with painless bulging of the left eye of three months duration, associated with diplopia. On the day of admission, he had a first-event witnessed generalized tonic-clonic seizure. The patient had a normal neurological examination except for left CN-Ⅵ palsy. Brain MRI revealed diffuse thickening and enhancement of the dura involving the left cavernous sinus (Figure 1). A computed tomography of the chest, abdomen, and pelvis with and without contrast was unremarkable for any sarcoidosis lymphadenopathy or malignancy. A left cavernous sinus dural biopsy revealed extensive chronic inflammation containing non-necrotizing granulomas, consistent with sarcoidosis.

TRIGEMINAL NERVE, OR CRANIAL NERVE-V

Involvement of the trigeminal nerve (CN-V) is exceedingly uncommon in patients with sarcoidosis[7]. Sarcoidosis can infiltrate any of the three divisions of CN-V, with or without eye involvement. Involvement of CN-V is usually sensory and unilateral, and commonly accompanied by other cranial neuropathies[20]. Clinical signs and symptoms include facial numbness, hypesthesia, and/or corneal ulcers. Biopsy of CN-V is not a common practice, and the physician must thus rely on the clinical presentation and neurological examination.

Three cases of isolated unilateral trigeminal nerve involvement in patients with sarcoidosis have been reported[32]. The first was of a patient with pulmonary

sarcoidosis who presented with complete unilateral ophthalmoplegia and cavernous sinus syndrome involving CN-V[33]. A case of another patient with mediastinal and parotid sarcoidosis and bilateral Gasser's ganglion cistern involvement has been reported with no ocular findings[34].

Absence of corneal sensation can result from impairment of trigeminal corneal innervation, a condition known as neurotrophic keratopathy. Gupta *et al*[35] reported a particularly rare case of isolated bilateral CN-V neuropathy in a patient with sarcoidosis who presented with neurotrophic corneal ulcers and was diagnosed with biopsy-proven cutaneous sarcoidosis. The patient also had decreased sensation to light touch involving all divisions of the trigeminal nerve bilaterally, with no other cranial neuropathies. After all potential causes of CN-V neuropathy were ruled out, isolated bilateral trigeminal neuropathy as a result of sarcoidosis was the confirmed diagnosis[35].

FACIAL NERVE, OR CRANIAL NERVE-Ⅶ

Of all the cranial nerve syndromes associated with sarcoidosis, peripheral cranial nerve-Ⅶ (CN-Ⅶ) palsy is the most common and is the single most frequent neurologic manifestation[36,37]. Facial neuropathy makes up 25%-50% of neurological manifestations of sarcoidosis[7,28]. Although usually unilateral, bilateral CN-Ⅶ involvement can occur, presenting with either simultaneous or sequential paralysis[37,38]. CN-Ⅶ can therefore be affected unilaterally, bilaterally, or simultaneously with other cranial nerves[39]. Sarcoidosis affects CN-Ⅶ either secondary to meningitic reaction or parotid gland inflammation, and may precede or follow parotitis. Clinical signs and symptoms include facial diplegia, peripheral facial palsy, and/or hemiageusia. Other potential etiologies including Lyme disease, human immunodeficiency virus, syphilis, brain stem lesions, leukemia, meningitis, Guillain-Barré syndrome, and diabetes mellitus need to be considered and investigated[40-42].

Facial nerve infiltration can occur at different anatomical locations. Rarely is the facial palsy caused by parotid inflammation[43] or part of uveoparotid fever (Heerfordt's syndrome), which includes fever, enlarged parotid glands, uveitis, and unilateral or bilateral facial neuropathy. In patients with sarcoidosis, CN-Ⅶ is more commonly affected as it traverses the meninges and subarachnoid space. Facial nerve paresis could also be due to intra-axial sarcoidosis-induced inflammation[43]. Necrotizing nerve ischemia and granulomatous infiltration of the epineurium are suggested mechanisms of facial neuropathy[44]. CN-Ⅶ involvement can be part of multiple cranial neuropathies, especially with meningeal infiltration[36,45]. In general, the prognosis for CN-Ⅶ is good, with over 80% of patients having a favorable outcome if treated early[46].

VESTIBULOCOCHLEAR NERVE, OR CRANIAL NERVE-Ⅷ

Involvement of cranial nerve-Ⅷ (CN-Ⅷ) has been reported as a neurological manifestation in 1%-7% of patients with sarcoidosis[7,45,47-50]. Clinical signs and symptoms include vertigo, tinnitus, deafness, and sensorineural hearing loss. Neurosarcoidosis should be entertained as a diagnosis in a patient with sensorineural hearing loss of an unknown source, especially if a diagnosis of systemic sarcoidosis is known. Several cases of sensorineural hearing loss have been reported in patients with sarcoidosis[51-54]. In a report by Babin *et al*[55], autopsy findings in a patient with a known diagnosis of sarcoidosis and deafness included perivascular granulomatous inflammation within the internal auditory meatus. The authors attributed the vestibulocochlear impairment to vascular occlusion, as the severity of cochlear destruction did not correlate with the degree of cochleae infiltration[55].

Cama *et al*[56] reported two patients with sudden hearing loss that was attributed to sarcoidosis, with different findings on brain imaging studies. The first reported case was of a 29-year-old man who presented with left-sided hearing loss and facial nerve paralysis. Initial evaluation revealed bilateral sensorineural hearing loss and right anterior uveitis. Brain MRI with gadolinium was normal. Further imaging studies revealed multiple small pulmonary cavities and abdominal lymphadenopathy. Percutaneous hepatic biopsy revealed giant-cell granulomas. The initial presenting symptom of hearing loss was attributed to systemic sarcoidosis with CNS involvement[56].

The second case was of a 44-year-old man with a known diagnosis of systemic sarcoidosis who presented with diplopia and unsteadiness, followed by sudden right-sided hearing loss a few weeks later. Initial evaluation revealed sensorineural hearing loss of a cochlear origin. Contrast-enhanced brain MRI was negative. One month later he had worsening of the right-sided and new left-sided hearing loss. Brain MRI with gadolinium showed bilateral enhancement of the internal auditory meatus. A follow-up MRI two months later showed diffuse enhancement of basal leptomeninges, myelinic sheath of both optic nerves, trigeminal nerves, and pial surfaces of the cerebellar folia. The patient's hearing impairment, secondary to CNS involvement of systemic sarcoidosis, remained stable on oral corticosteroids[56].

GLOSSOPHARYNGEAL NERVE, OR CRANIAL NERVE-Ⅸ

Isolated glossopharyngeal neuropathy associated with sarcoidosis is extremely rare[57]. Combined involvement of cranial nerves IX, X, and XI is the third most common cranial neuropathy after facial and optic nerves involvement[58]. The most common site of involvement is in the lateral medulla or subarachnoid space[57]. The main presenting symptoms are dysphagia and hoarseness of voice[57,58].

VAGUS NERVE, OR CRANIAL NERVE-Ⅹ

Cranial nerve-X (CN-X) involvement in neurosarcoidosis

is rare, with only a few cases reported in the literature[59]. Vagal neuropathy can occur in isolation as a manifestation of neurosarcoidosis or in combination with other cranial neuropathies. Neurosarcoidosis should be considered in a patient with vocal fold paresis of no apparent etiology. Two cases of CN-X involvement were reported in a retrospective review of 35 cases of confirmed neurosarcoidosis[3]. Additionally, Alon *et al*[60] conducted a retrospective study of a small cohort of 53 patients who presented with neurosarcoidosis and found only four with clinical or radiological findings suggestive of CN-X involvement. None of the four patients had a known diagnosis of systemic sarcoidosis. All four patients had vocal fold motion impairment. In one patient, a retropharyngeal mass was identified with biopsy-proven noncaseating granulomas, which extended to the jugular foramen several months later. The patient was found to have unilateral vocal fold paralysis and palatal weakness. Another patient with a history of chronic cough presented with right vocal fold paralysis and decreased gag reflex. A mediastinal lymph node biopsy revealed non-caseating granulomas. A third reported patient initially presented with unilateral throat and tongue burning sensation as well as vocal cord and tongue paresis. An MRI of the brain showed an enhancing mass in the jugular foramen extending into the right hypoglossal canal and second division of CN-V. Finally, a case of bilateral vagus and glossopharyngeal nerve enhancement was reported in a patient with biopsy-proven sarcoidosis who presented with palatal weakness and vocal folds paralysis[60].

SPINAL ACCESSORY NERVE, OR CRANIAL NERVE-XI

Isolated spinal accessory neuropathy has not been reported as a clinical manifestation of neurosarcoidosis. However, cranial nerve-XI neuropathy has been reported in combination with other cranial neuropathies. Clinical manifestations include ipsilateral sternocleidomastoid and trapezius muscle weakness.

HYPOGLOSSAL NERVE, OR CRANIAL NERVE-XII

Hypoglossal nerve involvement commonly occurs with other cranial neuropathies. As with CN-IX, -X, and -XI, the medulla and subarachnoid space are the most common sites of cranial nerve-XII involvement. The nerve is commonly affected as a result of a meningeal process, such as pachi meningitis, or focal granulomatous disease involving the medial medulla. The main presenting symptom is dysarthria[61,62], but patients can also have tongue deviation and atrophy.

Multiple cranial neuropathies of sarcoidosis

In most patients with neurosarcoidosis, more than one cranial nerve is involved[59]. Loor *et al*[45] reported a 26-year-old woman with an initial presentation of left-sided facial palsy and sensorineural hearing loss. MRI of the brain with gadolinium revealed enhancement of the left CN-Ⅶ and bilateral CN-Ⅷ. A chest X-ray demonstrated hilar lymphadenopathy. The patient later developed anosmia, and all her symptoms resolved after a course of steroid treatment[45].

Chapelon *et al*[3] reported a case of a woman with bilateral vestibular symptoms, as well as CN-Ⅶ, -IX, -X, and -XI involvement. Another case reported by Chapelon *et al*[3] was of a 21-year-old man with a history of confirmed sarcoidosis who presented with multiple cranial neuropathies (CN-Ⅶ, -X, -XI, -XII). As discussed earlier, the predilection of sarcoidosis to the base of the brain is a plausible explanation of multiple cranial neuropathies.

TREATMENT OF NEUROSARCOIDOSIS

Corticosteroids remain the gold standard treatment of patients with neurosarcoidosis, and patients with symptoms should be treated initially with pulse corticosteroid therapy[63]. If the use of steroids is limited secondary to resistance or adverse reactions, immunosuppression therapy is recommended.

According to recent recommendations made by Nozaki *et al*[64] in 2013, prednisone is the first-line of therapy in patients with cranial neuropathy secondary to neurosarcoidosis, particularly if CN-Ⅶ is involved, at a daily dose of 20-40 mg. If prednisone cannot be tapered to less than 10 mg per day within 3-6 mo, a higher dose or an alternative agent should be considered. Recurrence of symptoms has been reported when prednisone was tapered to less than 20-25 mg daily[64].

Immunomodulating agents include methotrexate, considered the first agent of choice that allows tapering the prednisone to 10-20 mg per day in one third of neurosarcoidosis patients[64]. Other immunosuppressant agents to be considered include azathioprine, cyclophosphamide, and cyclosporine.

CONCLUSION

Neurosarcoidosis is a rare manifestation of sarcoidosis. The diagnosis can be challenging, as many conditions can mimic neurosarcoidosis both clinically and radiographically. Sarcoidosis mononeuropathy may occur at different stages of the disease and even as the initial clinical manifestation of CNS involvement. Cranial neuropathy can present as an isolated entity of sarcoidosis in the absence of systemic involvement, which makes the diagnosis challenging and dependent on tissue biopsy. In these patients, extensive work-up is warranted to rule out infections and demyelinating conditions, as well as inflammatory and autoimmune diseases.

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MINIREVIEWS

Cerium oxide nanoparticles as promising ophthalmic therapeutics for the treatment of retinal diseases

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Abstract

Nanotechnology offers exciting new approaches for biology and medicine. In recent years, nanoparticles, particularly those of the rare metal cerium, are showing potential for a wide range of applications in medicine. Cerium oxide nanoparticles or nanoceria are antioxidants and possess catalytic activities that mimic those of super oxide dismutase and catalase, thereby protecting cells from oxidative stress. The retina is highly susceptible to oxidative stress because of its high oxygen consumption and high metabolic activity associated with exposure to light. Many retinal diseases progress through oxidative stress as a result of a chronic or acute rise in reactive oxygen species. Diseases of the retina are the leading causes of blindness throughout the world. Although some treatments may delay or slow the development of retinal diseases, there are no cures for most forms of blinding diseases. In this review is summarized evidence that cerium oxide nanoparticles can function as catalytic antioxidants *in vivo* in rodent models of age-related macular degeneration and inherited retinal degeneration and may represent a novel therapeutic strategy for the treatment of human eye diseases. This may shift current research and clinical practice towards the use of nanoceria, alone or in combination with other therapeutics.

Key words: Nanoceria; Age-related macular degeneration; Inherited retinal degeneration; Oxidative stress; Antioxidant

Core tip: This review outlines the recent findings that cerium oxide nanoparticles (nanoceria) may represent novel and broad spectrum therapeutic agents to treat retinal diseases including age-related macular degeneration, retinal angiomatous, inherited retinal degeneration, and fight inflammation and pathologies associated with oxidative stress.

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INTRODUCTION

Many retinal diseases including retinopathy of prematurity, inherited retinal degeneration, diabetic retinopathy, retinitis pigmentosa, glaucoma, and age-related macular degeneration are the leading causes of blindness in infants, adults, and the elderly, respectively. The etiology or development of many retinal diseases involves oxidative stress[1-4]. An imbalance between the production of reactive oxygen species (ROS) and the detoxification of their reactive intermediates causes oxidative stress[5]. Excessive ROS levels can damage lipids, proteins, and nucleic acids. This process subsequently leads to cell death unless it is neutralized by the oxidant defense system. The retina possesses the highest rate of oxygen metabolism and therefore is at higher risk of oxidative damage due to redox imbalance.

Besides traditional antioxidant agents, in recent years special attention has been given to cerium oxide nanoparticles or nanoceria as antioxidants in biological systems[6,7]. Cerium (Ce) is a rare earth element in the lanthanide series of the periodic table. Cerium oxide (CeO_2) nanoparticles are used extensively in a variety of applications such as oxygen sensors[8,9]. The underlying molecular mechanism for the action of cerium oxide nanoparticles is generally thought to be their dual oxidation state, depending on the reaction conditions[10,11]. Nanoceria switch between Ce^{4+} and Ce^{3+} states creating an oxygen vacancy. This capability of these nanoparticles is similar to that of biological antioxidants[12]. Because of these unique antioxidant properties nanoceria act as free-radical scavenger. Free radical scavenging by nanoceria functions by decreasing ROS and has potential uses in various biological applications[7]. It has been recently reported that cerium oxide nanoparticles possess neuroprotective[13,14], radioprotective[15], cardioprotective[16], anti-inflammatory[17], anti-invasive[18], pro-oxidative and antioxidative[19-23], anti-angiogenic[24], pro-apoptotic and anti-apoptotic[21,12] properties. During the past few years, much attention and efforts has been made at addressing the potential use of nanoceria as therapeutic antioxidants for the treatment of oxidative stress related diseases[25-27]. Due to their smaller particle size at about 5 nm in diameter, which allows for easier passage through cell membranes, non-toxic nature and excellent biocompatibility, cerium oxide nanoparticles also have the potential to be used as drug carriers and delivery agents.

In the last few years, our group is involved in developing cerium oxide nanoparticles as therapeutic agents for treatment of retinal diseases. We demonstrated for the first time that these nanoparticles are able to prevent the increases of intracellular ROS concentrations *in vitro* using primary cell cultures of rat retina and could protect retinal morphology and function *in vivo* using an albino rat light-damage model[28]. Next, in the homozygous *tubby* mutant mouse, which displays inherited early progressive cochlear and retinal degeneration that are similar to those of human Usher syndrome, we showed that cerium oxide nanoparticles preserve the retina by decreasing the concentrations of ROS, up-regulating the neuroprotection-associated genes expression; down-regulating apoptosis signaling pathways and/or up-regulating survival signaling pathways[29]. Furthermore, in an age-related macular degeneration (AMD) model and in particular for retinal angiomatous proliferation (RAP), the very low-density lipoprotein receptor knockout mouse (*vldlr*$^{-/-}$), we have reported that cerium oxide nanoparticles stopped the development and regression of pathological neovascularization[30]. Our data also demonstrated that nanoceria inhibited the expression of genes associated with inflammation, angiogenesis, and down-regulated MAP kinases, Akt, ASK1 and NF-κB signaling pathways[31,32]. This review aims to provide the recent findings and potential applications of nanoceria for the treatment of retinal diseases.

OXIDATIVE STRESS AND RETINAL DISEASES

Oxidative stress is defined as a disturbance in the balance between the production of ROS, which include hydrogen peroxide, superoxide anion, and hydroxyl radicals, and antioxidant defenses. Although ROS have important roles in regulating signal transduction and cellular function[33], their overproduction can damage lipids, proteins, and DNA, thus affecting many cellular and physiological mechanisms. Numerous pathological conditions have an oxidative stress component, including cardiovascular diseases[34], neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases[35-37], and cancer[38]. Oxidative stress has also been implicated in retinal diseases such as AMD, inherited retinal degeneration, diabetic retinopathy, retinitis pigmentosa, glaucoma and uveitis[1-4,39]. The retina is extremely vulnerable to ROS damage[40]. ROS can be formed in many ways including as a product of the respiratory chain in mitochondria, photochemical and enzymatic reactions as a result of the exposure to ultraviolet light, ionizing radiation, or heavy metal ions[41-47]. Retinal cells have the highest rate of oxygen metabolism of any cells and are frequently exposed to the damaging effects of oxidative stress due to the the excessive exposure to light.

AMD is the leading cause of severe and irreversible loss of vision in the elderly in the world. AMD is divided into two broad types: "dry" and "wet" that account for about 85% and 15% of cases, respectively. "Wet" or exudative AMD, is the most severe form of AMD and is associated with subretinal neovascularization. By contrast, "dry" also known as atrophic or non-exudative AMD, tends to exhibit a slow progression of the disease. This complex disease has both genetic and environmental risk factors with a number of gene polymorphisms being identified which increase susceptibility to environmental risk factors such as smoking, hypertension, diet, obesity, prolonged sun exposure, and oxidative stress[4,48,49]. While there is currently no cure for AMD, some treatments can prevent severe vision loss or decrease the progression of the disease considerably. AMD treatments include anti-

vascular endothelial growth factor (VEGF) therapy, laser surgery, photodynamic therapy, vitamins and nutritional supplements[50-55]. The abundance and complex interactions between the risk factors for AMD limit the effectiveness of therapeutic options. Therefore, new therapeutics is needed to target multiple pathophysiological aspects that contribute to development of AMD, most importantly oxidative stress.

There are other inherited and acquired diseases or disorders that may affect the retina. Retinitis pigmentosa (RP) is a heterogeneous group of inherited ocular diseases that result in a progressive retinal degeneration. RP is the largest Mendelian genetic cause of blindness affecting 1 in 3000 to 5000 people worldwide[54]. This disease exhibits abnormalities in the photoreceptors or in the retinal pigment epithelium of the retina, which lead to progressive visual loss. RP can be inherited in an autosomal dominant, autosomal recessive or X-linked manner[55]. RP may also occur as part of Usher syndrome and Bardet-Biedl syndrome[56]. Usher syndrome is the most common hereditary form of combined deafness and blindness in humans[55]. The oxidative stress hypothesis is supported by several lines of evidence in experimental models of Retinitis pigmentosa[57-60]. In addition, it has been found that Retinitis pigmentosa patients have reduced ocular antioxidant status and antioxidant imbalance in the peripheral blood[60]. Although there is no cure for RP, treatments are available for managing some aspects of its clinical manifestations[61].

CERIUM OXIDE NANOPARTICLES

Cerium belongs to the lanthanide series of rare earth elements. Although most of the rare earth elements of the periodic table exist in the trivalent state, cerium in an oxide nanoparticle can occur in either a 3+ (fully reduced) or 4+ (fully oxidized) state and may flip-flop between the two in a redox reaction. As a result of this, cerium oxides form oxygen vacancies or defects in the lattice structure[11,62]. It is these defects or reactive sites on the cerium oxide nanoparticles that serve as sites for free radical scavenging. Cerium oxide nanoparticles react catalytically with ROS, including hydroxyl radical, superoxide radical and hydrogen peroxide, providing antioxidant properties[12,63]. It has been demonstrated that cerium oxide nanoparticles act as a catalyst that mimics enzymatic antioxidants including superoxide dismutase (most apparent when cerium is in the 4+ state)[64] and catalase (most apparent when cerium is in the 3+ state)[65]. Various techniques including frame spray pyrolysis[66] and wet chemical methods[12,17] have been reported to synthesize cerium oxide nanoparticles. The radical scavenging activities of cerium oxide are even further increased when synthesized as a nanoparticle. Moreover, as the size of the cerium oxide nanoparticle decreases, there is a concurent increase of cerium in the +3 state, which may further enhance reducing power[67]. Smaller diameter nanocrystals containing more cerium (+3) were found to be more reactive toward hydrogen peroxide[68]. In addition, the presence of a surface coating did not prevent the reaction between the nanocrystal surface cerium (3+) and hydrogen peroxide[68]. Therefore, the most reactive nanoparticles are at about 5-10 nm diameter with the thinnest surface coating (*e.g.*, oleic acid). The radical scavenging properties of cerium oxide can be drastically increased during the reduction to the nanoscale.

Cerium oxide nanoparticles used in our studies were synthesized using wet chemical method as described previously[12]. Briefly, cerium nitrate hexahydrate was dissolved in distilled water and the solution was oxidized using excess of hydrogen peroxide. To maintain the synthesized nanoparticles in suspension, the pH of the solution was kept below 3.0. These cerium oxide nanoparticles contain individual crystallites of 3-5 nm and can be diluted in aqueous and cellular media. The size and shape of the particles was characterized using transmission electron microscope, zeta potential of the suspension was monitoring using dynamic light scattering and X-ray photoelectron spectroscopy was used to determine the surface oxidation state of the nanoparticles as reported previously by us[69].

BIOLOGICAL PROPERTIES OF CERIUM OXIDE NANOPARTICLES

Although cerium oxide nanoparticles have been widely used as oxygen sensors[9] and automotive catalytic converters[70], they have recently begun to be used in biological systems[6,7]. The ability of these nanoparticles to switch oxidation states and their antioxidant activity has a unique advantage for therapeutic implications. The biological properties using *in vivo* mice models of AMD and inherited retinal degeneration and potential applications of cerium oxide nanoparticles as ophthalmic therapeutics are discussed below.

Antioxidant properties

The antioxidant properties of nanoceria were investigated first in primary cell cultures of dissociated rat retinas. Chen *et al*[28] demonstrated by flow cytometric analysis of dichlorofluorescein (DCF) stained retinal cells that nanoceria particles (1, 3, 5, 10 or 20 nmol/L) can effectively inhibit hydrogen peroxide-induced rise of intracellular ROS. Next, we showed that cerium oxide nanoparticles possessed radical scavenging activity *in vivo* by preventing increases in retinal ROS in an albino rat light-damage model[28]. Furthermore, we explored the *Vldlr* knockout mouse, which carries a loss-of-function mutation in the *Vldlr* gene[71]. Studies have revealed that the *Vldlr*$^{-/-}$ mouse recapitulates many key characteristics in patients with AMD who have Retinal Angiomatous Proliferation, a form of wet AMD, and can serve as a unique mouse model of neovascularization-associated oxidative stress[72-74]. Our studies have revealed that a single intravitreal injection of 1 μL of 1 mmol/L (172 ng) nanoceria suspended in saline at postnatal day (P)7 greatly reduced the amount of ROS, measured by

two independent methods, DCF and dihydroethidium (DHE), in the *Vldlr*$^{-/-}$ retinas three weeks later at P28[28]. Similar results were obtained with three other biomarkers of oxidative damage, NADPH oxidase (p47phox), nitrotyrosine and 8-hydroxy-2-deoxyguanosine (8-OHdG). We further confirmed our previous observation by demonstrating that acrolein, a commonly used oxidative stress marker for detecting lipid peroxidation, is higher in *Vldlr*$^{-/-}$ retinas and nanoceria greatly reduced the level of acrolein[32].

Key mediators of the biological effects downstream of ROS include several signaling pathways such as MAP kinases, ASK1, and PI3K/Akt[75,76]. We hypothesized that if ROS were destroyed by cerium oxide nanoparticles, the downstream effects should be decreased. Therefore, we determined whether MAP kinases and Akt are elevated in the retinas of *Vldlr*$^{-/-}$ mice and whether nanoceria can inhibit their activation. Both kinases are elevated in *Vldlr*$^{-/-}$ retinas and a single intravitreal injection of cerium oxide nanoparticles for 1 wk inhibits the phosphorylation of ERK, JNK, and the p38 MAPKs, as well as Akt almost to control wild type (WT) mice treated with nanoceria[31]. We further examined the long-term therapeutic effects of cerium oxide nanoparticles in *Vldlr*$^{-/-}$ retinas and showed that phosphorylated ASK1, JNK and p38, as well as NF-κB are remarkably reduced by nanoceria treatment up to 6 wk post injection[32].

In another experimental paradigm, the *tubby* mouse was used as a model of inherited retinal degeneration to test the ability of cerium oxide nanoparticles to act as direct *in vivo* antioxidants. *Tubby* mice are homozygous for a mutation in the *Tub* gene and have hearing loss and retinal degenerations, major hallmarks of Usher syndrome[77]. To examine the ability of nanoceria to alter ROS, we determine the amounts of ROS by DCF and DHE methods in the retina of *tubby* mice at P18 injected intracardially with 20 μL of 1 mmol/L cerium oxide nanoparticles[29]. The levels of ROS in injected with nanoceria retinas were decreased to control levels. Moreover, we demonstrated that the expression of antioxidant-associated proteins, thioredoxin (Trx) and nuclear factor erythroid 2-related factor (Nrf2) is increased after nanoceria treatment. These results clearly suggest that cerium oxide nanoparticles can scavenge ROS in the retina and thereby inhibit oxidative stress in mice models of AMD and inherited retinal degeneration.

Anti-angiogenic properties

Angiogenesis is a process of forming new blood vessels that is a hallmark in the pathology of many diseases including AMD, diabetic retinopathy, and retinopathy of prematurity. Activators of angiogenesis include the VEGF, angiopoietins and members of the fibroblast growth factor (FGF) family. There is considerable evidence that increased production of ROS in the retina participates in retinal angiogenesis. We have shown that upregulation of retinal VEGF can be detected as early as P14 in *Vldlr*-/- mice[30]. To examine if nanoceria treatment could reduced angiogenesis by inhibiting VEGF, we determined the effect of nanoceria on VEGF protein expression in *Vldlr*$^{-/-}$ retinas at P14 and P28. We observed a significant decreased of VEGF in retinas of *Vldlr*$^{-/-}$ mice after a single injection of nanoceria at P7. We examined the localization of VEGF and found that cerium oxide nanoparticles inhibit the ectopic expression of VEGF in the outer nuclear cell layer (ONL) of the *Vldlr*$^{-/-}$ retina. Furthermore, using real-time PCR we demonstrated that cerium oxide nanoparticles dramatically decreased the levels of *Vegfa* expression in *Vldlr*-/- retinas[31]. Our PCR array results also showed that the expression of most of the *Fgf* genes, including *Fgf* 1, 2, 3, 5, 7, 9, 11, 21, and 22, are increased in the retina of *Vldlr*$^{-/-}$ mice and cerium oxide nanoparticles were able to decrease significantly their expression. These results clearly support our hypothesis that the rise in retinal VEGF in *Vldlr*$^{-/-}$ mice can be prevented by the scavenging activity of cerium oxide nanoparticles.

Anti-inflammatory properties

Oxidative stress is well known to increase not only angiogenesis, but to drive the onset of inflammation. There is substantial evidence to show that inflammation play a role in AMD[78]. Although some reports have shown that several inflammatory cytokines are elevated in *Vldlr*$^{-/-}$ retinas[72,79] the expression pattern of cytokines and their functions in the *Vldlr*$^{-/-}$ mice have not been thoroughly determined. Therefore, we examined the cytokine expression in the *Vldlr*$^{-/-}$ retina using a mouse cytokine PCR array that profiles 88 key cytokine genes[31]. We found that 37 cytokines were up-regulated and after one week of nanoceria injection 23 cytokines were down-regulated. Nanoceria markedly reduced the overexpression of Tlsp, Lif, IL-3, IL-7, IL-9, IL-12b, Lep, Ifn1, and others. This study suggests that cerium oxide nanoparticles have significant potential as anti-inflammatory agents.

Anti-apoptotic properties

Excessive production of ROS is the key event leading to cell death or apoptosis. The principle mechanism underlying retinal cell death and consequent blindness in several diseases is apoptosis. Apoptosis of neuronal cells is common to all mutations in *tubby* gene family members[80]. To determine the effect of cerium oxide nanoparticles on apoptosis in the retina of *tubby* mouse, the TUNEL assay was conducted[29]. The *tubby* retina demonstrated many more TUNEL positive cells that control retina. In this study, we also demonstrated that intracardial injection with cerium oxide nanoparticles significantly down-regulated caspase-3, 8, 9 and Bak1 expression. Likewise, we found that nanoceria markedly reduced the levels of caspase-3 in the retina of the *Vldlr*$^{-/-}$ mouse[32]. Taken together, it is obvious that cerium oxide nanoparticles down-regulate caspase-induced apoptosis in the retina of mouse models of AMD and inherited retinal degeneration.

Protection of retinal function

To examine the ability of cerium oxide nanoparticles to protect retinal function, retinal responses to the

light stimulus were determined by full field and serial intensity electroretinography (ERG) in tubby mice at P34[29]. Full field ERG showed that injections with cerium oxide nanoparticles improved rod function in *tubby* mice compared to control, saline injected group. Serial intensity ERG of scotopic a- and b-waves showed that both amplitudes were significantly increased in nanoceria injected *tubby* eyes. Moreover, no changes in retinal functions was detected in nanoceria or saline injected rats for 9 d and even after 4 mo post injection[69]. There were no changes in scotopic a- and b-waves, photopic b-wave, and flicker. These data suggest that cerium oxide nanoparticles did not have side effects in the healthy retina.

Toxicity

There is always a concern regarding the potential toxicity of nanomaterials for biological applications. Several reports have shown that cerium oxide nanoparticles (< 10 nm) are well tolerated by animals and are not toxic[25,81], while others provide conflicting data about toxicity[82,83]. Most likely this discrepancy could be due to variation in methods of synthesis or due to differences in physiochemical properties of nanoparticles, surface charge, aggregation of the particles. Nanoceria used in our studies were small in size (3-5 nm) and well dispersed. To determine the safety of cerium oxide nanoparticles for therapeutic use, the cytotoxic effects of the particles intravitreally injected in rat retina after 9, 60 and 120 d was examined[69]. We performed quantitative analyses on superior and inferior central retina, superior and inferior peripheral retina and we did not determine any reduction in thickness in the layers examined for injected with cerium oxide nanoparticles eyes. As mentioned above there were no changes in retinal function between nanoceria or saline injected rats. These results indicate that cerium oxide nanoparticles synthesized according to our procedure[12,69], are not toxic to the rat retina as evaluated by morphology and function up to 12 mo post injection.

Bio-distribution

We determined nanoceria distribution and clearance in the eye using inductively coupled plasma mass spectrometry[12,69]. We observed the highest concentration of cerium oxide nanoparticles in retinal portion of the eye. A small amount of cerium oxide nanoparticles 1 h post injection were detected in the lens and the rest of the eye cup. We determined that approximately 70% of injected cerium oxide nanoparticles were retained in the rat retina more than 120 d and the elimination half-life is calculated to be 414 d. Only trace amounts of cerium oxide nanoparticles were detected in the liver and kidney from 120 d injected rats. These results strongly suggest that cerium oxide nanoparticles are rapidly and preferentially taken up by retinal cells and the rate of elimination is very slow. It is not yet known the mechanism of uptake of nanoceria in retinal cells. Three possible endocytosis pathways may be involved in uptake of nanoparticles into cells, including caveolae-, clathrin-mediated endocytosis, and macropinocytosis. It has been reported that fluorescein-conjugated nanoceria were taken up by keratinocytes *via* clathrin- and calveolae-mediated endocytic pathways[84]. Recently another study indicated that nanoceria could be also taken up into cells through caveolae- and clathrin-mediated endocytosis. Nanoceria were distributed throughout the cytoplasm but not into nucleus[85].

CONCLUSION

Cerium oxide nanoparticles extended the life of photoreceptor cells and preserved vision for up to 4 mo in a mouse with inherited retinal degeneration. Nanoceria prevent development of pathological neovascularizations in the *Vldlr*$^{-/-}$ mouse (a model for Wet AMD) and also regress vascular lesions existing at the time of injection. Nanoceria have a half-life in the retina of 417 d and had no toxic effect on retinal structure and function when present for over a year. Nanoceria affect multiple signal transduction pathways by upregulating neuroprotective genes and downregulating pro-apoptotic and pro-inflammatory genes. Most recently, we showed that cerium oxide nanoparticles inhibit the growth of inherited retinoblastoma malignancies *in vivo* and shrink the volume of tumors present at the time of injection. Collectively, these data suggest that nanoceria are global antioxidants, which have "pan-disease" effectiveness against a number of degenerative eye diseases in multiple animal models and may be just as effective in the therapeutic treatment of many human eye diseases.

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Recent advances in management of retinoblastoma: A review

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Abstract

The management of retinoblastoma has evolved significantly over recent years. Current treatment options aim to preserve the globe as well as vision with minimum morbidity. High resolution imaging has improved tumor detection and is useful for prognosticating cases and monitoring response to treatment. Targeted chemotherapy such as intra-arterial and intra-vitreal chemotherapy has shown promising results and these routes are being increasingly employed world-wide for globe preservation. The advent of new radiotherapy techniques has led to improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. This review aims to highlight newer advancements in the field of diagnosis and management of retinoblastoma that have been introduced in recent times, with a special emphasis on globe-preserving therapy.

Key words: Retinoblastoma; Recent advances; Chemotherapy; Radiotherapy

Core tip: The management of retinoblastoma has improved significantly over the past few decades. There has been a paradigm shift from enucleation towards conservative treatment modalities that aim at vision and globe salvage. The purpose of this article is to review the literature on various key developments in the field of retinoblastoma, with particular emphasis on globe-conserving treatment.

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INTRODUCTION

The diagnosis and management of retinoblastoma (RB) often presents as a challenge to the ophthalmologist. Recent advances have contributed towards improving the clinical outcome of the most common intraocular malignancy seen in children. Evolution in imaging techniques has facilitated accurate diagnosis and staging

of RB. There has been a paradigm shift from enucleation towards conservative treatment modalities that aim at vision and globe salvage. The introduction of intra-arterial and intra-vitreal chemotherapy in recent times has shown encouraging results. The advent of newer radiotherapy techniques have led to greatly improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. The purpose of this article is to review the literature on various key developments in the field of RB, with particular emphasis on globe-conserving therapies. A brief overview of these recent advances is highlighted below.

IMAGING

Imaging plays a key role in the diagnosis of RB. With the introduction of high-resolution three-dimensional (3D) Fast Spin Echo (FSE) magnetic resonance imaging (MRI) and high resolution ultrasound, the diagnosis of RB is no longer a dilemma. Although computed tomograph scan is very useful in detecting calcification which can sometimes be missed on ultrasonography, it has been reported that high-resolution three-dimensional (3D) FSE T2 weighted imaging with thin sections (0.4 mm) and high Signal to Noise Ratio (SNR) can also detect calcification[1]. Gradient-echo T2 weighted MRI is also effective in detecting calcified structures[1]. Recently, it has been observed that the difference in Apparent Diffusion Co-efficient values on diffusion-weighted MRI can be helpful in differentiating between viable and necrotic tumor[2]. In addition, this modality can also be used to monitor the response of tumor to chemotherapy in cases of trilateral RB as well as in those eyes that are treated with globe salvaging therapies[2,3]. The presence of vitreous haemorrhage can pose difficulty in delineating the tumor, which can be overcome by T1-weighted MR images without the use of gadolinium-based contrast material[4]. Apart from its diagnostic value, MRI is also an established imaging modality for staging of RB[5]. Contrast-enhanced T1-weighted MR imaging with fat saturation is recommended to rule out optic nerve involvement as well as extra scleral involvement[6]. The sensitivity and specificity of MR imaging for depicting post-laminar optic nerve invasion has been reported to range from 50%-90%[4,5]. A retrospective study by Song *et al*[7] in cases of unilateral RB concluded that focal strong enhancement and enlarged optic nerve on MR films had better correlation with optic nerve invasion than optic nerve enhancement, tumor size and tumor location[7]. It is noteworthy that in some children, this enhancement can be due to aseptic cellutis or inflammation of soft tissues rather than true invasion[8]. A short course of systemic steroids and repeat MR imaging facilitates accurate staging in such cases and has been found to be useful in guiding further management[8].

Another application of imaging in RB is the use of high resolution ultrasound to detect the tumor in the fetus at its earliest stage[9]. Investigators have used high resolution ultrasound at 37 wk of gestation to detect a 2-3 mm elevated lesion in a fetus at risk of heritable RB[9]. Being a rapidly growing tumor, doubling time for RB is considered approximately 15 d[10]. Therefore, it has been suggested that infants proven to carry the family's *RB1* mutant allele can be delivered a few weeks early, to optimize the chances of retaining good vision with minimally invasive therapy[11].

CHEMOTHERAPY

Although enucleation is accepted as the standard treatment for advanced tumors, local and site selective delivery of chemotherapeutic drugs has shown encouraging results in salvaging the globe as well as vision in many eyes otherwise destined for enucleation. These newer therapeutic approaches are discussed briefly.

Super-selective intra-arterial chemotherapy

This novel approach has evolved rapidly over the last few years and has shown encouraging results in both early and advanced tumors[12,13]. Being a site directed therapy, it has considerably fewer systemic side-effects in comparison to conventional intra-venous chemotherapy. Over the last few decades, the selectivity of the technique has improved from using sites such as the internal carotid artery, supra-orbital artery and superficial temporal artery, to the currently used ophthalmic artery[14-18]. Melphalan is the drug of choice for intra-arterial chemotherapy and heparin (70 U/kg) is the anticoagulant used. There is no standardised dosing schedule, however, the conventional dose ranges from 3-5 mg per sitting[13,16,17]. Recently, Abramson *et al*[16] and Gobin *et al*[17] have recommended intra-arterial chemotherapy as a safe and effective treatment for advanced intra-ocular RB. Although intra-arterial chemotherapy has the advantage of fewer systemic side effects as compared to intravenous chemotherapy, some investigators consider melphalan as a more toxic agent than those drugs which are used for intravenous chemotherapy[19]. Exposure to fluoroscopy related radiation and ophthalmic artery occlusion are other concerns[19]. It has been suggested that a selective ophthalmic artery angiogram instead of carotid angiogram can be used to minimise radiation exposure[13]. Though not yet established as a primary treatment, intra-arterial chemotherapy has also been used as a first line treatment in less advanced cases of intraocular RB[12]. There are other investigators who consider it as a part of a multi-modal therapeutic approach[13,18]. Intra-arterial chemotherapy has been reported to be associated with an overall success rate of 55%-100% in salvaging the globe, in addition to the advantage of very low systemic toxicity[12,13]. Recently, Francis *et al*[20] have demonstrated that Carboplatin ± topotecan ophthalmic artery chemosurgery (OAC) can allow for prompt regression of tumors and can be curative as a single agent in combination with focal techniques, with ocular survival of 89.9% at two years. Furthermore, Carboplatin ± topotecan infusions have low hematologic and ocular toxicity and no statistically significant influence on electroretinogram responses, and can be used in conjunction with melphalan-containing OAC[20]. It has been recommended that children, especially

less than 6 mo of age at the start of treatment with carboplatin, should routinely undergo thorough long-term audiologic monitoring[21]. Recently, a single-centre retrospective study has compared the relative incidence of new intraocular lesions after treatment with carboplatin through intravenous (systemic) and OAC in naïve eyes, or those with prior treatment (systemic chemotherapy/external beam radiotherapy)[22]. The incidence reported were 56%, 2.4% and 8% respectively[22]. The systemic chemotherapy treated patients had multiple new lesions within months of treatment, as compared to fewer new lesions in the OAC group[22]. It was noted that previously irradiated eyes showed delayed appearance of new lesions. The new lesions were more common at a younger age and were usually located in the peripheral retina, which can be explained by the centrifugal development of retina[22].

Intravitreal chemotherapy

Another local route for drug delivery that has shown promising results in RB is intra-vitreal chemotherapy (IViC)[23,24]. However, this route is recommended only as salvage therapy for recurrent or recalcitrant vitreous seeds and should not be considered as a primary treatment[19]. In a study by Munier *et al*[23] in RB cases with recalcitrant vitreous seeds, melphalan was injected intravitreally in a dose of 20-30 μg (0.1 mL of 0.2 mg/mL) using anti-reflux procedure, followed by triple freeze-thaw cryoapplication to sterilize the needle track[23]. The procedure was carried out every 7-10 d and was repeated upto eight injections if a response could be documented, until complete seed fragmentation was observed or complete response was achieved[23]. Complete response was established if the seeds (1) completely disappeared (vitreous seeding regression type 0); or were converted into (2) refringent and/or calcified residues (vitreous seeding regression type Ⅰ); (3) amorphous, often non-spherical, inactive residues (vitreous seeding regression type Ⅱ); or (4) a combination of the last two (vitreous seeding regression type Ⅲ)[23]. The authors recommended that IViC could be repeated if vitreous recurrence occurred[23]. In their study, a success rate of 84.14% at 2 years was achieved[23]. A localised peripheral salt-and-pepper retinopathy at the injection site was the only complication noted in 10 eyes (43%)[23]. Another retrospective study on intra-vitreal chemotherapy by Shields *et al*[24] showed 100% (11/11) success rate with 1 to 4 cycles of monthly IViC (melphalan 20-30 μg) at 2 year follow-up[24].

Sub-conjunctival /sub-tenon chemotherapy

It has been observed that systemic chemotherapy alone may not be sufficient to treat Group C (eyes with focal vitreous or subretinal seeding and discrete retinal tumors of any size and location) and Group D (eyes with diffuse vitreous or subretinal seeding and/or massive, nondiscrete endophytic or exophytic disease) cases[25,26]. Local injections of chemo-therapeutic agents like sub-tenon or sub-conjunctival carboplatin have been used with varying degrees of success, usually as an adjuvant to systemic chemotherapy to avoid enucleation and external beam radiotherapy in cases of group C and group D retinoblastoma with vitreous/subretinal seeds. The Children's Oncology Group recommends use of 20 mg sub-tenon carboplatin along with chemoreduction and focal consolidation for Group C and D tumors[27]. Leng *et al*[28] have reported a favourable outcome with the use of sub-conjunctival carboplatin in RB tumors that progressed despite ablative therapy[28].

RADIATION THERAPY

Despite the established role of radiotherapy (RT) in RB, treatment modalities were shifted to primary chemotherapy combined with local treatment options such photocoagulation, cryotherapy and thermotherapy[29,30]. The high incidence of radiation induced growth deformities and second malignancies was attributed to external beam radiotherapy and RT was therefore reserved for tumours refractory to chemotherapy and local therapies. However, the assessments of risk by RT were based on outcomes of radiation delivery in the old era[31,32]. In recent times, there has been substantial advancement in radiation therapy and the advent of newer radiotherapy techniques has led to greatly improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. These newer radiotherapy techniques which include intensity modulated radiotherapy, stereotactic radiotherapy volumetric modulated arc therapy (VMAT), proton therapy, and helical tomotherapy (HT) provide highly accurate radiation delivery[33].

Proton beam therapy provides uniform dose coverage of the target and unlike photon beams, has no exit dose and distributes no energy beyond the target. These unique properties reduce the incidence of late effects of radiation. A study by Sethi *et al*[34] compared the risk of second malignancies in survivors of RB treated with photon and proton radiation therapy[34]. The observed 10 year cumulative incidence of RT induced second malignancies were significantly different in proton and photon modalities ($P = 0.015$)[34]. However, proton therapy is expensive and is currently not widely available. In another study on the dosimetric comparison of various RT techniques by Eldebawy *et al*[33], it was concluded that inverse image guided radiotherapy using VMAT or HT provides superior conformity index and improved orbital bone and brain sparing[33].

Plaque Brachytherapy is commonly used for recurrent and residual disease after failure with chemotherapy and local therapy. The American Brachytherapy Society Ophthalmic Oncology Task Force (ABS-OOTF) recommends primary brachytherapy for unilateral anterior lesions[35]. Small tumours less than 15 mm in base and up to 10 mm in thickness in the absence of vitreous seeding are eligible[35]. The choice of radionuclide is decided according to local availability and intraocular dose distribution. I^{125} and Pd^{103} are used in North America, whereas I^{125} and Ru^{106} are used in Europe. Dosimetry of plaques presents a unique challenge which is due to the steep dose gradient within the tumour and presence of criti-

cal structures within few millimetres of the radioactive source. However, the TG-129 reports that adoption of heterogeneous dose calculation methods in clinical practice would result in dose variation of > 10% and requires careful assessment[36].

GUIDELINES FOR PATIENT FOLLOW-UP

After completion of therapy, regular follow-up is extremely important in these children in order to detect any recurrence of tumor, new lesion, or metastatic disease. It is recommended to follow-up all affected cases till the age of 16 years and to conduct screening of unaffected relatives or mutation carriers till the age of five (reference: 2013 Copyright American Cancer Society) or seven years (reference: NHS England/E04/S(HSS)/a, Copyright NHS Commissioning Board, 2013).

To summarize, the management of RB has evolved significantly over the last few years. Worldwide, there is an increasing trend towards preservation of the globe and vision in RB affected children. Newer advancements in diagnostic and therapeutic modalities have resulted in improved treatment outcomes in these children. Familiarity with these diagnostic and treatment modalities is essential for optimum management.

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EDITORIAL

Corneal transplantation: Beyond the horizon

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Abstract

Evolving techniques in keratoplasty have undoubtedly led to thinner corneal grafts. These newer iterations of keratoplasty aim to reduce graft rejections, improve visual acuity and visual rehabilitation. Each technique poses its own advantages and disadvantages; the surgeon should select patients suitable for a particular technique while accounting for their surgical competency given the learning curve associated with these newer techniques. Alternatives to corneal transplant may have a role in addressing the shortages of corneal graft, these bioengineered material and medical treatment still need further studies to demonstrate its clinical applicability.

Key words: Cornea; Cell therapy; Keratoplasty; Bullous keratopathy; Techniques

Core tip: Review of the current status of corneal transplant, the issues encountered with current techniques, the potential and future treatment on the horizon.

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INTRODUCTION

Corneal transplantation remains the mainstay of treatment for visual rehabilitation for any corneal disease affecting its clarity. In the past decade, we have witnessed great strides in the advancement of lamellar keratoplasty, which involves removing and replacing only the diseased portions, gaining popularity over the tradition penetrating keratoplasty (PK) or full thickness keratoplasty. Ongoing refinements resulted in better equipment, harvesting and transplanting techniques. In this editorial, we will highlight the recent major advances in corneal grafting and other ongoing potential developments such as artificial cornea and cellular transplantation.

ANTERIOR LAMELLAR KERATOPLASTY

Deep anterior lamellar keratoplasty (DALK) aims to replace the diseased epithelium and corneal stroma while retaining the unaffected Descemet's membrane (DM) and endothelium. It has been used as an alternative to PK in corneal diseases that is confined to the anterior layers, such as keratoconus, corneal dystrophies and scars. As an extraocular procedure, the advantages include preserving the host endothelium, reducing surgical trauma, minimizing the risk of endothelial rejection, and achieving faster visual recovery compared with PK[1]. However, conversion to PK may be inevitable if there is intraoperative DM perforation, which is the most common complication. A major optical disadvantage compared with PK is the corneal stromal bed irregularity following manual lamellar dissection techniques, limiting the postoperative best corrected visual acuity (BCVA). Different techniques for DALK have been suggested to overcome this issue to remove the stroma with baring of the DM. Of these techniques, Anwar's big-bubble technique is one of the most popular techniques among corneal surgeons. Based on level Ⅱ evidence in 1 study and level Ⅲ evidence in 10 studies, DALK is found to have equivalent BCVA outcome with no advantage for refractive errors if the surgical technique yields minimal residual host stromal thickness[1]. Retrospective comparative case series with subgroup analysis revealed that the big-bubble technique gives better results than manual dissection and PK (2.2-2.5 lines difference), but manual dissection has lower BCVA compared with PK (1.0-1.8 lines difference)[2]. This study also demonstrated that DALK has better overall long-term, model-predicted graft survival (49.0 *vs* 17.3 years) and endothelial cell loss (-22.3% *vs* -50.1%) than PK.

Newer technology with the femtosecond laser allows more precise incision with customized graft shape, edge and lamellar plane to improve the matching of donor-recipient fit, and increased donor-recipient junction surface area contact interface[3]. Femtosecond laser assisted keratoplasty was first described in 2006 by Suwan-Apichon *et al*[4] and later by Price *et al*[5] and others[6]. Configuration such as "zigzag" or "mushroom" shaped wounds in both the donor and host were aimed at reducing postoperative astigmatism, improving wound integrity, and allowing earlier suture removal. Prospective studies using femtosecond laser-assisted PK found that the wound is more stable, particularly with the top hat and mushroom wound configurations[7], but refractive outcomes are not superior when compared to the conventional techniques[8]. Retrospective review comparing femtosecond laser mushroom configuration and manual trephine straight edge configuration using Melles' or Anwar's technique found that femtosecond laser assisted DALK achieves faster visual rehabilitation with a better BCVA at 3 mo, which was not significant at 6 or 12 mo; whereas mean spherical equivalent, cylindrical astigmatism, and keratometric cylinder were similar for all follow up[9]. Further well designed controlled trials are warranted to elucidate the role of femtosecond laser in DALK. It may have a complementary role when combined with manual stromal dissection or air injection to expose the DM in cases with irregular corneal thickness, such as keratoconus, corneal ectasia, and corneal scar, in order to facilitate a more uniform fashion of stromal excision to the DM[1]. Such potential technology for achieving better visual outcome is encouraging, but current use is limited by the high costs, especially in non-institutional practices or less developed economies.

EVOLUTION IN ENDOTHELIAL KERATOPLASTY

Modern day posterior lamellar keratoplasty (PLK) reached a breakthrough when Melles described an essentially sutureless technique to replace the posterior lamella using an air bubble for graft fixation in 1998[10]. A few years later, Terry and Ousley modified and simplified the PLK technique and coined the term deep lamellar endothelial keratoplasty (DLEK)[11]. Following the successes of DLEK, Melles introduced a Descemet's stripping technique in 2002 where a "Descemet roll" was obtained by stripping the DM with its endothelial layer from the posterior stroma in the donor, and implanted it after a "descemetorhexis" to prepare the recipient bed for transplanting this manually dissected donor lamellar button[12,13]. Further improvements continued in 2005 when Price modified the technique and named it Descemet stripping endothelial keratoplasty (DSEK)[14] a year later, Gorovoy simplified the challenging and time consuming manual dissection of donor tissue by using a microkeratome and named it Descemet stripping automated endothelial keratoplasty (DSAEK)[15]. In essence, DSAEK allows replacing the recipient's diseased endothelium and DM by the donor's healthy endothelium and DM attached with a thin section of corneal stroma.

Over the last decade, DSAEK has become the procedure of choice in treating corneal endothelial dysfunction, such as Fuchs endothelial dystrophy and pseudophakic bullous keratopathy. A systematic review by the American Academy of Ophthalmologist found that DSEK/DSAEK were similar to PK in terms of surgical risk, complication rate, graft survival, BCVA and endothelial cell loss, but superior to PK in allowing for much faster visual recovery, refractive stability, refractive outcomes, fewer wound and suture related complications, intraoperative and late suprachoroidal haemorrhage risk[16]. Although DSAEK produced good visual outcome in most cases, it is not as high as one would have hoped for. Part of this is attributed to the disturbed natural corneal posterior anatomy where the stromal donor-recipient interface results in higher order aberration and light scattering[17,18]. The thickness of the donor's stroma in DSAEK will also accentuate any mismatch between

the donor and recipient corneal curvatures. Compressive folds can also form between this interface when there is a mismatch between the curvature of the donor and recipient's cornea[19]. To overcome these challenges, modifications of endothelial keratoplasty to transplant only a strip of endothelial cells layer with the DM without the stroma was developed and named Descemet's membrane endothelial keratoplasty (DMEK) by Melles[20].

Eliminating this stromal interface and thickness variation, DMEK provides improved visual outcome, smaller incision width, and reduced risk of immunological graft rejection as compared with DSAEK[17,21,22]. The DSAEK graft thickness is about 70-250 μm while DMEK is about 14-20 μm, thus reducing the volume of donor tissue by 75%-90%[23]. For DSAEK/DSEK (and DLEK), significantly more cell loss was reported when using a 3.2 mm incision when compared to a 5 mm incision[24]. However it is possible to insert the DMEK graft *via* a 2.8 mm incision with comparable endothelial cell loss with a DSAEK graft performed with a 5mm incision, thus minimizing the postoperative astigmatism[24,25]. Kruse reported that within a 6 mo follow up, DMEK achieves better and faster visual rehabilitation as compared to DSAEK, but no difference in endothelial cells survival[21]. It is not uncommon for DMEK eyes to approach near instant visual recovery, with patients having BCVA of 20/40 on the first postoperative day and 20/20 or better within the first postoperative week[26]. DMEK is believed to have less graft rejections with the absence of the donor epithelium and stroma. Price's group performed a comparative case series and found that the Kaplan–Meier cumulative probability of a rejection episode at 1 and 2 years was 1% and 1% for DMEK; 8% and 12% for DSEK; and 14% and 18% for PK respectively, with a significant level of $P = 0.004$. The DMEK eyes thus were thus 15 times less likely to experience a rejection episode than DSEK eyes ($P = 0.008$) and 20 times lower risk than PK eyes ($P = 0.006$)[27].

BATTLE OF THE ENDOTHELIAL KERATOPLASTIES

Despite the significant reported benefits of DMEK over DSAEK, the road to acceptance is relatively slow among corneal surgeons. DMEK presents the surgeon with two main technical challenges and a relatively steep learning curve, preparing and handling the donor graft. Although the preparation of the DMEK donor has improved in the last few years, potential graft wastage remains a key challenge, especially to the newer DMEK and or lower volume surgeons. It is possible for the surgeon to decide whether the graft preparation is to be outsourced to an eyebank or performed during surgery[28]. Different techniques have been proposed in harvesting the donor graft: manual peeling with forceps[29,30] hydrodissection[31] and pneumatic dissection[32]. The forceps technique is the most widely adopted technique with reproducible tissue qualities in up to 98% of donor cornea in experienced hands[33]. The remaining 2% cornea demonstrated strong adhesions in the DM-stroma interface, either due to ultra-structural (peg-like interlocking) or biochemical abnormalities (increased staining intensities for adhesive glycoproteins)[33], which can result in multiple horseshoe shaped tears in the DM or lamellar splitting of the DM[34]. Previous case series described the successful implantation of accidental large tears in DM (torn into 2 pieces) into 3 eyes, unfolded and attached to the recipient's posterior stroma[35]. At 6 mo of follow up, BCVA ranged between 20/30 and 20/25, endothelial cell loss ranged 28%-32%, and all corneas remained clear without any signs of failure; thus even complete rupture does not preclude successful grafting.

Intraoperative handling of the graft continues to present challenges. During graft insertion, it is critical to maintain the correct orientation of the Descemet roll. Although several inserters have been well developed for DSAEK, the insertion technique in DMEK is yet to be standardized. Several designs have been published including glass injectors and intraocular lens injectors coupled with irrigation fluid under a predefined intraocular pressure to improve the success for delivery of the Descemet roll. Unfolding the graft is one of the more challenging step in DMEK, poor manipulation during insertion will traumatize the endothelial cells. The ease of unfolding depends on the tightness and orientation of the scroll, the anatomy of the anterior chamber, and the intraocular pressure. Grafts from young donors tend to have more scrolling and are thinner, hence more prone to tears; these factors make corneas from younger donor more difficult in harvesting and unrolling[36]. Liarakos *et al*[37] compiled a list of basic and auxiliary techniques along with an algorithm for selection. The high technical demands with insertion and manipulation render DMEK relatively unsuitable in eyes with shallow anterior chamber and / or complicated anatomy, such as those with anterior chamber intraocular lens, peripheral anterior synechiae, and those with an absence of a barrier between anterior chamber and vitreous[38]. Since DMEK grafts are very thin and lost to view in the anterior chamber, eyes with glaucoma shunt, large iris defect, and aphakic eyes are also some conditions less suited for DMEK. The technical challenges and complications associated with DMEK can be reduced once the surgeon has overcome his or her learning curve, but even in the hands of more experienced DMEK surgeons, reported complications rates were still not as low to the rates achieved with DSAEK[29,39,40]. Partial graft detachment requiring rebubbling is the most frequently encountered postoperative complication. Initially the rebubbling ranged between 63%-82%, with the increase in experience and technique modifications, the rebubbling rate was substantially reduced to 3%-17%[36]. The largest DMEK series reported to date evaluated the outcome of 500 consecutive cases and effect of technique standardization confirms the earlier findings that DMEK consistently gives higher visual

Table 1 Comparison between ultra thin-Descemet's stripping automated endothelial keratoplasty and Descemet membrane endothelial keratoplasty

	UT-DSAEK	DMEK
Corneal layers involved	A double microkeratome pass to achieve a thin layer of donor central posterior stroma with the Descemet membrane and endothelium attached	Donor Descemet membrane and endothelium only
Thickness	< 130 μm	14-20 μm
preparation by eyebanks	Widely available from eyebanks	Mostly prepared intraoperatively by surgeons, provided by a limited number of eyebanks
Donor selection	Same criteria as DSAEK, less stringent	Preferably in older donors, as grafts from younger donors are more difficult to harvest and unroll
Recipient selection	Same criteria as DSAEK, less stringent	Less suitable in recipient with a shallow anterior chamber or complicated anatomy
Technical challenges	Similar technique compared with DSAEK	Donor preparation, insertion and manipulation of graft present a learning curve
Operative time	Shorter	Longer
BCVA	Similar percentage of eyes achieving 20/20 at 1 yr, but DMEK allows faster visual recovery with a higher percentage at 6 mo	
Endothelial cell loss at 1 yr	Similar with around 35%	
Tissue loss	2.8%	4.2%
Primary failure	1.4%	8.1%
Rejection probability at 1 yr	2.44%	1%
Rejection rate at 1 yr	2.8%	5.7%
Graft dislocation (partial)	3.9%	9%-92%
Rebubbling rate	3.9%	3%-17%

UT-DSAEK: Ultra thin-Descemet's stripping automated endothelial keratoplasty; DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty; BCVA: Best corrected visual acuity.

outcome and faster visual rehabilitation[41]. The overall number of partial graft detachment reduced from 21.6% in the first 250 eyes to 10% in the following 250 eyes. Approximately half of these detachments may be classified as clinically insignificant partial detachment and did not require any intervention. The decision to rebubbling depends on the extent of graft detachment and how its evolution over time[42].

Compared with DSAEK, DMEK can achieve faster visual recovery, better visual outcomes, and reduced rejection rates. However, still more than half of the patients could not return to a vision of 20/20 in the absence of comorbidities; perhaps more than the presence of stromal interface exists in determining the final visual outcome[25,40]. It has also been proposed that posterior corneal higher order aberrations may be lessened in thinner graft due to less pronounced tissue irregularities. Several retrospective studies show contradictory evidence between graft thickness and final visual outcomes[43]. In 2011, Neff *et al*[44] reported that visual outcomes in DSAEK can be better than DMEK in patients with grafts thinner than 131 μm, correlating the morphologic characteristics of DSAEK graft with the final visual outcome for the first time. Busin, introduced an ultrathin (UT) DSAEK concept using two microkeratome passes, the first pass to debulk the donor tissue, and a refinement pass to achieve a thickness of less than 100 μm[45]. Insertion, deployment, and handling techniques are similar to that of DSAEK, obviating the need of the steeper learning curve of DMEK. The authors presented their prospective findings after a 2 year follow up period[46]. Comparing their results with the longest available follow up series, UT-DSAEK has almost identical outcome in comparison to DMEK[25] in terms of percentage of eyes recovering at least 20/20 BCVA over time, whereas the percentage DSAEK[47] patients were constantly lower for all time points. Although the speed of visual recovery after UT-DSAEK is slower compared with DMEK, there is no difference in the percentage of eyes with BCVA of 20/20 1 year postoperatively[25]. Endothelial cell loss of around 35% were comparable with DSAEK[48,49] and DMEK[25,50], suggesting that the double microkeratome technique does not adversely affect endothelial cell survival. Graft perforation were reported in 2.1% of the cases, which involved the use a 50 μm microkeratome head to perform the second pass in residual corneal central thickness of less than 190 μm. Inaccuracy in assessing the residual thickness through ultrasonic pachymetry can be improved *via* using anterior segment optical coherence tomography. Cases with peripheral perforation were used after eccentric punching and were managed successfully without tissue loss; there were no substantial difference in their final BCVA or endothelial cell density. Postoperative graft dislocation occurred in 3.9%, which is much less than the reported rate of 9%-92% after DMEK[25,40,51,52]. Unlike DMEK, UT-DSAEK grafts are similar to DSAEK grafts and maintain a shape on their own, making them more stable. In the event of graft detachment, they may not need rebubbling as they usually zipper down on their own, whereas the edges of DMEK detachments can continue to curl under leading to the persistence of cleft/interface[25,40]. DMEK remains the thinnest available endothelial graft and there are currently no definitive

studies comparing UT-DSAEK to DMEK. Table 1 is an overall summary of the key differences between the two techniques.

Descemet membrane endothelial transfer, where corneal clearance was noted after re-endothelialisation of the recipient's posterior stroma by a free floating donor's Descemet roll in the recipient anterior chamber after descemetorhexis has been reported[53]. This effect may have been due to the migration of endothelial cells to repopulate the recipient's stroma[54].

ENDOTHELIAL KERATOPLASTY REIGNS SUPREME?

Bullous keratopathy secondary to endothelial decompensation is one of the commonest causes of corneal transplantation. As grafts may be limited in some localities and or in eyes with poor potential, alternatives such as conjunctival flaps, anterior stromal puncture, amniotic membrane transplantation, photokeratectomy, bandage contact lens, collagen cross-linking, and endothelia cell injection are useful options[55].

Despite the promising reported results in lamellar keratoplasty literature, Coster *et al*[56] analysed long-standing Australian national corneal transplantation registry data, and contrary to previous findings, they found that lamellar procedures, whether endothelial or deep anterior, were associated with worse graft survival and visual acuity compared with PK for the same indications and over same time periods. The authors attributed their findings to the differences between a real world registry data from multiple surgeons versus data from a few single centre high volume surgeons, with a defined set of inclusion and exclusion criteria. Coster *et al*[56] also addressed the issue of learning curve, which can explain the poorer outcomes in the early stages of a new technique. They found that experienced surgeons (> 100 registered keratoplasties) achieved significantly better survival of endokeratoplasties ($P < 0.001$) than surgeons who had performed fewer grafts (< 100 registered keratoplasties). However, even in the hands of experienced, high-volume surgeons, endokeratoplasty failures can still occur. Registries provide large volume data over time, but are not without flaws. Changes in practice over time, such as patients selection and widely varying numbers of transplants between different hospitals, are factors that will influence the data[57]. The multicentre Cornea Preservation Time Study will soon provide us with the 3 year standardized graft survival data after. The results from this Australian registry study serves to remind us the importance in monitoring outcomes of newer techniques on a larger and broader scale.

ON THE HORIZON

Many patients will benefit from corneal transplant, however there is a limited supply of donors worldwide[58] and given sufficient time, allografts will eventfully fail. There has been a long interest in developing alternatives for restoring the corneal tissue structure and function. Keratoprosthesis such as Boston KPro and osteo-ondo-keratoprosthesis have helped patients save their vision in cases where keratoplasty have failed or contraindicated. The original Boston KPRo pioneered by Claes Dohlman is made up of polymethylmethacrylate (PMMA) consisting of a solid front plate and a porous back plate. With advances in the design by having pores in the back plate, a thread-less design, and complimenting it with soft contact lens use, the rates of corneal melt have decreased[59]. Retention rates ranging from 83%-100% have been reported within the first 2 years of implantation[60]. Recent studies have shown that a titanium design as compared to PMMA results in less postoperative inflammation, lower rates of frequency and severity or retroprosthetic membrane[61]. In 2013, the United States Food and Drug Administration approved a revised design of both Type Ⅰ and Ⅱ Boston KPro that eliminates the need for a locking ring use and uses titanium instead of PMMA as a back plate. The metallic appearance due to back plate may be cosmetically dissatisfactory for the patients; there is currently ongoing research on fabrication techniques to add brown or blue hue to improve the cosmetic appearance.

More recently, the use of decellularised extracellular matrixes (ECMs) have been proposed as a scaffold for corneal cell regeneration as it contains many structural and instructional macromolecules for organogenesis, where in wound healing such as corneal wound healing, the same ECM macromolecules contribute to tissue repair[62]. Cultured fibroblasts can secrete their own ECM to form sheets to reconstruct a stromal tissue with endothelial and epithelial cells seeded on each side of the reconstructed stroma[63]. However, the main drawback of this technique is the long duration needed to produce the thickness as seen in the human cornea.

Since collagen is the main structural component in ECM, this has been a target of interest. Recent rabbit experiments have demonstrated a biocompatible plastically compressed collagen scaffold in producing a translucent stroma with no oedema, inflammation or neovascularization, which can be a promising corneal scaffold for future artificial cornea[64]. Recombinant collagen has also been produced and is commercially available, which mimics the same amino acid sequence as human collagen. Type Ⅲ recombinant human collagen has been fabricated into corneal implants to enable corneal regeneration by endogenous cell recruitment in a phase I study involving 10 patients[65]. During the four year follow up period, there were no signs of inflammatory dendritic cells recruitment and rejection even in the absence of immunosuppression. Continued nerve and stromal cell repopulation to approximate the microarchitecture of normal cornea were reported, resulting in an average BCVA of 20/52

gained and more than 5 Snellen lines.

Co-emergent techniques, such as 3-D printing can enable printing of live cells, tissues and even organs for implantation. This is a new technology that involves creating physical objects from digital files. This is still an active and ongoing field of research, and thus far 3D bioprinting has resulted in successful printing of blood vessels and vascular networks[66], bones[67], ears[68] and so on. Its application in ophthalmology is currently limited, but recent progresses in exploiting naturally biomaterials with 3D bioprinting have a potential in generation of ocular tissues. In the future, this technology may one day play a role in producing cornea and other organs to be custom-tailored to the patients' needs.

The emergent strategies in cellular biology and tissue cultivation of corneal endothelial cells (CEC) aim to produce transplantable corneal endothelial cell sheets. It focuses on the culture of CEC retrieved from the donor's cornea, followed by transplantation into the recipient. *Ex vivo* human CEC models can overcome the G1 phase and complete the cell cycle; this occurs in the presence of appropriate growth factors[69]. The main factors that determine the mitotic capacity of human CEC *in vitro* includes method of culture, growth factors in culture medium, and viability of donor cornea; the process of isolation, preservation and expansion are critical in engineering human corneal endothelium which remains to be optimized with ongoing research[70]. Adult stem cells found in adipose tissue, bone marrow and umbilical cord blood have self-renewal and plasticity attributes, which have been widely studied as potential therapies in degenerative diseases[71]. Early studies with short term results have supported the use of adult stem cells as potential treatment for corneal diseases in animals[72,73]. There is an abundant literature on mesenchymal stem cells (MSCs) for corneal reconstruction based on *in-vivo* and *in-vitro* studies. MSCs are a type of multipotent progenitor cell with the ability to differentiate into different lineages of mesenchymal cells. They can infuse into an allogenic host without being rejected due to the low expression of surface co-stimulatory molecules[74]. Rabbit MSCs (Rb-MSCs) transplanted onto chemically injured rabbit cornea show an expression of corneal epithelium specific marker cytokeratin 3 (CK3) and promote the healing of the cornea epithelium *in-vivo*. These Rb-MSCs *in-vitro*, differentiate into cells with a morphology similar to the corneal epithelium and expresses CK3[72]. Animal studies have demonstrated a reduction in expression of various inflammatory factors after transplantation of MSCs in chemically injured rat's cornea. Furthermore, in contrast to its angiogenic effect in ischemic tissues and tumors, MSCs can down-regulate angiogenic factors and upregulate anti-angiogenic factors[75]. Through their differentiation capability and paracrine function, MSCs can promote corneal wound healing and reduce corneal neovascularization. Further experimental studies are needed before proceeding to clinical trials with MSCs in human eyes.

A strictly pharmacological approach in treating corneal dysfunction would be a very attractive option as it eliminates the need of donor grafts and morbidities associated in artificial corneas and transplantation of CECs. A selective Rho-associated kinase (ROCK) inhibitor Y-27632 can diminish the dissociation-induced apoptosis of human embryonic stem cells[76]. *In vitro* studies on primate CEC have shown that Y-27632 promotes cell adhesion and proliferation and inhibits apoptosis[77]. The application of Y-27632 ROCK inhibitor eye drops resulted in less corneal oedema and corneal endothelial wound healing *via* stimulating proliferation of CECs in rabbit[78]. Whereas in monkey, it enhanced wound healing of the corneal endothelium with a retained high endothelial cell density and the physiological hexagonal morphology with expression of functional proteins was also demonstrated[79].

Based on these promising animal studies, a pilot clinical study recruited 4 eyes with diffuse corneal oedema secondary to bullous keratopathy and 4 eyes with late onset of Fuchs corneal dystrophy were given Y-27632 eye drops. The 4 eyes with diffuse corneal oedema did not show reduction in corneal thickness or improvement in visual acuity. However, in 3 of the eyes with Fuchs corneal dystrophy, there was a reduction in corneal thickness which was maintained overtime[79]. Furthermore, one of these eyes demonstrated recovery of corneal clarity, with a BCVA of 20/20 at 2 wk after treatment; the endothelial function and the visual acuity were maintained up to 24 mo[80].

It is hypothesized that the inhibition of ROCK signalling may manipulate cell adhesion properties. When cultivated corneal endothelial cells combined with ROCK inhibitor were injected into the anterior chamber of animal eyes, endothelial cell adhesion was promoted and the cells achieved a high cell density and morphology similar to corneal endothelial cells *in vivo*, thus enabling the transplantation of cultivated CECs as a form of regenerative medicine[81]. These promising findings may pave the way for a new approach in treating corneal endothelial dysfunction.

CONCLUSION

Evolving techniques in refining the outcomes of anterior and posterior lamellar keratoplasty in the last decade have led to improved visual acuity and reduced rejection rates. As surgeons continue to modify and share their experiences, it will become easier for corneal surgeons to master the technical challenges related different facets of modern keratoplasty. The beauty of lamellar keratoplasty allows us to focus our treatment on the specific diseased corneal layer, where we can achieve more with less. In the future, we eagerly anticipate the alternative possibilities to corneal transplantation using bioengineered material and medical treatment, obviating the need and heavy demand on donor graft availability.

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REVIEW

New treatments for diabetic macular edema

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Abstract

This work comprehensively reviews the latest treatment options for diabetic macular edema (DME) used in its management and presents further work on the topic. Diabetic retinopathy is an important and increasingly prevalent cause of preventable blindness worldwide. To meet this increasing burden there has recently been a proliferation of pharmacological therapies being used in clinical practice. A variety of medical treatment options now exist for DME. These include non-steroidal anti-inflammatory drugs such as nepafenac, as well as intravitreal steroids like triamcinolone (kenalog). Long-term results up to 7 years after commencing treatment are presented for triamcinolone. Studies are reviewed on the use of dexamethasone (ozurdex) and fluocinolone (Retisert and Iluvien implants) including the FAME studies. A variety of anti-vascular endothelial growth factor (anti-VEGF) agents used in DME are considered in detail including ranibizumab (lucentis) and the RESTORE, RIDE, RISE and Diabetic Retinopathy Clinical Research Network (DRCR.net) studies. Bevacizumab (avastin) and pegaptinib (macugen) are also considered. The use of aflibercept (eylea) is reviewed including the significance of the DA VINCI, VISTA-DME, VIVID-DME and the DRCR.net studies which have recently suggested potentially greater efficacy when treating DME for aflibercept in patients with more severely reduced visual acuity at baseline. Evidence for the anti-VEGF agent bevasiranib is also considered. Studies of anti-tumour necrosis factor agents like infliximab are reviewed. So are studies of other agents targeting inflammation including minocycline, rapamycin (sirolimus) and protein kinase C inhibitors such as midostaurin and ruboxistaurin. The protein kinase C β inhibitor Diabetic Macular Edema Study is considered. Other agents which have been suggested for DME are discussed including cyclo-oxygenase-2 inhibitors like celecoxib, phospholipase A2 inhibitors, recombinant erythropoietin, and monoclonal anti-interleukin antibodies such as canakinumab. The management of DME in a variety of clinical scenarios is also discussed - in newly diagnosed DME, refractory DME including after macular laser, and postoperatively after intraocular surgery. Results of long-term intravitreal triamcinolone for DME administered up to seven years after commencing treatment are considered in the context of the niche roles available for such agents in modern management of DME. This is alongside more widely used treatments available

to the practitioner such as anti-VEGF agents like aflibercept (Eylea) and ranibizumab (Lucentis) which at present are the mainstay of pharmacological treatment of DME.

Key words: Diabetic macular edema; Diabetic macular oedema; Triamcinolone; Anti-vascular endothelial growth factor agents; Steroids; Non-steroidal anti-inflammatory drugs; Biologicals; Protein kinase C inhibitors

Core tip: Current evidence suggests the anti-vascular endothelial growth factor (anti-VEGF) agents aflibercept and ranibizumab are the most effective agents for most patients with diabetic macular edema. Aflibercept may be more effective when vision is very low. Other drugs retain niche roles including bevacizumab owing to lower costs, steroids like triamcinolone which can be effective many years later, dexamethasone and non-steroidal anti-inflammatory drugs like nepafenac. Also considered are anti-tumour necrosis factor agents like infliximab, anti-interleukins like canakinumab, anti-inflammatories including minocycline, rapamycin (sirolimus) and protein kinase C inhibitors midostaurin and ruboxistaurin. Fluocinolone implants, anti-VEGF agents bevasiranib and pegaptinib, cyclo-oxygenase-2 inhibitors like celecoxib, phospholipase A2 inhibitors and recombinant erythropoietin are discussed.

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INTRODUCTION

Diabetic retinopathy is the principle cause of blindness in younger adults[1,2]. Almost 350 million people are affected by diabetes worldwide and this massive prevalence is expected to double by 2030[3]. The blinding complications of the disease make it a major cause of global visual morbidity in many countries[4-17]. While previously retinal laser had been the mainstay of treatment, a variety of non-laser treatment options have become available relatively recently for the treatment of diabetic macular edema (DME)[18-33]. These include anti-vascular endothelial growth factor (anti-VEGF) agents and a variety of steroid preparations as well as non-steroidal anti-inflammatory drugs (NSAIDs). These agents, alone and/or in combination with macular laser, are used to treat DME in varying treatment regimes in different parts of the world. Newer agents like infliximab are also being used to treat DME and interest is growing in monoclonal anti-interleukin antibodies such as canakinumab. The evidence for the use of these modalities of treatment will be considered as well as other targets for inflammation such as minocycline, rapamycin (sirolimus) and the protein kinase C Inhibitors midostaurin and ruboxistaurin. Other agents which have been suggested for DME are discussed including cyclo-oxygenase-2 (COX-2) inhibitors like celecoxib, phospholipase A2 inhibitors and recombinant erythropoietin.

STEROIDS AND NSAIDS

Steroids are an older treatment for DME. Interest in these agents has recently been rekindled with the introduction of sustained release depot preparations. Despite new pharmacologic agents steroids still retain an important niche in modern clinical management - topical steroids are still used for the treatment of DME occurring after cataract surgery, as are NSAIDs.

Cataract surgery in patients with pre-existing DME may exacerbate the extent of edema[34-36]. It has been suggested by a number of studies that the incidence of DME increases after even uncomplicated cataract surgery in the absence of pre-operative DME[37-40]. Intensive postoperative topical steroids can help reduce macular thickness in postoperative DME, and may be given in combination with topical NSAIDs. A variety of NSAIDs have been used in this context. More recently a NSAID pro-drug, nepafenac 0.1%, administered topically to the eye, has been shown to have considerable efficacy with treatment usually taking 3-4 wk to make a significant benefit to visual acuity and macular thickness[41].

Triamcinolone (kenalog), a short-acting intravitreal steroid, is better-established in clinical practice and has been shown to improve visual acuity and central macular thickness in DME even several years after starting injections in selected patients[42]. Triamcinolone still retains a niche in the management of DME[42-61]. For example some patients do not want to undergo three intravitreal loading doses required in most anti-VEGF treatment protocols for DME. Further, evidence exists for long-term retinal complications including atrophy with anti-VEGF use in age-related macular degeneration, and the drugs are not freely available in a sterile form in all parts of the world[62]. A further practical utility is that triamcinolone permits the effect of intravitreal steroids, including on intraocular pressure, to be evaluated in patients before administering a longer-term depot steroid for DME. Identification of steroid-responders prior to administering a longer term depot steroid can be of significant benefit to selected patients where such a tendency is suspected[43]. Patients from initial work by the authors of 92 eyes administered intravitreal triamcinolone (IVTA) over 5 years have been followed up for a total of 7 years[42]. Inclusion criteria comprised all eyes with diabetic macular oedema injected with 4 mg/mL IVTA till treatment failed or was discontinued, often owing to the emergence of anti-VEGF treatment (frequently after 7 years). Exclusion criteria were subjects with non-diabetic oedema (uveitis, vascular, post-operative) and baseline foveal ischaemia. Visual

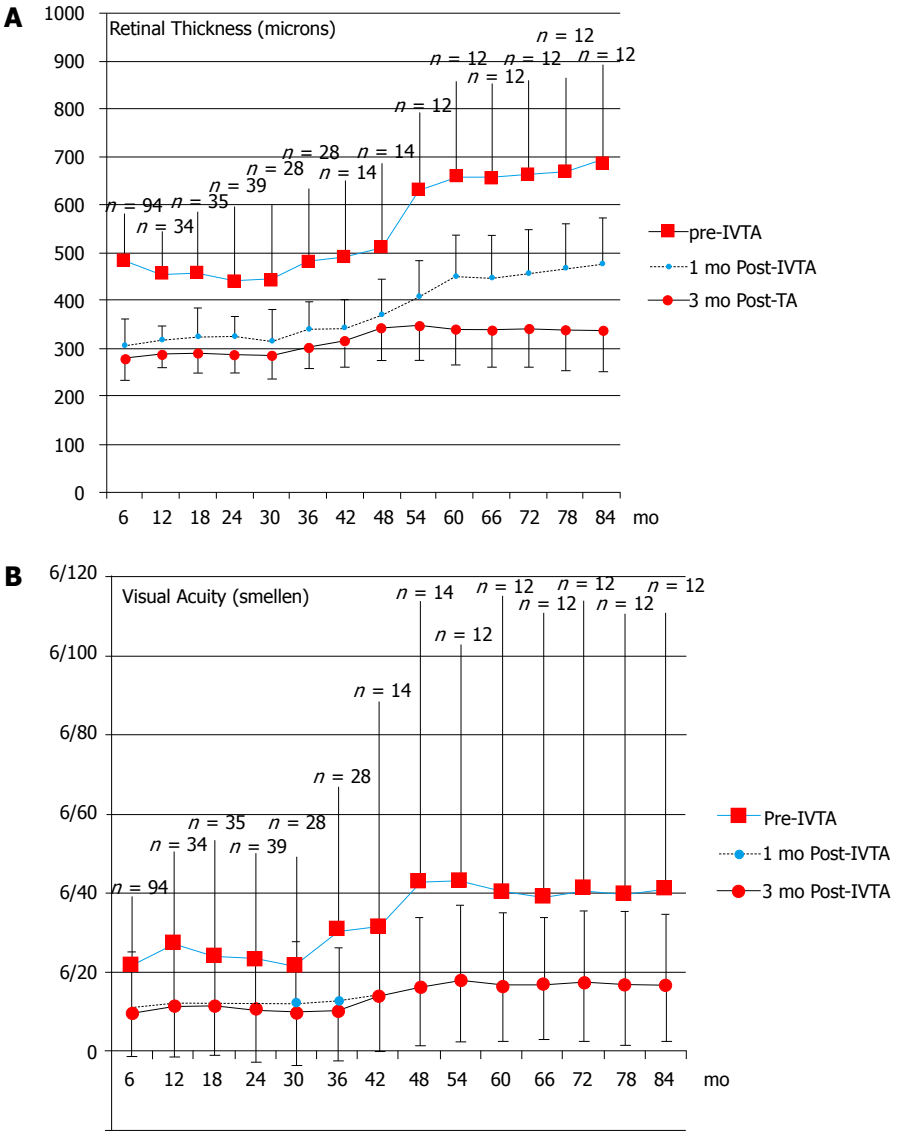

Figure 1 Mean retinal thickness (A) or visual acuity (B) following intravitreal triamcinolone injections over 7 years. Number of intravitreal triamcinolone injections from a cohort of 92 eyes receiving intravitreal triamcinolone (IVTA) in a given 6-mo period and up to 84 mo (seven years) later. Note that the initial number for n is recorded as 94 in this graph as two eyes from the 92 in the cohort received two injections in the first six month period. There was a significant improvement in macular thickness both between number of IVTA administration and one month later, and also between one month and three months following IVTA administration ($P < 0.02$, Wilcoxon matched-pairs signed rank tests) and also between one month and three months following IVTA administration ($P < 0.04$, Wilcoxon matched-pairs signed rank test).

acuity, central retinal thickness from optical coherence tomography prior to, 1 mo after (± 1 wk) and 3 mo post-IVTA (± 2 wk), the presence of complications, and fundus fluorescein angiographic data were recorded. Repeat IVTA injections continued to be effective in improving visual acuity and reducing DME in 76% of subjects ($P < 0.02$), including after multiple injections (mean 10 IVTA injections/patient by seven years) (Figure 1). In 24% of subjects foveal ischaemia limited outcome, usually 36-54 mo post-initial treatment. In 8% ($n = 7$) of subjects one repeat injection of IVTA was sufficient to stop leakage or cause a persistent reduction in macular thickness on OCT in excess of 100 microns for 2 to 3 years. IVTA could offer significant sustained visual benefit and reduction in macular thickness up to 7 years after initiation of therapy in some select patients, including after multiple injections. In certain subjects not selected for anti-VEGF treatment therapeutic potential was limited by the development of foveal ischaemia 2 to 7 years after treatment was commenced.

However it is worth remembering that treatment with IVTA is associated with cataract and also glaucoma which is significant in over 50% of patients[43]. Triamcinolone has also been associated with a reduction in progression of diabetic retinopathy but only in eyes with proliferative diabetic retinopathy, which is relevant since this can co-exist with DME[63]. However in this context the newer anti-VEGF agent ranibizumab remains more effective than triamcinolone, and also reduces progression of diabetic retinopathy in the absence of proliferative disease, a situation where triamcinolone is

of limited value[63].

Dexamethasone sustained-release intravitreal implant (Ozurdex, Allergan, Inc.) is a relatively new drug that is injected as a depot into the eye at a dose of 0.7 mg. It is not used in aphakes as the depot may migrate to the corneal endothelium and cause corneal decompensation. It has been combined with laser photocoagulation and compared with laser treatment alone in diffuse DME in a 12-mo multicentre randomised controlled trial conducted by Callanan *et al*[64]. Patients with diffuse DME on fluorescein angiography had a greater mean improvement in best corrected visual acuity (BCVA) with Ozurdex combined with laser treatment in comparison to laser therapy alone (7.9. to 2.3 letters). There was also an additional reduction in vascular leakage with the additional Ozurdex implant beyond the use of laser therapy alone. Predictably there was an increase in intraocular pressure with Ozurdex. By month 12 of the study there was no significant difference between the two groups, though during the study consistent improvements in visual acuity were found in patients treated with combined Ozurdex and laser. Sustained release depot steroids are relatively contraindicated in patients with glaucoma and in non-pseudophakes but they do offer utility in patients who are unwilling to undergo the higher injection frequency necessitated with intravitreal ranibizumab. The initial implantation method could cause serious technical complications till the recent past, however the current injection technique and injectors are much safer and experience and confidence in their use has grown recently.

Fluocinolone has been used in two delivery systems to treat DME. First a non-bio-erodable extended-release implant was sutured onto the sclera (Retisert, Bausch and Lomb, Rochester, New York). Two phase-Ⅱ studies showed benefit to macular thickness in DME[65]. Later an extended-release injectable device (iluvien, alimera, alpharetta, georgia) was studied, including in the FAME studies[66]. These were two Phase Ⅲ randomised control trials of 956 patients with persistent DME who had previously undergone macular laser. Patients received either intravitreal fluocinolone acetonide or sham injection. By the end of the study 28% of patients receiving fluocinolone acetonide found an improvement in BCVA of 15 letters at 24 mo as opposed to 16% of sham-treated patients[66]. Both modes of fluocinolone acetonide administration have been associated with cataract formation and a rise in intraocular pressure.

ANTI-VEGF AGENTS

VEGF is elevated in the aqueous and vitreous humour in proportion to the extent of DME[67]. Monoclonal antibodies (anti-VEGF agents) have been used to target VEGF. Ranibizumab (Lucentis) has rapidly become the default treatment for DME in many countries in view of significant prolonged improvements in visual acuity[68,69]. Muether *et al*[70] studied VEGF-A levels in aqueous humour samples from 17 eyes in patients with DME before injection of intravitreal ranibizumab. They found total suppression of VEGF-A in all patients after ranibizumab injections for, on average, 33.7 d (median 34 d) with considerable variation between individuals (range: 27-42 d). RESTORE was a 12-mo phase Ⅲ randomised controlled trial with 345 subjects. It found ranibizumab either on its own or when combined with laser therapy was better than laser in terms of improving mean BCVA for the entire duration of the study[68]. These improvements have been found to continue into 36 mo after commencing treatment in a phase Ⅲ 3-year randomised controlled trial conducted by Brown *et al*[71].

RIDE and RISE are also phase Ⅲ randomised clinical trials and aim to evaluate the safety and efficacy of intravitreal ranibizumab in DME[69]. The proportions of patients gaining 15 letters or more from baseline in month 36 were as follows in the sham, 0.3 mg, and 0.5 mg ranibizumab groups (patients receiving sham injections were able to cross over to 0.5 mg in the third year of the study): in RIDE 19.2%, 36.8%, and 40.2%, respectively, and in RISE 22.0%, 51.2%, and 41.6%, respectively. The incidence of serious adverse events which might possibly be related to anti-VEGF suppression were 19.7% in the 0.5 mg ranibizumab group compared with 16.8% in the 0.3 mg group.

Unlike ranibizumab there is considerably less data on outcomes for bevacizumab (avastin), which worldwide is another widely-used anti-VEGF agent[72]. There is evidence that in patients with a central macular thickness of 400 μm the retina is less responsive to bevacizumab in comparison with ranibizumab[73]. In a randomised study of 60 eyes out of 45 patients who completed the study Nepomuceno *et al*[67] compared intravitreal bevacizumab with intravitreal ranibizumab in DME. While there was a significant rise in mean BCVA in both groups, as well as at all stages of the study ($P < 0.05$), this benefit was significantly greater in the group of eyes receiving intravitreal ranibizumab compared with the intravitreal bevacizumab group throughout weeks 8 ($P = 0.032$) and 32 ($P = 0.042$). Mean central subfield thickness improvement was noted in both groups at all study visits but with no difference between the groups. Intravitreal injections can be very painful for some patients (occasionally excruciatingly so) and it is hence worth noting that the mean number of injections administered was significantly higher ($P = 0.005$) in the group receiving intravitreal bevacizumab (9.84) over the intravitreal ranibizumab group (7.67). The conclusions of the authors of this study are important. Through one whole year of follow-up, while intravitreal bevacizumab and intravitreal ranibizumab appear to be associated with a similar reduction in central macular thickness, intravitreal ranibizumab is associated with greater improvement in BCVA at some visits. Further, intravitreal bevacizumab is associated with a greater number of intravitreal injections.

The evidence suggests that ranibizumab certainly

appears more effective than bevacizumab for the management of DME. However in developing countries cost is an important factor to bear in mind, as ranibizumab (lucentis) is vastly more expensive than bevacizumab (avastin). The Diabetic Retinopathy Clinical Research Network have reported that ranibizumab can cause transient regression of proliferative diabetic retinopathy[49]. Other workers have shown it may decrease the cumulative probability of deterioration of diabetic retinopathy[74]. These factors are relevant to appraising the drug in DME especially where proliferative disease is co-existing.

An interesting concept with relevance to the clinician is whether VEGF suppression may prevent postoperative diabetic macular oedema in patients undergoing cataract surgery. It has been shown that VEGF levels in aqueous humour peak one day after cataract surgery and normalize one month after cataract surgery[75]. In a randomised controlled trial Chae *et al*[76] evaluated whether intravitreal ranibizumab administered at the time of cataract surgery prevents macular edema in patients without DME but with otherwise stable diabetic retinopathy. The sham group compared with the ranibizumab group had significantly greater increases in central macula thickness and macula volume, and worse BCVA from baseline to six months postoperatively. This suggests that ranibizumab is an effective prophylactic agent in reducing the severity and risk of DME at the time of phacoemulsification cataract surgery. However, in this regard, bevacizumab has also been shown to be effective when used in this capacity in two randomised controlled trials, one of 30 eyes by Salehi *et al*[36] and one of 68 eyes undergoing cataract surgery by Cheema *et al*[77].

Intraocular pressure rises acutely after intravitreal injection. However evidence is accumulating that anti-VEGF agents may increase the risk of long-term sustained rises in intra-ocular pressure. Very recently a major randomised control trial of 582 eyes from 486 patients has been published by Bressler and colleagues to address this issue. Patients were randomised to intravitreal ranibizumab with deferred macula laser or to sham injection with early laser. The researchers found evidence for sustained long-term pressure rises necessitating topical pressure-lowering treatment in patients receiving ranibizumab. The cumulative probability of a sustained elevation of intraocular pressure or commencing of pressure-lowering treatment at 3 years was 9.5% for patients in the ranibizumab arm *vs* 3.4% for patients in the sham injection arm[78].

Aflibercept (eylea) is a recombinant fusion protein which binds to VEGF serving as a "VEGF Trap" thereby inhibiting the action of VEGF-A, VEGF-B and placental growth factor[79,80]. The DA VINCI study enrolled 221 patients with centre-involving DME and a BCVA of between 20/40 and 20/320 who were randomised into four groups each receiving various dosing regimes of intravitreal VEGF-Trap and one other group receiving macular laser in place of VEGF-Trap[80]. Improvements in BCVA were found in eyes injected with VEGF-Trap of 8.5 to 11.4 letters *vs* 2.5 letters in eyes receiving laser. By week 52 eyes receiving VEGF-Trap displayed a mean change in BCVA of 9.7 to 13.1 letters *vs* a loss of 1.3 letters in eyes receiving laser. As there was no significant difference between groups receiving VEGF-Trap this supported the lower dosing frequency regime of 8-weekly rather than 4-weekly injections with VEGF-Trap. The VISTA-DME and VIVID-DME studies were large studies of aflibercept which aimed to have sufficient power to study the safety profile of VEGF-Trap[81]. They were both similarly designed phase 3 randomised control trials enrolling in total 872 patients with DME who were randomised to various dosing regimes of intravitreal aflibercept or macular laser. The study groups joined their findings to increase the power of the study. Eyes receiving aflibercept performed significantly better by week 52 after starting treatment and in terms of safety profile aflibercept was well-tolerated.

Most recently the Diabetic Retinopathy Clinical Network has published a randomised control trial of 660 patients comparing aflibercept, ranibizumab and bevacizumab[82]. The principle outcome studied was the effect of intravitreal injections of these agents on visual acuity at one year. At low levels of initial visual acuity aflibercept was more effective in improving visual acuity at one year, while at higher initial levels of visual acuity the three agents were very similar in their effect of visual acuity at one year.

Pegaptinib (macugen) is a smaller molecule - a pegylated anti-VEGF agent aptamer which binds anti-VEGF. It has been studied in 260 subjects with DME and BCVA of 20/50 to 20/200. Subjects were randomised to receive either intravitreal pegaptinib or sham injection every 6 wk for 102 wk. Subjects received macular laser at 18 wk. By the end of the study subjects treated with pegaptinib gained on average 6.1 letters of vision compared with 1.3 letters in the sham group ($P < 0.01$). There was a similar incidence of side effects in the two groups, suggesting an acceptable systemic safety profile[83].

Bevasiranib is small interfering RNA molecule (siRNA) which inhibits intracellular transcription of VEGF messenger-RNA[84]. The RACE trial studied different doses of bevasiranib given for 3 mo[85]. Macular thickness was reduced from weeks 8 to 12 with improvements in visual acuity.

ANTI-TUMOUR NECROSIS FACTOR AGENTS - INFLIXIMAB

Tumour necrosis factor (TNF) is an important cytokine which has a fundamental role in the activity of the immune system as well as the human cell cycle. Infliximab is a monoclonal antibody that targets human TNF. It is typically administered systemically every 4-8 wk. The drug is currently at an early stage of

evaluation in the context of reducing severity of diabetic retinopathy and studies are only of small numbers of patients. However the results offer some promise. A clinical improvement in vision from DME has been noted after two infusions of infliximab in 4 of 6 studied eyes with DME by Sfikakis *et al*[86]. A subsequent small Phase Ⅲ study by the same group found an improvement of almost 25% in visual acuity in infliximab-treated eyes over eyes treated with placebo[87]. Systemic side effects were minimal. These side effects can sometimes be serious and are theoretically reduced by intravitreal formulation, which also enables the drug to be targeted to the retina. The drug has been formulated for intraocular use recently and intravitreal infliximab has recently been tried in Behcet's Syndrome, and is likely to be trialled in DME in the near future[88].

MINOCYCLINE, RAPAMYCIN, PROTEIN KINASE C INHIBITORS, ANTI-INTERLEUKIN AND OTHER AGENTS

It is well-recognised that inflammation has a role in DME[89]. Recently it has been suggested that up-regulation of the immune system in diabetes may in part be due to neuropathy of the bone marrow causing increased synthesis of inflammatory white cells and reduced production of endothelial progenitor cells affecting the permeability of the blood-retina barrier[89,90]. The increased inflammation may affect the hypothalamus to induce insulin resistance. Suppressing inflammation has been a target in DME. Recently minocycline, administered systemically, has been found to reduce central macular thickness in DME together with improvement in vision and vascular leakage[90]. It has been postulated that this is by inhibiting retinal microglial function, which otherwise shows a pattern of activation and aggregation in regions of DME[89].

Rapamycin (sirolimus) is a macrolide antibiotic which also suppresses the immune system[91,92]. It forms an intracellular complex which inhibits the mammalian target of rapamycin (mTOR), which is a protein kinase integrating growth factor-activated signals. These include those promoting VEGF-mediated angiogenesis. A "double" effect of rapamycin is that by inhibiting mTOR it may also down-regulate VEGF transcription. A small pilot study of five adult participants with DME has suggested a reasonable safety profile for rapamycin administered *via* this route and some potential benefit to vision and macular thickness, however the relatively small numbers preclude any conclusive statement on its efficacy in DME[93].

Hyperglycemic states induce *de novo* synthesis of diacylglycerol which activates protein kinase C (PKC)[94]. The oral PKC inhibitor midostaurin is both a protein kinase C inhibitor and anti-VEGF inhibitor, making it an attractive drug for use in DME. Further, the oral selective PKC β inhibitor ruboxistaurin may also have potential for improving or maintaining visual acuity in DME. A randomised study of 141 patients with DME receiving a variety of oral doses of PKC412 (which is midostaurin) *vs* placebo showed a significant reduction in macular thickness and a small improvement in visual acuity of 4.36 letters (P = 0.007) in patients receiving 100 mg per day of PKC412 by 3 mo[95]. However, gastrointestinal side effects were common owing to the lack of specificity of this group of drugs, and dose-related effects on glycaemic control and hepatotoxicity were also noted. In view of this the authors suggested targeting the drug for local ocular delivery. In the PKC-DRS2 study oral ruboxistaurin reduced the extent of sustained moderate visual loss, delayed progression of DME, reduced the need for laser treatment and improved visual outcomes in patients with nonproliferative diabetic retinopathy[96,97]. The protein kinase C β inhibitor Diabetic Macular Edema Study specifically studied outcomes in DME and showed that patients administered oral ruboxistaurin had less progression of DME compared with a placebo group during a 30-mo period[98].

Not all pharmacological agents have proven to be of benefit in treating DME. On the basis of the efficacy of NSAIDs it was thought that COX-2 inhibitors may be of benefit in diabetic retinopathy. However studies of the COX-2 inhibitor celecoxib have not shown any significant benefit in improving vision in DME, though did find some reduction in leakage on angiography[99]. Other drugs targeting the immune system are currently being studied in trials including phospholipase A2 inhibitors, recombinant erythropoietin, and anti-interleukin antibodies[89,100]. In fact a large number of potential agents have been suggested for use in diabetic retinopathy to target various components of the inflammatory pathway, many of which have not found clinical use. The most promising at present seem agents such as canakinumab which are monoclonal antibodies targeting interleukin. Animal studies have shown breakdown of the blood retina barrier and neurotoxicity to ganglion cells in the inner retina occurs in diabetes under the effect of oxidative stress and pro-inflammatory cytokines such as interleukin[100]. Studies in humans of antibodies blocking these pathways are still at an early stage but are being conducted to assess the effect of canakinumab in DME[89].

CONCLUSION

Evidence from a number of human studies and trials show several pharmacological agents have benefit in DME, to varying degrees. Till very recently the efficacy of ranibizumab seemed greatest, and remains accompanied by a large body of evidence, and a good ocular safety profile. Very recently evidence has emerged from a large RCT that aflibercept may be more efficacious in patients with poor vision at baseline[82]. However a variety of other drugs also carry benefits. These different drugs are relevant and important to consider as practical alternatives to ranibizumab and grid/focal macular laser, both of which may be perceived to be costly in some

healthcare systems across the world. Further, DME is often a refractory and recurrent disease and diabetics undergo cataract and vitreoretinal surgery more frequently than most patients - clinical scenarios where the plurality of therapeutic options is highly useful for managing this common sight-threatening disease.

Most new pharmacological therapies are being investigated as multiple inflammatory pathways are involved in the development of DME[100]. In the longer term adjunctive treatments which block these pathways will likely be used alongside suppressors of vascular leakage[19,100]. For example, while ranibizumab reduces retinal oedema in DME, in future agents which protect ganglion cells may be used adjunctively alongside suppressors of capillary leakage to provide a multi-faceted approach to the management of DME.

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REVIEW

State of the art management of diabetic macular edema

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Abstract

Macular edema following diabetic retinopathy is one of the ocular complications associated with diabetes, and it is the leading cause of visual loss in the active young and middle aged population in developed countries. While all patients with diabetes particularly those with diabetic retinopathy are at increased risk of developing eye complications, early detection and timely intervention may prevent or delay loss of visual acuity. Systemic management of diabetes through combined control of blood sugar, hypertension, and hyperlipidemia has remained the most effective method to prevent diabetic retinopathy and its progression. Development of diabetic retinopathy and related complications require, surgical and medical interventions including photocoagulation, vitrectomy, and intravitral drug injection to preserve vision. Considering recently most popular treatment of diabetic macular edema (DME) including intravitreal anti-vascular endothelial growth factor (VEGF) agents, several issues such as ideal regimen, duration of treatment, combination therapy and long -term safety have remained unanswered yet and deserve further investigations. In this review, all the articles that had investigated such treatment modalities for DME as well as pharmacokinetic, efficacy, safety, dose and frequency of intravitreal pharmacologic agents and also the effect of macular ischemia, initial macular thickness and optical coherence tomographic patterns of DME on the final outcomes of treatment with Intravitreal drugs are reviewed. In summary, literature searches reveal that almost all studies that have been published up to now provide some evidence that support the use of intravitreal anti-VEGF agents for treatment of either naïve or persistent DME in short and long term up to two years.

Key words: Intravitreal vascular endothelial growth factor inhibitor agent; Clinically significant diabetic macular edema; Diabetic retinopathy; Macular laser photocoagulation; Intravitreal steroid

Core tip: There are multiple treatment approaches for diabetic macular edema so in this article we reviewed almost all treatment modalities for diabetic macular edema and efficacy and side effects of them.

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INTRODUCTION

Recent published studies have been dramatically modifying the management paradigm of diabetic macular edema (DME). The Recent protocols based on these studies have substituted pharmacotherapy instead of the standard treatment of macular laser photocoagulation for DME. Nowadays, the strategy for treatment of DME is to find some ways for either preventing DME formation or early intervention in a symptomatic stage of diseases to preserve vision. In the past, Laser photocoagulation was the only evidence based standard treatment available for subjects with CSME, defined by the early treatment diabetic retinopathy study (ETDRS)[1]. However, the beneficial effect of macular laser photocoagulation (MPC) on DME was attractive, because it reduced the risk of moderate visual loss by 50% at that area[1]. For diffuse DME, MPC was even less effective and based on one study, applying modified MPC, visual acuity (VA) improvement observed in only 14.5% of the eyes[2]. Moreover, diabetic retinopathy clinical research network (DRCR. Net) has recently shown a VA improvement of more than 5 letters in 51%, 47% and 62% of cases using MPC at 1, 2 and 3 years follow-up, respectively[3,4]. Destructive nature, adverse effects and suboptimal efficacy of MPC have led investigators to find alternative treatments. Pharmacotherapy of DME with systemic and intravitreal drugs especially intravitreal steroids and anti-vascular endothelial growth factor (VEGF) agents such as Pegaptanib, bevacizumab, ranibizumab, and aflibercept have been the focus of the most recent attentions. The use of intravitreal drugs is becoming more popular; however several issues such as optimal medication, length of treatment, combination therapy and long-term safety of agents are still not clear enough and deserve further investigations. The present review article attempts to provide some answers for common questions in this regard on the basis of published literatures.

EPIDEMIOLOGY

DME is the major cause of visual loss in the active young and middle aged patients worldwide. While the risk of DME has been shown to vary with a number of factors including the type of diabetes, disease duration, and insulin dependence, it is expected to grow along with the prevalence of diabetes. Almost 285 million people have diabetes and one fourth of them will finally develop macular edema. The rise in the incidence of diabetes is a major public health concern worldwide and diabetic retinopathy, as the most common microvascular complication of diabetes, may lead to blindness in the working aged population. Based on one study, it has been estimated that one out of 12 Americans with diabetes aged $\geqslant$ 40 has vision threatening retinopathy. The number of people with type 2 diabetes is growing particularly in countries with low socioeconomic conditions. Some epidemiologic studies has shown the association of high incidence of diabetic retinopathy with poor control of hyperglycemia and hypertension, which both are more common in countries with limited access to health care. According to another study, within a 10 year period the chance of developing macular edema was almost 20.1% in patients with type I diabetes, 25.4% of type 2 patients receiving insulin and 13.9% of type 2 patients not receiving insulin. DME may cause severe visual loss if remain untreated, with up to 33% of cases losing 3 lines of vision after 3 years[1,5-9].

PATHOPHYSIOLOGY OF DME

For pathogenesis of DME several physiological mechanisms have been postulated up to know. The exact mechanism by which hyperglycemia initiates the vascular disruption and results in the blood retinal barrier (BRB) breakdown in diabetic retinopathy have remained poorly understood. Several hypotheses are contributed to DME formation including: (1) increase in hydrostatic pressure that was described by Starling. Similar to congestive heart failure, DME can be considered as a congestive macular edema. Based on Starling law, hydrostatic and oncotic pressure counteract each other; the difference between such pressures is responsible for the movement of fluid between tissue beds and intravascular spaces. Changes in vessel diameter along with increased hydrostatic pressure can contribute to edema. Furthermore, the above-mentioned mechanism can increase in shear stress which may damage endothelial cells or may cause endothelial decoupling over time[10-12]; (2) ischemia secondary to hypoxia can lead to a decrease in oxygen tension in retina resulting in vascular dilation and this can increase macular edema by raising hydrostatic pressure. An increase in oxygen tension may reduce macular edema by reversing the aforementioned mechanism[13]; (3) hyperglycemia per se or together with other mechanisms may induce endothelial dysfunction and cause more vascular damage[14,15]. Hyperglycemia disrupts the retinal neurovascular unit through biochemical abnormalities that may damage or induce apoptosis of endothelial cells, pericytes, microglia, and neurons. The effects of intracellular hypoglycemia include free radical induction (oxidative stress), protein kinase C (PKC) activation, advanced glycation end-product formation, and increased hexosamine pathway flux[13]; and (4) increased VEGF production: VEGF mediates angiogenesis through promoting endothelial cell migration and proliferation. Among the various VEGF factors, VEGF-A, is a critical regulator of ocular angiogenesis and vascular permeability[16-20].

All above described aberrations result in hypoxia, ischemia, inflammation, and alteration of the vitreoretinal interface.

The following factors have also been involved

in the pathogenesis of macular edema formation and breakdown of BRB: increased placental growth factor (PLGF), hepatocyte growth factor l, nitric oxide, peroxynitrite and on the other hand an increase in inflammatory mediators such as tumor necrosis factor-α, transforming growth factor-β, intercellular adhesion molecule-1 and interleukin-6[21-31]. It is important to note all cases of macular edema following diabetic retinopathy can not be accounted for by a single molecular target. Instead, overlapping and interrelated molecular pathways play a role in both initiating vascular damage and prolongation of tissue damage that further increase chronic macular edema.

SYSTEMIC TREATMENT OF DME

The purpose of systemic treatments in DME is either to reduce the risk of retinopathy development in diabetic patients or to decrease the risk of progression of existing retinopathy or maculopathy to more severe forms. Systemic treatments mostly focus on metabolic and blood pressure control which are modifiable risk factors for DME. Renin-angiotensin system inhibitors and angiotensin converting enzyme blockers like lisinopril, candesartan, enalapril and losartan are treatment modalities which have shown high probability of slowing the progression of retinopathy[32,33]. Lipid lowering agents such as fenofibrate and statins may be useful for treating DME[34-41].

PHARMACOKINETICS OF INTRAVITREAL DRUGS USING FOR DME

Bevacizumab

Bevacizumab, a recombinant humanized monoclonal immunoglobulin antibody, is a VEGF inhibitor agent with molecular weight of 149 KDa. One experimental study has demonstrated that the elimination half-time of bevacizumab was 4.88 d from vitreous and 4.32 d from aqueous after its intravitreal injection in rabbits[42]. The half-life of bevacizumab in aqueous humor and vitreous after intravitreal injection of 1.5 mg were 7.58-9.82 d and 10 d, respectively[43,44]. Another experimental study has also demonstrated that intravitreal bevacizumab (IVB) concentration more than the median inhibition concentration which was determined to be 22 ng/mL would last for about 78 d[45,46]. Intra-ocular injections of anti-VEGF agents have systemic absorption and some studies have shown that small doses of bevacizumab can reach the fellow eye. The concentration of bevacizumab in the vitreous of the rabbits' uninjected eye increased gradually, from 0.35 ng/mL at day 1 to 11.7 ng/mL at week 4 while its concentration in the vitreous of injected eye is 400 μg/mL at day 1 and 10 μg/mL at day 30[42].

Ranibizumab

Ranibizumab is a humanized monoclonal antibody fragment with a molecular weight of 48 KDa and binds to all isoforms of VEGF-A. Multiple experimental studies have disclosed that vitreous and aqueous elimination half-life was calculated to be 2.88-9 d and 2.84-7.19 d, respectively[47-51]. Another study has demonstrated that after Intravitreal injection of ranibizumab, it was distributed rapidly to the retina (6-24 h), and the concentrations were approximately one third of primary amount in the vitreous and bioavailability to the retina was 50% to 60%[51]. Based on experimental and clinical studies significant biological activity of ranibizumab (0.5 mg) usually persists for 30 d after intravitreal injection[50].

Aflibercept

Aflibercept has a VEGF-Trap activity. It is a fusion protein with high VEGF binding activity and molecular weight of 110 KDa and binds to VEGF-A, VEGF-B and placental growth factor. VEGF Trap has a very high VEGF-binding affinity about 140 times more than that of ranibizumab. A study has demonstrated that aflibercept could be detected in the rabbit's vitreous cavity until day 28 and the average retention time with standard error after correction for radioactive decay was 4.58 ± 0.07 d[52]. One study has revealed that after injection of aflibercept with doses of 0.5, 2 and 4 mg, the intravitreal an anti-VEGF activity similar to ranibizumab at 30 d, would occur at 73, 83 and 87 d, respectively[53].

Pegaptanib

Pegaptanib is a small 28-base RNA aptamer that specifically binds and blocks the 165-amino-acid isoform of VEGF (VEGF165) and, therefore, has no pan-VEGF activity. The available data for systemic pharmacokinetics of pegaptanib refer to measurements after intravenous injection in rhesus monkeys. Its measured elimination half-live was short (9.3 h)[54].

Intravitreal corticosteroids

Corticosteroids reduce the breakdown of the blood-retinal barrier and experimentally have been disclosed to down regulate VEGF production too. Pharmacokinetic of the most popular corticosteroids being used for the treatment of DME is described below.

Triamcinolone acetonide

Triamcinolone acetonide is a potent anti-inflammatory and anti-angiogenic agent. A human study has demonstrated that intravitreal triamcinolone acetonide (TA) retention time was 141.8 ± 39.6 d in patients with retinal vein occlusion and 114.5 ± 59.6 d in patients with macular edema secondary to diabetic retinopathy[55]. Another experimental study has disclosed that half-life of preservative free triamcinolone acetonide in the vitreous, after intravitreal injection of 4, 16, and 4 mg triamcinolone containing preservative, were found to be 24, 39, and 23 d, respectively[56]. The triamcinolone acetonide concentration in serum

after intravitreal high-dose injection did not increase significantly. It's concentration reached from 0 μg/L preinjection to 0.065 ± 0.21 μg/L postinjection[57].

Sustained-release dexamethasone intravitreal implant

Dexamethasone, as one of the potent corticosteroids family, has been demonstrated to suppress inflammation by inhibiting multiple inflammatory cytokines which usually result in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells. OZURDEX® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone. After intravitreal sustained- release dexamethasone injection (0.7 mg), investigators were able to detect it in the retina and vitreous till 6 mo, with peak concentrations during the first 2 mo in one experimental study[58]. Another experimental study has evaluated the dexamethasone pharmacokinetics after sustained-release dexamethasone intravitreal implantation in nonvitrectomized and vitrectomized eyes. Dexamethasone could be detected in both nonvitrectomized and vitrectomized eyes for up to 31 d. There were no statistically significant differences in dexamethasone concentration between nonvitrectomized and vitrectomized eyes at any follow up ($P > 0.05$). The maximum concentrations of dexamethasone in retina of nonvitrectomized eyes was 4110 ng/mL and in retina of vitrectomized eyes was a bit lower (3670 ng/mL)[59].

Fluocinolone acetonide sustained delivery device

Solubility of fluocinolone acetonide is much lower than dexamethasone (almost 1/24). Duration of the effect of intravitreal Retisert implant is about three years. In fluocinolone acetonide sustained delivery device–implanted eyes, the mean levels of drug in the vitreous varied from 0.10 to 20.21 mg/mL within 54 wk. The mean levels did not show statistically significant difference at various time points. Fluocinolone acetonide could not be detected at any follow up in the aqueous of drug device-implanted eyes or in the aqueous or vitreous of fellow eyes that did not contain a device[60].

PUBLISHED RESULTS OF BEVACIZUMAB FOR DME

Bevacizumab is still an off-label treatment for DME. Efficacy of bevacizumab based on published randomized clinical trials can be categorized into two major groups: (1) intravitreal bevacizumab for of naïve DME; and (2) intravitreal bevacizumab for refractory DME (Table 1).

Intravitreal bevacizumab for treatment of naïve DME

One randomized clinical trial that has been published in 3 separate reports (publications are related to the same study) demonstrated that improvement of VA of the IVB over the combined IVB/IVT and MPC treatment that was observed at month 6 did not sustain for 2 years. The authors concluded that despite better efficacy of IVB over combined IVB/IVT and MPC in short term, the magnitude of its effect lessened over time. Based on that study IVB provided a better visual outcome at 6 mo in comparison to MPC, however any alteration in CMT beyond the six-week time point corresponded to the vision change was not detected. Interestingly no adjunctive effect of IVT could be demonstrated in short and long term[61-63]. DRCR. Network also conducted a randomized clinical trial of the short- term effect of IVB for DME (24 wk) and demonstrated subgroups of cases that had received 1.25 and 2.5 mg bevacizumab at baseline and 6 wk had a larger reduction in CMT at 3 wk and an approximately one line improvement in vision at 12 wk when compared to a group that were treated by MPC alone at baseline. The combination of IVB and MPC had no short- term benefit in DRCR Network study[64]. One clinical trial has reported that IVB was an effective drug for treatment of DME and adding IVT did not affect the outcomes except for elevating the intraocular pressure (IOP)[65]. Another study has reported that VA and CMT at 12 mo were comparable in eyes that were treated with IVB, IVB/IVT and IVT and no beneficial effect of the combination injection was detected[66].

Intravitreal bevacizumab for refractory DME

Refractory cases of DME are defined as cases who do not response to macular photocoagulation. In one randomized clinical trial, the authors reported that three, 6 wk-interval injections of bevacizumab at had a more beneficial effect on refractory DME. In this study the addition of triamcinolone in the first injection although induced earlier visual improvement; however, it did not cause any significant additive effect during follow-up[67]. More recently Bevacizumab or Laser Therapy study has reported the two years results of comparing intravitreal bevacizumab (1.25 mg) *vs* MPC for the treatment of persistent center-involving CSME in 80 cases. According to this study, the median gain in BCVA was higher for IVB in comparison to MPC (+9 letters for IVB *vs* +2.5 letters for MPC). The median of treatments were 13 for IVB and 4 for MPC groups. Mean central macular thickness (CMT) reduction in 24 mo was slightly greater in IVB group (-146 μm) *vs* the MPC group (-118 μm) but it was not statistically significant[68]. Several other case series have also provided evidence supporting beneficial effect of IVB for persistent DME with the logic that persistence or recurrence of DME after MPC may be attributed to the creation of more VEGF by the ischemic retina, which eventually may raise to persistent or recurrent DME despite MPC[69-71].

In summary, literature searches for present study disclosed that almost all relevant published studies have provided evidences supporting IVB for treatment of either naïve or persistent DME in short and long terms up to two years.

Table 1 Summary of the studies using intravitreal Bevacizumab for treatment of diabetic macular edema

Ref.	Purpose	Study design	Out comes measures	IVB dose	Interval of injection	Naive or refractory/ DME	Duration of study	Number of eyes	Treatment regimen	Results
Soheilian *et al*[61]	IVB or IVB, IVT or MPC	Randomized clinical trial	BCVA, CMT	1.25 mg	-				(1) 1.25 mg IVB; (2) IVB/ IVT/ 1.25 mg IVB and 2 mg IVT; and (3) MPC	Group B and C had a greater reduction in CMT at 3 wk and 1 line better median VA over 12 wk there were no significant differences between group B and C. Combining MPC with IVB resulted in no apparent short term benefit
Soheilian *et al*[62]	IVB or IVB/ IVT or MPC	Randomized clinical trial	BCVA, CMT	1.25 mg	12 wk	Naïve	24 wk	150 eye	(1) 1.25 mg IVB; (2) IVB/ IVT 1.25 mg IVB and 2 mg IVT; and (3) MPC	The significant treatment effect on VA was demonstrated in the IVB group at all follow- up visits and in the IVB/ IVT group at 6 and 12 wk. CMT Changes were not significant among the groups in all visits
Soheilian *et al*[63]	the same as above	randomized clinical trial	BCVA, CMT	1.25 mg	12 wk	Naïve	2 yr	150 eyes	The same as above	The significant superiority of VA improvement in the IVB group, which had been noted at month 6, did not sustain thereafter up to 24 mo, and the difference among the groups was not significant at all visits. The reduction of CMT was more in the IVB group in relation to the other two treatment groups however, the difference among the groups was not significant at any of the follow-up visits
DRCR.Net[64]	IVB for DME	Randomized phase 2 clinical trial	CMT, BCVA	1.25 mg 2.5 mg	6 wk	Naive	24 wk	121	(1) Foal MPC12 or (2) 1.25 mg IVB at base line and 6 wk; (3) 2.5 mg IVB6 at baseline and 6 wk or (4) 1.25 mg at baseline; and (5) 1.25 mg IVB at base line and 6 wk + MPC at 3 wk	The significant treatment effect on VA was demonstrated at both 6 and 12 wk in the IVB group and only at 6 wk in the IVB/IVT group. Significant CMT reduction was observed in eyes in the IVB and IVB/ IVT groups only up to 6 wk, however, CMT changes were not significant in the groups
Marey *et al*[65]	IVB or IVB/ IVT for DME	Randomized clinical trial	VA and CMT	1.23 mg		Naïve	12 wk	90	(1) IVB; (2) IVB and IVT (4 mg); and (3) IVT	There was significant improvement in the VA in the three study groups at week 6 and 12. Comparing the visual acuity results at 6 wk between the 3 study groups there was no significant difference and also between each pair of the three study groups; however at week 12, there was high significant difference (P = 0.004) and between each pair there was high significant difference between IVT and IVB/ IVT groups (P = 0.001), significant difference between groups IVT and IVB and no significant difference between group IVB/ IVT and IVB. Comparing the CMT showed the same results

Lim *et al*[66]	IVB or IVB/ IVT or IVT	Randomized 3arm clinical trial	BCVA, CMT	1.25 mg	6 wk	Naïve	12 mo	111 eyes	IVB group, two IVB injections with 6 wk intervals; IVB / IVT (2 mg IVT + 1.25 mg IVB); 2 mg IVT	The IVB/ IVT group and IVT group showed better visual acuity and reduced CMT at 6 wk and 3 mo. However, no significant difference in VA and CMT was observed between 3 groups. No significant differences in VA or CMT were observed between the IVB/ IVT and IVT group during the follow- up
Ahmadieh *et al*[67]	IVB or IVB/T for refractory DME	Randomized clinical trial (Placebo-Controlled)	CMT BCVA	1.25 mg	6 wk	Refractory	24 wk	115 eyes	(1) three injection of 1.25 mg IVB at 6 wk intervals; (2) IVT (2 mg) followed by two injections of IVB at 6 wk intervals; and (3) sham injection	CMT was reduced significantly in both IVB and IVB/ IVT groups. Significant improvement of BCVA was seen in both IVB and IVB/ IVT groups. No significant differences were detected in the changes of CMT and BCVA between the IVB and IVB/IVT groups
BOLT study[68]	IVB or MPC for DME	Randomized clinical trial	BCVA	1.25 mg	6 wk	Refractory /DME	12 mo	80 eyes	IVB MPC	The mean ETDRS BCVA at 12 mo was 61.3 ± 10.4 in the IVB group and 50.0 ± 16.6 in the MPC group. The IVB group gained a median of 8 ETDRS letters, whereas the MPC group lost a median of 0.5 ETDR letters. At 12 mo, CMT decreased from 507 ± 145 μm at baseline to 378 ± 134 μm ($P < 0.001$) in the IVB group, whereas it decreased to a lesser extent in the MPC group, from 481 ± 121 μm to 413 ±135 μm ($P = 0.02$)

IVB: Intravitreal bevacizumab; IVP: Intravitreal pegaptanib; IVR: Intravitreal ranibizumab; IVT: Intravitreal triamcinolone; IVTL: Intravitreal triamcinolone plus laser; IVVTE: Intravitreal VEGF Trap Eye; DME: Diabetic macular edema; BCVA: Best corrected visual acuity; CMT: Central macular thickness.

PUBLISHED RESULTS OF RANIBIZUMAB FOR DME

There are multiple clinical trials (READ-2, REVEAL, RESTORE, RESOLVE, RIDE, RISE and DRCR.net) that have investigated the effect of intravitreal ranibizumab for the treatment of DME. In such comparison studies the efficacy of intravitreal ranibizumab with macular photocoagulation or the combination of intravitreal ranibizumab and MPC (READ-2, RESTORE and REVEAL) was evaluated. Some other studies have compared the response of DME to intravitreal ranibizumab with sham group (RESOLVE, RIDEand RISE). Furthermore, DRCR. net has compared the effect of intravitreal ranibizumab and prompt laser with deferred laser treatment for DME.

READ-2 was the first large RCT (n = 126) which made a comparison between ranibizumab (0.5 mg) alone, ranibizumab combined with laser and laser alone. In a period of 6 mo, BCVA improved dramatically in ranibizumab group compared with laser alone. Adding laser to ranibizumab did not provide further BCVA gain at 6 mo. In this study with two years follow up disclosed that use of ranibizumab caused more benefits for patients with DME. Furthermore, when ranibizumab was combined with focal or grid laser treatments, the residual edema and frequency of injections were decreased as well[72,73]. In two similar studies REVEAL study (n = 396) and RESTORE study (n = 345)] in 12 and 24 mo follow up, the same results as READ-2 study was achieved[74,75]. In RESOLVE study 151 cases were randomly assigned to two doses of ranibizumab (0.3 and 0.5 mg) and sham injection. This study disclosed that the maximum improvement of best corrected visual acuity (BCVA) at one year was obtained in 0.3 mg group (11.8 letter gain) comparing to the 0.5 mg group (8.8 letter gain) or sham injection (1.4 letter loss)[76]. In other two similar studies in terms of the design (RISE and RIDE) 0.3 and 0.5 mg of ranibizumab with sham injection were compared. In the RISE study, a better visual outcome (≥ 15 letters gain) was observed in the 0.3 mg group at two years, However in the RIDE study a better outcome was reported in the 0.5 mg group. In both of these studies a rapid sustainable VA improvement was reported and risk of loosing visual acuity decreased[77]. In another

clinical trial DRCR.net, compared ranibizumab (0.5 mg) plus prompt laser (3-10 d after ranibizumab injection) and deferred laser (≥ 24 wk after ranibizumab) with sham injection plus prompt laser, and with triamcinolone plus prompt laser. In this study both groups that had received ranibizumab had a better VA improvement than triamcinolone or laser alone groups within 12 mo. Two-year results were similar to 1-year results. Three-year results of this study, however, suggested that focal/grid laser treatment shortly after intravitreal ranibizumab led to no better, and possibly even worse vision outcomes than deferring laser treatment (≥ 24 wk) in eyes with center involving DME[78,79]. One recent published study compared intravitreal bevacizumab with ranibizumab in DME cases and reported that both of these agents had similar effects on macular thickness reduction through one year follow up although the average injection number was greater in the bevacizumab group[80] (Table 2).

PUBLISHED RESULTS OF PEGAPTANIB FOR DME

Two studies have evaluated pegaptanib for the treatment of DME and both have compared it with sham injection. Macugen Diabetic Retinopathy Study group in a clinical trial including 172 cases compared 0.3, 1 and 3 mg of intravitreal pegaptanib with sham injection. This study demonstrated that in 36 wk pegaptanib had better VA outcomes. The treatment groups showed more decrease in central retinal thickness and they also required less additional therapy with photocoagulation at follow-up. In this study 0.3 mg was the most efficacious dose[81,82]. Another study including 260 cases compared pegaptanib (0.3 mg) and sham injection and were able to show a better VA improvement in the pegaptanib group within 24 mo. However, there was no significant difference in the proportion of patients with ≥ 10 letter improvement[83] (Table 3).

PUBLISHED RESULTS OF AFLIBERCEPT FOR DME

The effect of Aflibercept (AFL) on macular edema secondary to diabetic retinopathy has been evaluated in three clinical trials. DaVinci study included 219 cases, Which were randomized to the following schedules: 0.5 mg every 4 wk, 2 mg every 4 wk, 2 mg monthly for 3 mo, then every 8 wk, and 2 mg monthly for 3 mo followed by treatment as required and these groups were compared with laser treatment alone. All aflibercept groups had a statistically better BCVA and CMT change than the laser group at 6 mo. The most effective regimen that caused better VA improvement and CMT reduction was 2 mg every 4 wk; however, the difference between the groups was not significant. All aflibercept groups showed a significantly better BCVA compared to laser at 12 mo[84,85].

In VIVID and VISTA studies patients were randomized to 2 mg Intravitreal AFL every 4 wk (2q4) plus sham laser and 2 mg Intravitreal AFL every 8 wk (2q8) following 5 initial monthly doses plus sham laser and macular laser treatment plus sham treatment. In VIVID-DME, BCVA in intravitreal AFL treated eyes was improved by +10.5 letters (2q4) and +10.7 letters (2q8) from baseline up to week 52, compared to an increase of only +1.2 letters for laser only ($P < 0.0001$ for both intravitreal AFL arms compared to laser). In VISTA-DME, BCVA was improved by +12.5 letters (2q4) and +10.7 letters (2q8) compared to the stable result of +0.2 letters in the laser group ($P < 0.0001$). (Unpublished data, presented only at EURETINA, September 2013) (Table 4).

PUBLISHED RESULTS OF INTRAVITREAL CORTICOSTEROIDS FOR DME

Intravitreal triamcinolone

Multiple studies have evaluated the efficacy of intravitreal triamcinolone on naïve or refractory DME. Some of these studies compared the efficacy of intravitreal triamcinolone alone with laser alone whereas some others compared the efficacy of intravitreal triamcinolone alone, combined intravitreal triamcinolone and laser with laser alone. The results of intravitreal triamcinolone alone compared to sham injection have been reported by some investigators. The effect of intravitreal triamcinolone either alone or combined with anti-VEGF agents has been assessed by some other researchers too.

Overall, three doses of triamcinolone acetonide 1, 4 and 8 mg have been assessed in different reports. DRCR.net group evaluated 1 and 4 mg intravitreal triamcinolone in comparison to laser alone. This study disclosed that laser therapy caused a better VA improvement within 24 mo[86]. In two other published reports 4 mg intravitreal triamcinolone injection was compared with laser alone. However no significant BCVA improvement was reported in both groups at 6 and 12 mo[87,88]. The effect of triamcinolone on persistent cases of DME has been evaluated in two studies with different results. The efficacy of 4 mg of triamcinolone comparing with sham injection was assessed and disclosed that mean BCVA improved more significantly in intravitreal triamcinolone injection group up to 24 mo; furthermore, five-year results of the same study confirmed earlier results[89]. Conversely the second study has compared frequent intravitreal triamcinolone injection with the conventional laser therapy for refractory macular edema secondary to diabetic retinopathy, but no further benefits of intravitreal triamcinolone injection was observed[88].

The comparison of the results of intravitreal triamcinolone with anti-VEGF agents have been described earlier.

Table 2 Summary of the studies using intravitreal Ranibizumab for treatment of diabetic macular edema

Name of study	Purpose	Study design	Outcomes measures	IVR dose	Interval of injection	Naive or refractory /DME	Duration of study	Number of eyes	Treatment regimen	Results
READ-2 study[73]	IVR for DME	3-arm RCT	BCVA and CMT	0.5 mg	1 and 2 mo	Naïve or refractory	2 yr	126	Group 1 (IVR, *n* = 42 eyes) injections of 0.5 mg ranibizumab at baseline, 1, 3 and 5 mo Group 2 (L, *n* = 42 eyes) focal/grid laser at baseline and 3 mo if CMT ⩾ 250 μm Group 3 (IVRL, *n* = 42 eyes) IV injections of 0.5 mg ranibizumab at baseline and 3 mo, followed by focal/grid laser treatment 1 wk later	BCVA changes (letters) *P* value IVR +7.24 0.0003 *vs* L L -0.43 IVRL +3.80 CMT changes (μm) IVR -106.3 All < 0.01 *vs* baseline L -82.8 IVRL -117.2
RESTORE study[74]	IVR for DME	3-arm RCT	BCVA and CMT	0.5 mg	1 mo	Naïve or refractory	1 yr	345	Group 1 (IVR, *n* = 116 eyes) IV ranibizumab plus sham laser Group 2 (IVRL, *n* = 118 eyes) 0.5 mg IV ranibizumab plus active laser Group 3 (L, *n* = 111 eyes) laser treatment plus sham injections	BCVA changes (letters) *P* value IVR +6.1 SD6.43 < 0.0001 IVRL +5.9 SD7.92 < 0.0001 L +0.8 SD8.56 CMT changes (μm) *P* value IVR -118.7 < 0.0002 IVRL -128.3 < 0.0001 L -61.3
REVEAL study[75]	IVR for DME	3-arm RCT	BCVA and CMT	0.5 mg	1 mo	NR	1 yr	396	Group 1 (IVR 0.5 mg + sham laser, *n* = 133) day 1, month 1, 2 and pro-renata thereafter based on BCVA Group 2 (IVR 0.5 mg + active laser, *n* = 132) day 1, month 1, 2 and pro-renata thereafter based on BCVA Group 3 (sham injection + active laser, *n* = 131)	BCVA (letters) and CRT(μm) changes: *P* value IVR + sham laser +6.6; -148.0 < 0.0001 IVR +laser +6.4; −163.8 < 0.0001 Laser + sham +1.8; -57.1
RESOLVE study[76]	IVR for DME	3-arm RCT	BCVA and CMT	0.3 and 0.5 mg	1 mo	Naïve and refractory	1 yr	151	Group 1 (IVR 0.3, *n* = 51 eyes) 0.3 mg (0.05 mL) IV ranibizumab, 3 monthly injections Group 2 (IVR 0.5, *n* = 51 eyes) 0.5 mg IV (0.05 mL) ranibizumab, 3 monthly injections Group 3 (C, *n* = 49 eyes) sham	BCVA changes *P* value IVR 0.3 +11.8 SD6.6 < 0.0001 *vs* C IVR0.5 +8.8 SD11.0 < 0.0001 *vs* C C -1.4 SD14.2 CMT (μm) *P* value IVR0.3 -200.7 SD122.2 < 0.0001 *vs* C IVR0.5 -187.6 SD147.8 < 0.0001 *vs* C C -48.4 SD153.4
RISE study[77]	IVR for DME	3-arm RCT	BCVA and CMT	0.3 and 0.5 mg	1 mo	Naïve or refractory	2 yr	377	Group 1 (IVR 0.3 mg, *n* = 125 eyes) Group 2 (IVR 0.5 mg, *n* = 125 eyes) Group 3 (C, *n* = 127 eyes): sham injection	BCVA changes (letters): *P* value IVR0.3 +12.5 < 0.0001 IVR0.5 +11.9 < 0.0001 C +2.6 CFT (μm): IVR0.3 -250.6 < 0.0001 IVR0.5 -253.1 < 0.0001 C -133.4
RIDE study[77]	IVR for DME	3-arm RCT	BCVA and CMT	0.3 and 0.5 mg	1 mo	Naïve or refractory	2 yr	382	Group 1 (IVR 0.3 mg, *n* = 125 eyes) Group 2 (IVR 0.5 mg, *n* = 127 eyes) Group 3 (C, *n* = 130 eyes): sham injection	BCVA (letters) and CMT (μm): *P* value IVR0.3 +10.9, -259.8 < 0.0001 IVR0.5 +12.0, -270.7 < 0.0001 C +2.3, -125.8

DME: Diabetic macular edema; BCVA: Best corrected visual acuity; CMT: Central macular thickness. IVR: Intravitreal ranibizumab.

Table 3 Summary of the studies using intravitreal Pegaptanib for treatment of diabetic macular edema

Ref.	Purpose	Study design	Out comes measures	IVP dose	Interval of injection	Naive or refractory /DME	Duration of study	Number of eyes	Treatment regimen	Results
Cunningham *et al*[81]	IVP for DME	RCT	BCVA and CMT	0.3, 1 and 3 mg	1 mo	Naive	36 wk	172	Group 1 (IVP0.3, *n* = 44 eyes) 0.3 mg IV pegaptanib (90 μL) [median 5 injections (range 1-6)] Group 2 (IVP1, *n* = 44 eyes) mg IV pegaptanib (90 μL) [median 6 injections (range 3–6))] Group 3 (IVP3, *n* = 42 eyes) 3 mg IV pegaptanib (90 μL) (median 6 injections (range 1-6) Group 4 (C, *n* = 42 eyes): sham injection	BCVA changes (letters) *P* value IVP0.3 +4.7 0.04 IVP1 +4.7 0.05 IVP3 +1.1 NS C -0.4 CMT changes (μm,) IVP0.3 -68.0 0.02 IVP1 -22.7 NS IVP3 -5.3 NS C +3.7
Sultan *et al*[83]	IVP for DME	RCT	BCVA and CMT	0.3 mg	6 wk	Naive	2 yr	260	Group 1 (IVP, *n* = 133 eyes): 0.3 mg IV pegaptanib Group 2 (C, *n* = 127 eyes) sham injection	BCVA changes (letters) *P* value IVP +5.2 < 0.05 C +1.2 CMT (OCT): Decrease in CMT IVP ⩾ 25%: 31.7% NS ⩾ 50%: 14.6% NS C ⩾ 25%: 23.7% ⩾ 50%: 11.9%

DME: Diabetic macular edema; BCVA: Best corrected visual acuity; CMT: Central macular thickness; IVP: Intravitreal pegaptanib.

Table 4 Summary of the study using intravitreal Aflibercept for treatment of diabetic macular edema

Name of study	Purpose	Study design	Out comes measures	IVA Dose	Interval of injection	Naive or refractory /DME	Duration of study	Number of eyes	Treatment regimen	Results
DA VINCI[84,85]	IVVTE for DME	RCT	IVA f or DME	0.5 and 2 mg	1 and 2 mo	Naïve or refractory	1 yr	221	Group 1 (IVVTE1, *n* = 44 eyes): IVVTE, 0.5 mg every 4 wk Group 2 (IVVTE2, *n* = 44 eyes): IVVTE, 2 mg every 4 wk Group 3 (IVVTE3, *n* = 42 eyes): IVVTE, 2 mg for 3 initial mo then every 8 wk Group 4 (IVVTE4, *n* = 45 eyes): IVVTE, 2 mg for 3 initial months then as needed Group 5 (L, *n* = 44 eyes): laser photocoagulation Laser modified ETDRS protocol	BCVA changes (letters) *P* value IVVTE1 +8.6 0.005 IVVTE2 +11.4 < 0.0001 IVVTE3 +8.5 0.008 IVVTE4 +10.3 0.0004 L +2.5 CMT(μm) IVVTE1 -144.6 0.0002 IVVTE2 -194.5 < 0.0001 IVVTE3 -127.3 0.007 IVVTE4 -153.3 < 0.0001 L -67.9

DME: Diabetic macular edema; IVTL: Intravitreal triamcinolone plus laser; IVVTE: Intravitreal VEGF Trap Eye; IVA: Intravitral aflibercept.

Intravitreal fluocinolone implants

The efficacy of fluocinolone implant for treatment of DME has been evaluated in two clinical trials. In one of them (FAME study) 0.2 and 0.5 μg per day of fluocinolone was compared with sham injection in patients that were treated with laser. After two years, both doses showed a significant improvement in vision[90]. In the other study 0.59 mg of fluocinolone was compared with laser or no treatment. Significant improvement in VA was observed in the implant group during 9, 18, and 24 mo in comparison with the standard care group. Flucinolone implant group had a significantly higher proportion of eyes showing no evidence of increase in CMT at 6 mo, 1 year, and 2

Table 5 Summary of the studies using intravitreal steroid for treatment of diabetic macular edema

Agent	Number of patients	Total dose (daily release	Duration	Main outcomes
IVTA[86]	693	4 mg TA (Trivaris and triesence) (unknown)	Approximately 3 mo	Less favorable results *vs* photocoagulation at 24 and 36 mo
Fluocinolone acetonide implant (ILUVIEN)[90]	956	180 μg (0.5 μg or 0.2 μg/d)	Up to 3 yr	Generally favorable outcomes at 36 mo
Fluocinolone acetonide implant (retisert)[91]	197	500 μg FA (0.59 μg/d)	2.5 yr	Effective DME therapy at 36 mo, however high risks of cataract and glaucoma
Dexamethasone drug delivery system (ozurdex)[92]	171	750 μg dexamethasone (estimated approximately 6.25 μg/d)	Approximately 4 mo	Generally favorable outcomes at 90 d

DME: Diabetic macular edema; IV: Intravitreal; IVTA: Intravitreal triamcinolone; TA: Triamcinolone; FA: Fluocinolone acetonide.

years. The effect of flucinolone implant has persisted up to 30 mo according to these studies[91].

Intravitreal dexamethasone implants

Several clinical trials have shown the efficacy of intravitreal dexamethasone implant for the treatment of DME. In most of published studies use of 0.7 mg of the drug showed a significantly higher proportion of letter gain compared to no treatment group. However lower doses (0.35 mg) of dexamethasone implant did not show statistically significant improvement compared with observation. With further follow up (6 mo), no significant difference between both dexamethasone groups and no treatment group was observed[92]. In the second study, comparison was made between dexamethasone plus laser with laser alone. A better improvement of vision was reported in the dexamethasone plus laser group at 9 mo, However no significant difference between groups during 12 mo of follow up was detected[93] (Table 5).

INTRAVITREAL AND TOPICAL NSAIDS

Pivotal role of prostaglandins in formation of cystoids macular edema after cataract surgery has yielded that the use of NSAIDs, true inhibition of biosynthesis of prostaglandins, for treatment of DME. Many investigators have reported that immune reaction plays some roles in retinal vascular diseases such as DME. In addition to their role as inflammatory mediator, prostaglandins induce angiogenesis. Increase in prostaglandin E2 (PGE2), the major prostaglandin in the retina has been found in various pathologic conditions such as DME. One study demonstrated that PGE2 induces VEGF[94-96]. Topical nepafenac as a prodrug is a non-selective COX inhibitor and hydrolyze into amfenac by uveal tissue and retina. This agent can penetrate into the posterior segment and causes inhibition of some morphologic changes like leukostasis, apoptosis and degeneration of retinal capillary endothelial cells[97,98]. Two small case series showed topical nepafenac significantly decreased CMT and caused an improvement in VA in cases with DME[99,100]. Several studies demonstrated that topical NSAID may prevent cystoids macular edema (CME) after cataract surgery in cases with diabetes mellitus[101,102].

Two small case series in patients with refractory DME diabetic macular edema refractory to photocoagulation who received two different dosages (500 and 3000 μg) of intravitreal ketorolac, demonstrated a significant VA improvement with no meaningful decrease in macular thickness[103,104]. In one recent study[105] the efficacy of intravitreal diclofenac (500 μg/0.1 mL) with bevacizumab was compared in cases of naïve DME. They reported that in both groups visual acuity significantly improved and visual acuity in patients who received intravitreal diclofenac injection was better than patients who received intravitreal injection of bevacizumab up to 12 wk. However, this functional improvement was noticed without a reduction in macular thickness[105].

SAFETY OF USING INTRAVITREAL AGENTS

Serious ocular adverse effects of intraocular injections may include uveitis, endophthalmitis and retinal detachment. According to the available literatures, intravitreal bevacizumab injections for DME seem not to result in more sever ocular side effects than other treatments, however longer follow-up is still awaitening. The patients with DME are usually younger than patients with senile macular degeneration (AMD) and as a result, they may develop more cataract and glaucoma with multiple intravitreal injections. There are several studies that provide data on the systemic safety of intravitreal VEGF inhibitors. It should be noted that many of the published studies are not valid enough to detect significant differences among study groups with respect to low frequency adverse events. In the CATT study, the rates of serious systemic adverse effects such as CNS stroke, death and heart infarction were almost equal in cases who received either intravitreal bevacizumab or ranibizumab. The rate of severe systemic adverse events and hospitalizations were higher in bevacizumab-treated cases (24.1%) than those who had received ranibizumab (19%)[106]. However, on the basis of currently available literature, such greater systemic risks have not been reported

in DME patients yet. Another concern for treatment of DME by anti-VEGF agents is possible development of retinal atrophy, for which literature is still deficient. However recent sub analysis of the CATT study has evaluated more than 1000 patients with wet AMD to determine the risk factors for geographic atrophy (GA). Subjects had no visible GA at enrollment. Within two years treatment with either ranibizumab or bevacizumab, GA was developed in 18.3%. Risk factors for GA development comprised poor visual acuity, retinal angiomatous proliferation, foveal intraretinal fluid, monthly dosing, and treatment with ranibizumab. The authors recommend that patients be informed about the possible development of GA as a result of monthly anti-VEGF injection, particularly Ranibizumab in AMD cases[107]. Therefore, it can be concluded that in a similar fashion patients with DME may also be prone to development of retinal atrophy, considering their need for further intravitreal injections. This hypothesis needs to be proven by larger studies with long term follow up[108] because it is not still clear that development of GA in CATT study was due to progress in natural course of AMD alone or use of VEGF inhibitor agent. Furthermore cataract formation and increased IOP are common side effects of intravitreal corticosteroid injections and risk of interventional procedures, such as cataract surgery, laser trabeculoplasty, and incisional glaucoma surgery, increase with use of such agents. Outcomes of one clinical trial of IVTA plus laser *vs* laser treatment alone have demonstrated that 61% of patients with DME who had received IVTA required cataract removal *vs* 0% of patients receiving laser therapy alone after two years. Cataract progression was observed in approximately 43% of patients implanted with Retisert (fluocinolone) after one year follow up. Cataract removal was required in 91% of phakic eyes and 33.8% required surgery for ocular hypertention within four years. In the FAME study on phakic population, cataract surgery was performed in 80% of the 0.2 μg per day FAc group, 87% of the 0.5 μg per day FAc group, and 27% of the sham group[89,91,109]. FAME study reported that the percentages of patients who required incisional glaucoma surgery were 8.1% in 0.5 μg per day FAc group and 4.8% in 0.2 μg per day FAc group[109].

Endophthalmitis after intravitreal injections although rare, is a potentially vision-threatening complication and one recent study have estimated this risk to be about one in every 3000 injections or less. Additionally this study reported that bevacizumab, which was prepared by a compounding pharmacy, was associated with greater risks of developing contamination[110].

VITRECTOMY

Some pathologic vitreous changes has been involved as a cause of DME by several mechanical and physiological mechanisms, including macular traction and concentrating of vasopermeable factors in the macular area[111]. A recent published study by DRCR.net evaluated visual and anatomical outcomes of pars plana vitrectomy (PPV) without concomitant cataract surgery for DME in eyes with moderate vision loss and vitreomacular traction. According to this report although CMT was decreased in most of their cases, however visual acuity did not change and the results disclosed that gain of VA $\geqslant$ 10 letters was obtained in 38%, while 22% developed worsening of vision at 6 mo. Another report of DRCR.net interestingly demonstrated that achieving better visual outcomes observed on those cases who had a worse initial visual acuity and also in eyes which epiretinal membrane was removed[112,113]. Anyway, the results of vitrectomy in patients with DME without vitromacular traction are controversial; some studies have demonstrated that vitrectomy with or without ILM removal did not improve vision in DME cases without evident vitreoretinal traction[114,115]. But some other studies have demonstrated that vitreoretinal surgery with or without removal of internal limiting membrane had a beneficial effect in eyes with diffuse non-tractional DME[116,117]. The follower of this idea believes that by vitrectomy, oxygenation of the macula improves and on the other hand the clearance of vasopermeable factors such as VEGFs increases.

LASER

ETDRS disclosed that MPC (focal or grid) can lead to reduction of visual loss in at least 50% of cases. The efficacy of MPC may be attributed to closure of disturbed microaneurysms, although its real mechanism of effect is still unknown[118,119]. It has been hypothesized that by reduction of O2 demand following MPC, some autoregulation mechanisms cause a decrease in blood flow of retina and this eventually reduces edema[120,121]. Few biological studies suggested that the absorption of edema may be due to some changes in the biochemical processes inside the RPE cells[122-127]. Reduction of DME following grid MPC is a support hypothesis for indirect effect of MPC on macular edema[2,128-130]. In one published report two technique of MPC were compared: (1) modified-ETDRS (mETDRS); and (2) mild macular grid (MMG). In the latter technique small mild burns were placed in the whole area of macula, with or without edema, and also microaneurysms were not treated directly. After 1 year follow up, the MMG technique was shown to be less effective than mETDRS technique in reduction of CMT, although visual outcomes in both treatment groups was almost the same[131]. Interestingly one of the most important DRCR.net studies also confirmed the long term better effect of MPC in comparison to intravitreal triamcinolone injection for the treatment of DME. Based on this study short term (6 mo) effect of IVT was better than MPC. However long term effect of MPC was much better and an improvement of more than 5

letter was reported in 62% of caeses after 36 mo follow up[4,86,132]. Subthreshold laser photocoagulation using micropulse laser has recently been the focus of most recent attention for treatment of DME with variable and controversial results. Using this kind of laser may cause little or even no damage to the surrounding retina[132-134]. However future larger randomized studies should prove the result of these preliminary studies.

In conclusion, despite the enthusiasm for using several new pharmacologic agents for DME, laser photocoagulation still remains the gold standard for care of DME cases especially those with focal, non-center involving macular edema.

PROPHYLACTIC TREATMENT FOR DME IN ASSOCIATION WITH CATARACT SURGERY

Progression of DME and development of cystoid changes (CME) are very common after phacoemulsification and also other techniques of cataract removal in cases with diabetic retinopathy[135-137]. Increase in VEGF production following surgical trauma and induction of inflammation may be a cause for formation of CME[29]. Based on one report 6% of the controls and 12% of diabetic eyes developed CME, clinically up to 6 wk after cataract surgery. In this study, eyes with mild to moderate NPDR, and no macular edema was reported to be as good as normal eyes during 6 mo in terms of VA improvement[138]. One study has demonstrated that prophylactic post-operative ketorolac 0.4% may reduce the frequency and severity of macular edema in diabetic eyes after cataract surgery.

One small clinical trial assessed the role of intravitreal bevacizumab injection during cataract surgery in post-operative increase of CMT in cases with moderate or severe NPDR and CMT of less than 200 μm. This report showed that 4 wk after cataract surgery, their controls had a higher macular thickness in comparison to bevacizumab injected group. However, after 6 mo no major differences in CMT and post-operative visual acuity between two groups could be detected[139].

The management of established DME in the presence of cataract is even more important because in some diabetic patients with DME, performing MPC is not possible because of the presence of cataract. All types of cataract surgery even without any complication may worsen DME in such patients; therefore the management of these cases may be more challenging if they undergo phacoemulsification alone. In one retrospective study, the authors reported that phacoemulsification with combined IVB and IVT injection in patients with DME and cataract provided a decrease in CMT along with some gain in VA at 3 mo[140]. In cases with DME and concurrent cataract, some small case series have demonstrated that phacoemulsification and bevacizumab injection at the end of surgery may be helpful and provide some gain in vision. However, no significant change in postoperative CMT, was reported in one study that ranibizumab had been injected simultaneous with cataract surgery. Based on this report, the improvement in vision was due to cataract removal without important change in macular edema[141].

In conclusion, the prophylactic role of anti-VEGF therapy on development of DME and even CME in diabetic cases during cataract surgery is still not clarified and needs to be proven in larger studies with longer follow up. For established DME in the presence of cataract, however, the combination of IVB and phacoemulsification seems to be logical even in the absence of large supportive studies.

INITIAL MACULAR THICKNESS, PATTERNS OF DME AND RESPONSE TO TREATMENT

The development and progression of Ocular coherence tomography (OCT) technology has provided precise measurement and assessment of retinal layers in DME.

Changes in retinal layers in DME has been classified into four types: (1) spongy like retinal swelling; (2) CME; (3) subretinal fluid accumulation; and (4) retinal detachment due to vitreomacular traction[142-144]. CMT findings and parameters are important factors in making decision and selection of type of treatment in DME. It has been shown that foveal thickening more than 180 μm by OCT may be the earliest detectable sign of DME[58]. One study showed that MPC has a 50% chance to decrease CMT in cases with more than 60% increase in CMT in relation to normal value, while increasing CMT of more than 130% has the probability of less than 2.5% for such a decrease in CMT[145]. One study has demonstrated that in cases of DME with CMT of more than 300 μm had the worst response to MPC[146]. In another recently published report, it has been demonstrated that in short term (up to 6 wk) the eyes with various initial CMT showed a better VA improvement by IVB than MPC. This better response to IVB persisted only in the eyes with initial CMT of $\geqslant$ 350 μm up to 36 wk[147]. One study has evaluated the effect of different treatment modalities on morphological variants of DME and they have reported that the only beneficial effect of MPC was on spongy like DME[148]. Some studies have reported that the effectiveness of IVB on diffuse DME was dependent on the OCT pattern; it was more effective on spongy like patterns than those associated with CME and SRD[149,150]. Furthermore VA and CMT changes are not always parallel in DME and other factors like duration, amount and degree of edema, existence of hard exudate as well as macular ischemia could have confounding effects.

COST OF TREATMENT

The relative cost of bevacizumab and other anti-VEGF

agents has been another concern in clinical practice. A comparison between the costs of these agents has shown that wholesale prices of the medications range from $1950 per dose for ranibizumab, $1850 per dose for VEGF-Trap eye, and $995 per dose for pegaptanib, to less than $50 per dose for bevacizumab. Recently with availability of intravitreal corticosteroid implants, the cost of treatment is even growing higher. That is why the use of bevacizumab is increasingly becoming more popular and more acceptable throughout the world especially among uninsured patients and in developing countries[151,152]. One cost-benefit analyses study has been reported that multiple modalities for treatment of DME did not show significant changes in terms of cost benefit ratio. The following situations have been reported: (1) For DME cases with VA < 20/200, intravitreal triamcinolone caused a better benefit in comparison to MPC; (2) in pseudophakic cases with DME treatment by VEGF inhibitors was as equally effective as laser combined with IVT; (3) DME cases with VA of > 20/32 got more benefit by laser; and (4) use of aflibercept yielded an almost similar visual results in comparison to other treatment options. In conclusion with achieving similar results, choose of cheaper treatment option can yield 40% to 88% money saving[153].

OTHER TREATMENTS UNDER STUDY AND ONGOING TRIALS

Currently, several studies are evaluating the comparative efficacy of different other pharmacologic agents based on different molecular targets to prevent or delay the progression of DME and their results are still pending. Here, some of the most salient of these studies are breifely mentioned: comparing ranibizumab and bevacizumab, evaluation of two regimen for intravitreal ranibizumab, "treat and extend" and "PRN", using VEGF Trap (aflibercept) in VIVID and VISTA trials, comparing combined intravitreal Fasudil and Bevacizumab with intravitreal Bevacizumab alone[154,155]. There is a noticeable study conducting by DRCR.net through which the safety and efficacy of 3 VEGF inhibitors (ranibizumab, bevacizumab and aflibercept) are comparing.

FUTURE HORIZON

Therapeutic resistance is a major conflict for both patients and physicians. There are different types of resistance. The effect of therapy might be temporary thus retreatment is required. Therapeutic resistance is influenced by multiple factors, related to the patients, disease itself, time of therapeutic intervention, patient's comorbidities and other medications in use.

Diabetes induces inflammatory proteins that persist at elevated levels despite normoglycaemia. Retinal inflammation in diabetes is most likely driven by retinal glial cells and these cells release proinflammatory and neurotoxic substances such as tumor necrosis factor-α when they are activated[156]. Once the inflammatory cascade is activated, anti-VEGF therapies may not be effective. Anti-VEGF agents are useful at early stages when simple mechanisms are inducing edema, but in advanced stages corticosteroids affect a large number of pathways and seem to be more effective. In FAME study, it has been shown that only in patients with prolonged disease, the greatest potential for improvement by intravitreal Flucinolone was observed[109]. Future studies should focus on other recently diagnosed physiologic and biologic targets involved in inflammatory response in patients with diabetes.

SUMMARY AND PRACTICAL GUIDELINE FOR MANAGEMENT OF DIABETIC MACULAR EDEMA

For 30 years, MPC has been the mainstay of treatment for DME. Nevertheless, owing to substantial advances in understanding of DME mechanisms, the management of such cases has been dramatically changed. Recent clinical trials suggest that anti-VEGF therapy should be the first choice of treatment in cases with the center involving DME and visual acuity of 20/30 or less[157]. For cases with non-center involving DME macular photocoagulation is still the standard treatment. Current evidence is largely based on studies on ranibizumab and bevacizumab, although regarding aflibercept, additional data are forthcoming. Bevacizumab or ranibizumab injection should be administered on a monthly basis for at least 3 visits and then as needed depending on the visual acuity stability and OCT findings during follow-up[157]. One most recent published randomized clinical trial on 660 cases compared 2 mg aflibercept with bevacizumab 1.25 mg and ranibizumab 0.3 mg. After one year follow up it was concluded that all three agents improved vision but the relative effect depended on baseline visual acuity. In cases with mild initial visual acuity loss no significant difference among the study groups could be detected. However in cases with worse initial visual acuity aflibercept was more effective for improvement of vision. No significant difference in the rates of serious adverse events between the groups was reported[158]. For cases in which the response to anti-VEGF treatment is unsatisfactory, ETDRS laser treatment should be administered after 6 mo[157]. In cases of DME with peripheral capillary non-perfused area, targeted laser photocoagulation of the involved area has been recommended even in the absence of proliferative changes. For advanced non-responding cases to anti-VEGF agents, intravitreal corticosteroid implants can be tried out. When vitreomacular traction is detected by spectral domain OCT, vitrectomy is indicated; such cases may also benefit from adjunctive intravitreal anti-

VEGF and corticosteroid therapy too[157].

DESCRIPTION OF EVIDENCE

Literature search was conducted in September 2013 in PubMed and Scholar Google with no date restriction and was limited to studies published only in English. The search strategy used the terms including diabetic macular edema, the treatment of diabetic macular edema, systemic therapy for diabetic macular edema, intravitreal bevacizumab, ranibizumab, aflibercept, pegaptanib, triamcinolone, dexamethasone, fluocinolone, NSAIDs for the treatment of DME, the safety of intravitreal drugs, pattern of diabetic macular edema, macular ischemia, and the dose and frequency of intravitreal drug injections.

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MINIREVIEWS

Current understanding and management of aggressive posterior retinopathy of prematurity

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Abstract

Aggressive posterior retinopathy of prematurity (ROP), previously referred to as "Rush disease", is a rapidly progressive form of ROP. This form of ROP typically presents in very low birth weight babies of early gestational age. Historically, anatomical and functional outcomes have been poor with standard treatment. This review is designed to discuss current knowledge and treatment regarding this aggressive form of ROP. Recommendations regarding management of these difficult cases are detailed.

Key words: Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity; Photographic Screening for Retinopathy of Prematurity; Aggressive posterior retinopathy of prematurity; Retinopathy of prematurity; Intravitreal bevacizumab; Early Treatment of Retinopathy of Prematurity Study; Stanford University Network for Diagnosis of Retinopathy of Prematurity

Core tip: Neonates with aggressive posterior retinopathy of prematurity often have unfavorable visual outcomes due to the aggressive and destructive nature of the disease. Treatment options, including laser and anti-vascular endothelial growth factor therapy can change the course of the disease, but both with potential side effects. Case studies and recommendations regarding the management of these complicated cases are reviewed.

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INTRODUCTION

Retinopathy of prematurity (ROP) occurs in premature infants of early gestational age and low birth weight. While screening and treatment options have advanced, it remains a major cause of childhood blindness in middle and high income countries[1]. Aggressive posterior ROP (APROP) is a rapidly progressing form of the disease characterized by "plus" disease and a more posterior location. The advent of anti-vascular endothelial growth factor (VEGF) therapy for the treatment of retinal neovascularization has provided a new treatment

approach for ROP[2,3]. The purpose of this article is to review the current knowledge regarding ROP and discuss treatment guidelines regarding APROP.

CLINICAL FEATURES AND PATHOGENESIS

In normal retinal development, vasculogenesis begins around 17 wk postmenstrual age (PMA)[4]. Vessels originate at the optic nerve and grow peripherally towards the ora serrata. Normal development can continue until about 39-40 wk, near the time of birth[4].

Abnormal angiogenesis related to ROP can be divided into two phases of oxygenation[4]. Phase I begins at the time of premature birth when increased levels of oxygen relative to the *in utero* environment cause downregulation of VEGF. A decrease in VEGF terminates vessel formation at the vascular-avascular junction. In Phase Ⅱ, large areas of avascular retina trigger the release of hypoxia-induced factors, which leads to greater VEGF production. In turn, elevated VEGF drives the abnormal angiogenesis characteristic of ROP. Elevated VEGF levels in eyes with active ROP have been well documented. For example, in infants with Stage 4 ROP, VEGF is present in the vitreous at significantly higher levels compared to non-ROP controls[5]. Infants with active neovascularization demonstrate the highest levels of VEGF, further confirming the causative impact of VEGF in ROP pathogenesis.

In addition to the role in retinal development and ROP pathogenesis, VEGF is an important growth factor in normal development of many organ systems, including central nervous system pathways, lungs, and solid organs[6,7]. The long term effect of VEGF suppression following anti-VEGF therapy in the eye or systemic circulation is unknown.

Stages and zones

ROP is characterized by zones and stages. Zone 1 is a circular area extending from the optic disc with a radius twice the distance from the center of the disc to the center of the macula. Zone 2 forms a ring around Zone 1 extending to the nasal ora serrata. Zone 3 is the remaining retinal area on the temporal ora.

Stage 1 ROP is defined as a flat demarcation line between the vascular and avascular regions of the retina. Progression to Stage 2 is indicated by the development of an elevated ridge at the avascular/vascular junction. Stage 3 is signified by abnormal neovascularization at the ridge. Stage 4 has two designations. Stage 4A is a partial retinal detachment not involving the macula and Stage 4B is a partial retinal detachment including the macula. Stage 5 is total retinal detachment. Vascular activity is denoted by the presence of "plus disease" which indicates increased blood flow to the point of causing vascular dilation and tortuosity. Other indicators of plus disease include engorgement of the iris vessels, vitreous haze, and pupillary rigidity.

APROP (formerly known as Rush disease) is defined as Zone 1 or posterior Zone Ⅱ ROP with Stage 3 and the presence of plus disease. The neovascularization often appears flat and anterior to the ridge tissue. In APROP, eyes can rapidly progress from Stage 1 to Stage 3 with a high risk for progressing to retinal detachment.

EPIDEMIOLOGY

Indicators for the potential development of ROP are low birth weight and early gestational age. In the Early Treatment of Retinopathy of Prematurity Study (ETROP), which enrolled infants born from 2000-2002, the incidence of ROP amongst infants weighing < 1251 g was 68%[8]. This finding was very similar to the earlier Cryotherapy for Retinopathy of Prematurity study (CRYO-ROP), which enrolled patients from 1986-1987, suggesting a fairly steady incidence of ROP despite advances in neonatal care and better outcomes for premature infants[8]. The ETROP study did show an increased percentage of infants with Zone 1 ROP over the CRYO-ROP study, possibly due to the greater survival of extremely premature infants. The ETROP study also indicated a racial disparity, with Caucasian infants more likely to develop severe ROP than African-American infants[8]. Worldwide, developing nations are reporting more cases of ROP cases as they acquire better neonatal care. Other developing countries report ROP at higher average birth weights, suggesting the need to tailor screening protocols based on the population[1].

After ROP develops, many eyes spontaneously regress without treatment. It is common for the areas of ROP to involute with down grading of the stage followed by continued growth of normal retinal vessels into the periphery. A study of 82 infants with subthreshold disease showed a predictable course of involution[9]. All 82 infants reached complete involution with the majority reaching complete involution between 39-75 wk PMA. On average, the higher the stage of ROP, the longer it took for involution to be completed[9].

Unfortunately APROP usually leads to less favorable outcomes. One study from Australia found that in a cohort of 304 infants with ROP, 2.5% had developed APROP[10]. Rates of retinal detachment for infants exhibiting APROP treated with laser vary, but appear to remain high. A study of 22 eyes treated by laser found an 18.2% detachment rate[11]. A larger study of 109 eyes with APROP treated by laser showed a 17.4% detachment rate[12]. Risk factors for progressing to detachment despite confluent laser photocoagulation were gestational age of less than 29.5 wk, hemorrhages, need for repeat treatment, and new onset fibrovascular traction after treatment. The BEAT-ROP study showed a lower detachment rate, with only a 2.9% detachment rate for APROP treated with intravitreal bevacizumab and 2.7% for laser[2]. However, BEAT-ROP focused on outcomes within 54 wk post-menstrual age, and data indicates that bevacizumab treatment may delay the timeline of recurrence[3].

CLINICAL TRIALS

Treatment

The standards set by the cCRYO-ROP trial recommended treatment at Stage 3 ROP with at least 5 contiguous or 8 total clock hour sectors in Zone 1 or 2 with plus disease[13-25]. The ETROP study built upon these results by setting an earlier treatment threshold for laser photocoagulation[26-41]. The study showed treatment benefit for any stage in Zone 1 with plus disease, Stage 3 Zone 1 with or without plus disease, and Stage 2 or 3 with plus disease in Zone 2 (type 1 ROP). For type 2 ROP (Zone 1, Stage 1 or 2 without plus and Zone 2, Stage 3 without plus) close observation is recommended.

The BEAT-ROP trial tested the efficacy of intravitreal bevacizumab (IVB) injection versus laser ablation in a randomized trial[2]. Recurrence of ROP within 54 wk PMA for laser in Zone 1 disease was significantly higher than with IVB (42% *vs* 6%). However for Zone 2 disease the difference between the two therapies was not significant. The trial also showed that while laser permanently ablated the retina, IVB allowed for continued vascularization in the peripheral retina.

A chief critique of Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) was the trial's end point of 54 wk. The mean age at which infants with Zone 1 ROP were treated was 34.5 ± 1.4 wk for IVB and 33.7 ± 1.6 wk for laser. The mean interval between recurrence and treatment was 19.2 ± 8.6 wk for IVB and 6.4 ± 6.7 wk for laser in infants with Zone 1 ROP. Given the ranges encompassed by 1 or 2 standard deviations from the means, many recurrences may have fallen outside of the 54 wk endpoint[3]. This suggests that for Zone 1 ROP, where IVB showed a statistically significant better outcome, the BEAT-ROP trial may not have given a full assessment of bevacizumab's ability to prevent recurrence. Furthermore this study was not powered for safety.

Several case reports and case series have indicated the need for a longer duration of monitoring after bevacizumab treatment[42-44]. In one series, 17 eyes in 9 patients developed recurrence after IVB at a mean age of 34.1 wk PMA[43]. The mean age of recurrence was 49.3 wks and the mean age of retinal detachment was 58.4 wk PMA. This series also indicated an altered pattern of recurrence after IVB. Recurrence after laser often presents anterior to the vascular-avascular junction. After IVB, recurrence was noted more posterior to the initial site of extraretinal fibrovascular proliferation. Anterior recurrence was seen in 47% of the eyes. Posterior recurrence alone appeared in 12% of eyes, and 41% showed in both areas[43]. Whereas regression following laser is predictable, treatment with IVB appears to result in short term regression with less predictable long term reactivation.

In addition to the late recurrence following IVB, there are concerns about the systemic effects of administering IVB injections in infants. While not statistically significant, out of the seven infants who died before the BEAT-ROP endpoint, five were in the IVB treatment arm. One study of 11 patients identified bevacizumab in the systemic circulation after IV injection[45]. There was a statistically significant negative correlation between the serum VEGF titers and the serum bevacizumab titers. Given the role of VEGF in various developmental processes, systemic bevacizumab may pose a risk to preterm infants.

Screening

There has been great interest in the use of telemedicine in screening for ROP. With the number of pre-term infants rising globally and a limited pool of ROP screeners, telemedicine presents a method to satisfy the high demand for screening. The Photographic Screening for Retinopathy of Prematurity (PHOTO-ROP) study investigated the use of telemedicine in conjunction with conventional bedside indirect ophthalmoscopy (BIO)[46-48]. After imaging both fundi using the RetCam-120, traditional BIO was performed. The reading center or bedside clinician then determined which eyes demonstrated clinically significant ROP (CSROP), or ROP severe enough to warrant on-site examination, or ETROP type 1, ROP severe enough to warrant treatment. Using BIO as the reference standard, digital imaging provided sensitive and specific detection of CSROP and ETROP type 1, suggesting it is an effective tool to use in conjunction with traditional screening. Using the reading center data as the reference standard, imaging showed high specificity and positive predictive values, but weaker sensitivity, negative predictive value, and accuracy, suggesting the limitations for using digital imaging as the primary screening modality[47].

The Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP) structured their trial to better assess the ability for digital imaging to be used as the primary screening tool[49-54]. Their study used RetCam Ⅱ imaging without simultaneous bedside indirect ophthalmoscopy. Infants were imaged with the same frequency as recommended for BIO. If treatment-warranted ROP (TW-ROP) was identified, follow-up took place using BIO. Digital imaging showed a 100% sensitivity, 99.8% specificity, 93.8% positive predictive value, and 100% negative predictive value[43]. The success of the SUNDROP trial suggests that as imaging technology improves, so does the validity of using a telemedicine approach for ROP screening.

LONG TERM OUTCOMES

Laser

ROP is associated with the long term development of myopia, and more severe ROP is associated with worse visual outcomes[13,55]. Given this baseline tendency towards myopia, it has been difficult to definitively prove a connection between laser treatment and refractive error. Both the CRYO-ROP and ETROP trials found high

rates of myopia in patients receiving ablation, but credited the tendency to greater severity of ROP[13,26]. One retrospective study showed that of 43 infants treated by laser, 73% scored 6/12 (20/40) or better on the Snellen acuity chart[56]. However, there was a strong correlation between the refractive error of each eye and the number of laser burns applied. Of the infants with APROP, all of whom received treatment, 40% developed myopia[10]. The authors cautioned that the correlation between refractive error and laser burns includes multiple confounding factors like the need for more laser burns stemming from more severe ROP. In the APROP subset they concede that laser often yields poor functional vision despite improved structural outcomes.

Intravitreal bevacizumab

The landmark BEAT-ROP trial yielded favorable results, but questions over the full efficacy and safety of the drug remain[2-3]. The BEAT-ROP trial enabled a comparison of refractive outcomes between laser treatment and bevacizumab[57]. There was a significantly lower percentage of infants treated with IVB who developed high and very high myopia. The BEAT-ROP group also found a strong correlation between refractive error and laser burns. Given the study's design of comparing infants with similar severity ROP but different treatment methodology, these results indicate laser ablation plays a role in the development of myopia. Myopia of prematurity, regardless of ROP status, stems from abnormal anterior segment development. The BEAT-ROP group hypothesizes that the greater preservation of the peripheral retina and extension of retinal vessels past the neovascular ridge in IVB treated eyes allows for the continued production of local growth factors necessary for normal anterior segment development, leading to better refractive outcomes[57].

While IVB seems to allow for better visual outcomes, it can result in abnormal vascularization of the retina. One study examined outcomes in infants with APROP or posterior Zone Ⅱ with plus disease that regressed after one IVB injection[58]. Fluorescein angiography (FA) revealed incomplete vascularization of the peripheral retina in 11/20 (55%) of eyes. Of these, 9 showed fluorescein dye leakage at the vascular-avascular junction. In comparison, laser therapy completely prevents vascularization past the ridge. Treatment with IVB provides an opportunity for continued vascularization in the periphery, but the development of abnormal peripheral retina is also a potential outcome.

Adult ROP: Baby boomers and the ablation generation

Prior to the 1940s premature birth was often fatal, resulting in no recognition of ROP. With advancement in neonatal survival, ROP emerged as a diagnosis with the baby boomer generation. One study examining 47 patients aged 45 or older that were diagnosed at birth with ROP, but received no treatment. In this study, 88.4% had posterior segment pathology resulting from ROP[59]. Retinal folds were seen most frequently, with retinal detachments, retinal pigmentation, lattice-like degeneration, and retinal tears. Early onset cataract was noted with 74.5% having undergone cataract surgery. Within this group, 51.2% exhibited BCVA of 20/200 or worse[59].

The CRYO-ROP trial began in the 1980s and ushered in the next wave of ROP infants, the ablation generation. The most recent publication reports the visual acuity and anatomical outcomes at 15 years[14]. Of particular interest was the development of retinal folds and detachments in eyes which had no evidence of unfavorable outcomes at 10 years. During this 5 year period, identification of progressive retinal disease occurred in 4.5% (6) of treated eyes and in 7.7% (7) of control eyes. Data from both generations highlights the importance of maintaining close follow-up with ROP patients well past infancy.

Report of a case: A male infant was born at 24 wk gestation with a birth weight of 420 g. At 32 wk, anterior segment examination showed a prominent tunica vasculosa lentis in both eyes and dilated fundus examination showed Stage 2, Zone 1 disease with preplus (Figure 1). One week later, the ROP had significantly worsened with presence of plus disease and flat Stage 3 with extensive hemorrhages at the junction of avascular and vascular retina.

Informed consent for intravitreal bevacizumab injection was obtained from the patient's parents. Intravitreal bevacizumab was injected without complication. One week following treatment, regression of Stage 3 and reduction of plus disease occurred. The active ridge completely regressed and normal vasculogenesis continued into Zone 2. At approximately 55 wk, the patient underwent an exam under anesthesia with Retcam photos and fluorescein angiography. Examination showed apparently normal vascularization to mid Zone 2 (Figure 2). Fluorescein angiogram showed evidence of the previous ridge (arrow). At the junction of vascular and avascular retina, areas of neovascularization were present with extensive areas of avascular retina in the periphery (Figure 3). Concern regarding late reactivation of ROP following IVB injection prompted laser photocoagulation to areas of avascular retina.

TREATMENT RECOMMENDATIONS

The data from the BEAT-ROP study, shows improved outcomes for Zone 1 APROP treated with IVB compared to laser, but no difference for posterior Zone 2 disease. Considering the importance of VEGF in the developing neonate[5,6] and the unknown long term systemic effects of IVB, the use of IVB is generally reserved for Zone 1 APROP. Reactivation and late retinal detachment following IVB is a serious concern with multiple reports citing retinal detachments beyond 60 wk PMA[43,44]. In order to closely monitor these neonates,

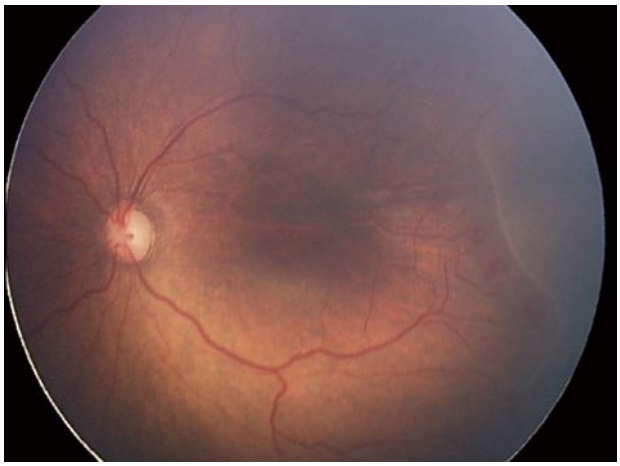

Figure 1 Previous 24 wk infant post menstral age of 32 wk presents with stage 2, zone 1 with preplus which rapidly progresses to aggressive posterior retinopathy of prematurity within 1 wk (image not shown).

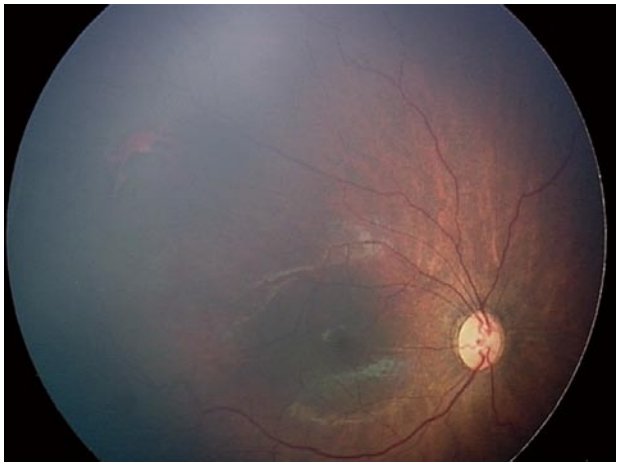

Figure 2 Previous 24 wk infant status post bevacizumab injection a for aggressive posterior retinopathy of prematurity. RetCam imaging of the right eye reveals regressed retinopathy of prematurity with vascularization into zone 2. Plus disease is no longer present. The patient is post menstral age of 55 wk.

we recommend weekly examinations following IVB until the child is discharged from the NICU. Following discharge, the infant is examined every 2 wk until 55-60 wk and then undergoes an exam under anesthesia, fluorescein angiogram and Retcam photos. If incomplete vascularization or neovascularization is noted, laser photocoagulation is performed. The infants are followed until 70 wk or until noted to have complete vascularization at time of EUA and FA. In our series of over 30 infants, no retinal detachments have occurred following this protocol.

CONCLUSION

APROP can present with uncontrolled neovascularization in Zone 1 that can rapidly progress to retinal detachment. Treatment with laser ablation alone can result in less than favorable outcomes. Use of anti-VEGF

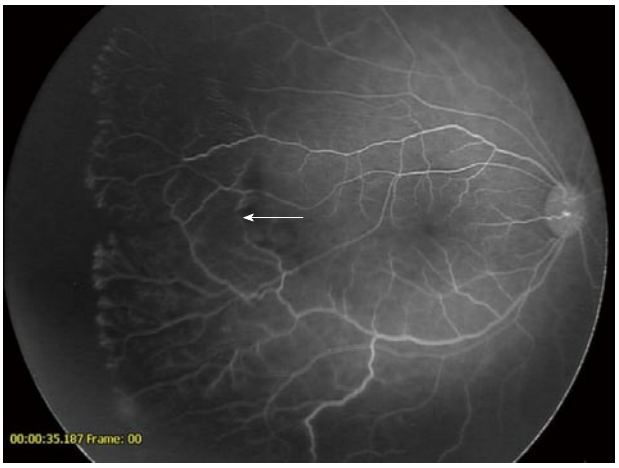

Figure 3 Fluorescein angiogram of the right eye reveals extensive areas of avascular retina. There is a well demarcated line of advancing vessels with areas of neovascularization present. The arrow depicts the original area of the stage 3 ridge in zone 1 at the time of bevacizumab injection.

agents has shown promising results for the treatment of APROP, but because of unknown systemic and long-term effects on neonatal development, judicious use is recommended. In addition, long term follow up after IVB is necessary to monitor for the development of late recurrence.

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ORIGINAL ARTICLE

Retrospective Study

Traumatic cataracts in children: Visual outcome

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Abstract

AIM: To review results of traumatic cataracts in children.

METHODS: Only those pediatric patients who fitted in the definite inclusion criteria were considered for study enrollment. They were further examined for any kind of co-morbidities because of trauma, operated upon for traumatic cataracts with intraocular lens implantation. Amblyopia if present was treated. All were re-examined at the culmination of six-week postoperative period. According to the Birmingham Eye Trauma Terminology System the traumatic cataract cases were divided into group 1 (open globe) and group 2 (closed globe), and then determinants of visual acuity were compared.

RESULTS: There were 544 eyes in group 1 and 127 eyes in group 2 in our study of 671 eyes with pediatric traumatic cataracts. Visual acuity at the end of 6 wk after surgery in the operated eye was > 6/60 in 450 (82.7%) and ⩾ 6/12 in 215 (39.4%) eyes in the open globe group and > 20/200 in 127 (81.8%) and ≥ 6/12 in 36 (28.4%) eyes in the closed globe group (P = 0.143), and the difference between the groups was not significant in children. Overall, 402 (39.4%) eyes gained ⩾ 6/60 and > 5/12 in 238 (35.4%) cases. Surgical treatment caused a significant difference in visual outcome (P = 0.000). When we compared achieved visual outcome with ocular trauma score predicted vision, no significant difference was found.

CONCLUSION: Traumatic cataracts in children may have better outcome and ocular trauma score is a useful predictive method for the ocular trauma in children.

Key words: Traumatic cataract; Betts; Ocular trauma score; Visual outcome

Core tip: We have studied visual outcome in children in one of the largest published database for cases of traumatic cataracts in children. We have also studied validity of ocular trauma score in case of ocular injuries in pediatric age group.

Shah MA, Shah SM, Chaudhry AH, Pannu S. Traumatic cataracts in children: Visual outcome. *World J Ophthalmol* 2015; 5(2): 80-85 Available from: URL: http://www.wjgnet.com/2218-6239/full/v5/i2/80.htm DOI: http://dx.doi.org/10.5318/wjo.v5.i2.80

INTRODUCTION

Very few studies have attended to the challenge of ocular injuries in rural regions, though trauma itself is one of the leading reasons behind monocular blindness in the developed countries[1,2]. The probable causes of ocular injury vary in rural and urban regions and need to be looked into. Aiming available means in the right direction to strategize the prevention of such injuries requires knowledge regarding the etiology of injury[3,4]. Pediatric ocular trauma essentially is prognostically bad and hence is a burden to the society. This can be taken care of to some extent with the help of aforementioned knowledge of etiology of injury.

Trauma to the eye is capable of giving rise to cataracts. There is no difference in the methods which are employed to assess the visual outcome.

The standardization of ocular injury documentation was greatly facilitated following the introduction of Birmingham Eye Trauma Terminology System (BETTS)[5] in regular practice. Hence, the reviewing of visual outcomes will prove to be revealing. In this study, visual outcomes in eyes operated for cataracts resulting from trauma were analyzed at our centre. Also, post-treatment predictors of visual outcomes were studied. Our hospital is situated in an area which is predominantly inhabited by tribal populace (around 4.2 million), where certified eye specialists cater to them with a quality service at a very reasonable and low cost.

MATERIALS AND METHODS

We started this study following attaining authorization from hospital management and research board. Guardians' (of the patients) written permission was also procured. In 2002 this research was proposed as a retrospective review. All children ($\leqslant$ 18 years old) who developed traumatic cataracts in any of the eyes detected and treated between 2003 and 2009 were registered in this research. Only those who were ready to join and those without any other severe physical collateral injury were taken in. All details related to the cases were obtained from our records and brought together by employing a pre-checked online form. A full history consisting of particulars of trauma, details of its management and type of surgery done to treat it was accumulated. BETTS format (available online) was employed first and subsequent visits reports were collected. In a similar way surgery details were gathered.

All patients with traumatic cataracts were split into two parts, namely, closed globe and open globe injuries. Open globe injuries were again sub-grouped into rupture and laceration injuries. This later type was again subdivided into trauma resulting in intraocular foreign body, perforating and penetrating traumas. Contusion and lamellar laceration were the sub-categories of closed ball injuries.

The usual demographic aspects were recorded, but the main attention was given to the facts related to the time and type of injury, the objects responsible for injury and movement as well as activity at the time of trauma. Also verified were the treatment and details of earlier examinations.

By means of accepted protocol, thereafter, all the patients underwent examination, in which we tested visual acuity according to age as per guidelines laid down by American Academy of Ophthalmology (AAO). Slit lamp examination was carried out for anterior segment.

Depending on the extent of lenticular opacity, all the cataracts were categorized as membranous cataract in those cases where organized lens matter and capsule formed a visually inseparable membrane, rosette cataract where rosette pattern was noted, and white soft cataract when the anterior chamber displayed loose cortical matter along with ruptured capsule.

To assess posterior segment B-scan examination was carried out where media did not permit, otherwise indirect ophthalmoscopy with +20D lens was done[6].

The operative procedure was chosen depending on the state of lens and other ocular tissues. Cataracts with large, harder nuclei were necessarily dealt with by phacoemulsification technique. Softer ones were aspirated either co-axially or bimanually. Membranous cataracts were operated through pars-plana or anterior route with membranectomy and anterior vitrectomy.

Corneal injuries were prioritized and hence repaired first, whereas cataract was managed later on. However, recurrent inflammation was a rule rather than exception in patients who were operated upon previously for injury, which made the anterior vitreous body hazy and required anterior or pars plana vitrectomy and/or capsulectomy (in older patients). In children under two years of age pars plana lensectomy along with anterior vitrectomy was a regulation procedure. Here primary intraocular lens implantation was not considered.

As far as medical management is concerned, cycloplegics and steroids in topical form were given in all cases of which did not have infection. The severity of inflammation in anterior and posterior segments in the surgically treated eye decided the extent of medical treatment. All operated cases were reviewed on the 1st, 3rd, 7th and 14th day. At the end of six weeks of surgery, refraction was ascertained. The routine follow-up review was planned after 3 d, then every week for six weeks, every month for three months and quarterly for 1 year.

Visual acuity of all patients was checked according to AAO directives on all review visits. Slit lamp examination for anterior and indirect ophthalmoscopes for the posterior segment was essentially done at follow-ups. Visual acuity more than 20/60 at the time of refraction examination was considered as having an acceptable grade of vision.

All these follow-up examination data were fed online by means of a format developed by the International

Table 1 Age and sex distribution

	Sex		Total
	F	M	
0 to 2	6	7	13
3 to 5	27	52	79
6 to 10	74	179	253
11 to 18	88	238	326
Total	195	476	671

F: Female; M: Male.

Table 2 Patient entry and visual outcome at six weeks

Vision	Entry		Total
	Self	ORD	
< 1/60	19	0	19
1/60 to 3/60	68	30	98
6/60 to 6/36	74	53	127
6/24 to 6/18	125	55	180
> 6/12 to 6/9	178	53	231
Uncooperative	11	5	16
Total	475	196	671

P = 0.000. ORD: Outreach department.

Society of Ocular Trauma and sent to a Microsoft Excel Spreadsheet. Time and again thorough appraisal of the data was done on a regular basis to make sure its completion. SPSS17 was utilized to evaluate the data, and a biostatician certified data analysis report.

RESULTS

In this study we had 671 patients, all of whom had traumatic cataracts. 544 (81.07%) eyes had open globe injuries, and 127 (18.9%) were of closed globe injury type. 70.9% (496) were males, and 29.2% (196) were females. The average age was 10.53 ± 4.2 years (range, 0-17 years) (Table 1).

Analysis (by means of statistical tests and cross tabulation) of many factors related to demographic details such as socio-economic condition (79% belonged to lower stratum), locality (95% were from rural backdrop) and patient entry (P = 0.000) revealed that none of them had any significant bearing on visual acuity after 6 wk (Tables 2-5).

Causative agent of injury and person's physical movements as well as type of activity were also not noteworthy reasons as far as six-week post-operative visual acuity was concerned. The most frequent agent causing trauma was stick.

Evaluation of visual acuity before and after surgery revealed that management did essentially increase the visual acuity (Table 6).

Co-axial or bi-manual aspiration of the ruptured cataract with cortical matter in the anterior chamber (in 48.6% cases among the open globe group) showed better visual acuity (Table 7).

In eyes which were greatly inflamed, we routinely did primary posterior capsulotomy with anterior vitrectomy. This also did not influence the six-week postoperative visual acuity to any extent.

Table 3 Objects causing the injury

Object	Number (n)	Percentage (%)
Ball	9	1.4
Cattle horn	11	1.7
Cattle tail	2	0.3
Finger	5	0.8
Fire	19	2.8
Glass	7	1.1
Thorn	23	3.4
Others	59	8.8
Sharp object	59	8.8
Stone	72	10.7
Unknown	60	8.8
Stick	345	51.4
Total	671	100.0

Table 4 Activity at the time of the injury

Object	Number (n)	Percentage (%)
Fall	11	1.7
Making a fire	19	2.8
Housework	110	16.4
Employment	38	5.6
Others	85	12.7
Walking	8	1.1
Playing	370	55.1
Travelling	22	3.4
Unknown	8	1.1
Total	671	100.0

The achieved visual acuity after 6 wk of surgery was > 6/60 in 450 (82.7%) and ⩾ 6/12 in 215 (39.4%) eyes in the open globe group and > 20/200 in 127 (81.8%) and ⩾ 6/1236 (28.4%) eyes in the closed globe group (P = 0.143), and the difference between the groups was not significant in children. Overall, 402 (39.4%) eyes gained ⩾ 6/60 and > 5/12 in 238 (35.4%) cases. Surgical treatment caused a significant difference in visual outcome (P = 0.000). When we compared achieved visual outcome with ocular trauma score predicted vision, we did not find a significant difference (Tables 8-10, Figure 1).

DISCUSSION

Our study compared patients with open- and closed-globe injuries who developed traumatic cataracts. Open globe injury associated cataracts had improved vision following surgical treatment (Tables 6 and 7).

Various authors have reported different results in children with traumatic cataracts. Shah *et al*[4] reported 20/60 or better in 56% of their cases; Gradin Morgan[7,8] reported 20/60 or better in 64.7%; Krishnamachary *et al*[9] 6/24 or better in 74%; Kumar *et al*[10] 6/18 or better in 50%; Staffieri *et al*[11] 6/12 or better in 35%; Bekibele *et al*[12] 6/18 or better in 35.6%; Brar *et al*[13] 0.2 or better in 62%; Cheema *et al*[14] 6/18 in more than 68%; Karim *et al*[15] 0.2 or

Table 5 Age and visual outcome at six weeks

Postoperative vision	Age category				Total
	0 to 2	3 to 5	6 to 10	11 to 18	
< 1/60	2	32	76	83	193
1/60 to 3/60	1	3	37	35	76
6/60 to 6/36	7	25	29	19	80
6/24 to 6/18	1	8	35	40	84
6/12 to 6/9	1	8	53	89	151
6/6 to 6/5	1	2	21	60	84
Uncooperative	0	1	2	0	3
Total	13	79	253	326	671

P = 0.000.

Table 6 Pre-treatment and post-treatment vision comparison

Postoperative vision	Preoperative vision						Total
	< 1/60	1/60 to 3/60	6/60 to 6/36	6/24 to 6/18	6/12 to 6/9	Uncoo-perative	
< 1/60	182	4	6	0	1	0	193
1/60 to 3/60	70	5	1	0	0	0	76
6/60 to 6/36	55	8	15	1	0	1	80
6/24 to 6/18	71	10	2	1	0	0	84
6/12 to 6/9	125	17	7	1	1	0	151
6/6 to 6/5	64	10	6	4	0	0	84
Uncooperative	2	0	0	0	0	1	3
Total	569	54	37	7	2	2	671

P = 0.000.

Table 7 Comparative study of morphology of cataract and visual outcome

Postoperative vision	Morphology					Total
	Memb-ranous	Rosette	Soft fluffy	Sublu-xated	Total	
< 1/60	45	1	71	2	74	193
1/60 to 3/60	15	2	29	0	30	76
6/60 to 6/36	15	4	29	0	32	80
6/24 to 6/18	20	2	39	0	23	84
6/12 to 6/9	16	6	90	0	39	151
6/6 to 6/5	3	7	53	2	19	84
Uncooperative	0	0	3	0	0	3
Total	114	22	314	4	217	671

P = 0.000.

Table 8 Type of injury and visual outcome at 6 wk

Vision	Category		Total
	Closed	Open	
1/60	6	12	18
1/60 to 3/60	19	80	99
6/60 to 6/36	29	97	126
6/24 to 6/18	39	138	177
> 6/12	30	206	236
UC	6	9	15
Total	127	544	671

P = 0.05. UC: Uncorrected vision.

Table 9 Comparison of ocular trauma scorevisual outcome

Final visual outcome	Ocular trauma score					Total
	1	2	3	4	5	
UC	2	2	9	0	2	15
No PL	6	13	0	0	0	19
HM, PL	2	27	72	0	0	101
1/200 to 19/200	0	15	112	0	0	127
20/200 to 20/50	0	40	134	4	0	178
⩾ 0/40	0	9	218	4	0	233
Total	10	106	545	8	0	671

P = 0.000. OTS: Ocular trauma score; UC: Uncooperative; HM: Hand movement; No PL: No light perception.

Table 10 Comparison of final visual outcome according to ocular trauma score

Vision category	OTS-1		OTS-2		OTS-3		OTS-4	
	Achi-eved final visual acuity	OTS Predi-cted final visual acuity	Achi-eved final visual acuity	OTS Predi-cted final visual acuity	Achi-eved final visual acuity	OTS Predi-cted final visual acuity	Achi-eved final visual acuity	OTS Predi-cted final visual acuity
No PL	75	73	12	16	0	2	0	1
PL HM	25	17	25	26	13.5	11	0	2
1/200 to19/200	0	7	14	14	21.3	15	0	2
20/200 to 20/50	0	2	38	38	24.5	28	50	21
⩾ 20/40	0	1	0	4	40.5	44	50	74
P	0.265		0.22		0.22		0.172	

Values are percentage of cases. No PL: No light perception.

better in 62%; Knight-Nanan *et al*[16] 20/60 or better in 64%; Bienfait *et al*[17] 0.7 in 27%; and Anwar *et al*[18] 20/40 or better in 73%.

Using a polymethyl methacrylate lens, Verma *et al*[19] reported a visual outcome similar to that found in our study. Eckstein *et al*[20] and Zou *et al*[21] reported that primary intraocular lens implantation is important for a better visual outcome, similar to our results. Also similar to our results, Vajpayee *et al*[22] and Gupta *et al*[23] reported primary insertion of an intraocular lens with posterior capsule rupture.

Shah *et al*[24] reported that a better visual outcome was achieved when intervention was done between 5 and 30 d in adults with traumatic cataracts. As in our study, Rumelt *et al*[25] found no significant difference between primary and secondary implantation. Staffieri *et al*[11] performed primary implantation in 62% of cases *vs* 82% in our study. Kumar *et al*[10] and Verma *et al*[19] advocated primary posterior capsulotomy and vitrectomy for a better outcome; our results concurred with these findings.

We are not aware of any such study. Shah *et al*[26] reported a comparison between open- and closed-globe injuries in the general population. We are also not aware of another large series of successfully treated traumatic cataracts in children. In our study, final visual outcomes were achieved according to the

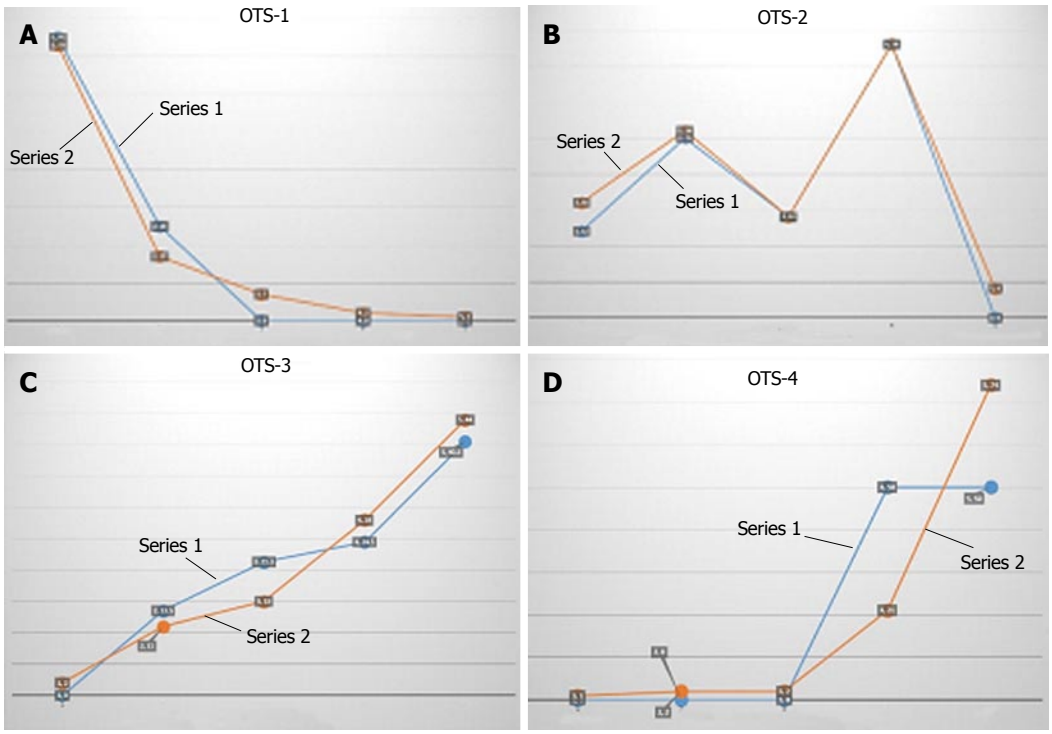

Figure 1 Comparison between ocular trauma score and achieved results. A: Comparison between OTS and achieved results in OTS-1 score category; B: OTS-2 score category; C: OTS-3 score category; D: OTS-4 score category. OTS: Ocular trauma score.

OTS[27] prediction in children with traumatic cataracts. Lesniak *et al*[28] reported no significant differences between the final visual acuities and the visual acuities predicted by OTS in children. Sharma *et al*[29] proposed that the OTS calculated at the initial examination may be of prognostic value in children with penetrating eye injuries. However, Unver *et al*[30] suggested that OTS calculations may have limited value as predictors of visual outcome in a pediatric population. Lima-Gómez *et al*[31] reported estimates for a 6-mo visual prognosis, but some of the variables required evaluation by an ophthalmologist. Using the OTS, 98.9% of the eyes in the general population could be graded in a trauma room. Knyazer *et al*[32] reported the prognostic value of the OTS in zone-3 open globe injuries, and Yu Wai Man *et al*[33] claimed equal prognostic effectiveness of both the OTS and CART in the general population. Although similar findings have been reported by others[32,33], our study presents one of the largest reported databases following cases of pediatric traumatic cataracts classified according to BETTS. Despite the long time delay between injury and treatment in many of the cases in our study, the OTS was still relevant.

In conclusion, satisfactory visual outcome can be achieved in children with traumatic cataracts, and no significant difference was found amongst open and closed globe injuries in pediatric age group.

This study shows the comparative evaluation of patients having closed globe injuries and open globe injuries in those cases who developed traumatic cataract. Final visual result achieved in cases of traumatic cataracts in pediatric patients can fairly be foretold with the help of ocular trauma score.

COMMENTS

Background

Ocular trauma in children in less explored area of visual outcome following cataract surgery in children was studied here.

Research frontiers

Surgical treatment has made a significant difference in outcome. No significant difference found in open globe and closed globe injury groups. Ocular trauma score is a valid predictive model for visual outcome in children.

Innovations and breakthroughs

This study addressed the probably largest published database for traumatic cataracts in children classified according to the Birmingham Eye Trauma Terminology System, and compared visual outcome according to ocular trauma score.

Applications

Morphological consideration of traumatic cataracts and treatment guidelines according to the morphological classification may be useful.

Terminology

BETTS: Birmingham Eye Trauma Terminology System; OTS: Ocular trauma score.

Peer-review

This study presents important data that would be of interest.

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SYSTEMATIC REVIEWS

Systematic review of macular ganglion cell complex analysis using spectral domain optical coherence tomography for glaucoma assessment

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Abstract

AIM: To review the use of spectral domain optical coherence tomography (SD-OCT) for macular retinal ganglion cells (RGC) and ganglion cell complex (GCC) measurement in glaucoma assessment, specifically for early detection and detection of disease progression.

METHODS: A systematic review was performed by searching PubMed, Medline, and Web of Science for articles published in English through July 2014 describing the various macular SD-OCT scanning strategies developed for glaucoma assessment. The review focused on papers evaluating the use of macular RGC/GCC SD-OCT to detect early glaucoma and its progression. The search included keywords corresponding to the index test (macular ganglion cell/RGC/GCC/Spectral domain OCT), the target condition (glaucoma), and diagnostic performance. The RGC/GCC SD-OCT scanning strategies used to assess glaucoma of most commonly used SD-OCT instruments were described and compared. These included the Cirrus high definition-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, United States), RTVue (Optovue, Inc., Fremont, CA, United States), Spectralis (Heidelberg Engineering, Heidelberg, Germany) and the 3D OCT 2000 (Topcon Corporation, Tokyo, Japan). Studies focusing on the ability of RGC/GCC SD-OCT to detect early glaucomatous damage and on the correlation between glaucomatous progression and RGC/GCC measurement by SD-OCT were reviewed.

RESULTS: According to the literature, macular RGC/GCC SD-OCT has high diagnostic power of preperimetric glaucoma, reliable discrimination ability to differentiate between healthy eyes and glaucomatous eyes, with

good correlation with visual filed damage. The current data suggests that it may serve as a sensitive detection tool for glaucomatous structural progression even with mild functional progression as the rate of change of RGC/GCC thickness was found to be significantly higher in progressing than in stable eyes. Glaucoma assessment with RGC/GCC SD-OCT was comparable with and sometimes better than circumpapillary retinal nerve fiber layer thickness measurement.

CONCLUSION: An increasing body of evidence supports using macular RGC/GCC thickness as an indicator for early glaucoma. This might be a useful tool for monitoring disease progression.

Key words: Glaucoma; Optical coherence tomography; Spectral domain optical coherence tomography; Retinal ganglion cell; Ganglion cell complex

Core tip: Glaucoma is an optic neuropathy characterized by structural changes followed by functional deficits. Diagnosing early signs of the disease and detecting its progression are challenging. This review focuses on the most common macular retinal ganglion cells/ganglion cell complex spectral domain optical coherence tomography (SD-OCT) scanning strategies developed for glaucoma assessment (Cirrus high definition-OCT, RTVue, Spectralis and 3D OCT 2000) described in the literature published through July 2014; specifically, studies that assessed the ability to diagnose early glaucoma and glaucoma progression. The findings highlight the central role of macular SD-OCT in identifying subjects with early and progressive anatomical and functional glaucomatous damage.

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INTRODUCTION

Glaucoma is the leading cause of irreversible loss of vision, globally. In 2013, glaucoma was estimated to affect 64.3 million people 40-80 years-of-age, with this number increasing to 76.0 million by 2020 and 111.8 million by 2040[1]. Glaucoma is an optic neuropathy characterized by loss of retinal ganglion cells (RGC), thinning of the circumpapillary retinal nerve fiber layer (cpRNFL) and the neuroretinal rim, and increased cupping[2,3]. It is often asymptomatic until the later stages and structural alterations usually appear before functional changes and prior to repeatable visual field deficits[4-6]. Early detection of the disease can lead to earlier treatment that might improve prognosis. The primary challenges in glaucoma assessment are diagnosing early signs of the disease and detecting disease progression.

Various tools are used for glaucoma assessment. Optical coherence tomography (OCT) has become a main modality. OCT is a micron-level, diagnostic method that uses 800-840 nm wavelength infrared light to provide high-resolution, non-invasive neural imaging. It is based on the principal of Michelson interferometry[7]. An interference pattern is produced by splitting a beam of light into two. The two bouncing beams, one beam from the targeted tissue and the other from a reference mirror, and then recombined through the use of semi-transparent mirrors[8].

OCT has become a well-established tool for diagnosing and monitoring diseases of the retina, choroid[8-11] and optic nerve head (ONH)[12-14], as well as anterior-segment conditions[15,16]. Time-domain (TD) and more recently spectral-domain (SD) OCT have significantly improved the ability to manage patients with retinal diseases and glaucoma[17].

OCT is commonly used for glaucoma to assess ONH and retinal nerve fiber layer (RNFL) thickness[18]. RNFL thickness measurements with OCT have good reproducibility, an established structural–functional relationship and can detect glaucoma progression[19,20]. OCT has improved the ability to discriminate healthy eyes from those with glaucoma[17,20,21]. However, cpRNFL thickness measurement with OCT is limited by significant variations in the shape and size of the ONH, refractive error, axial length and peripapillary atrophy. Healthy eyes sometimes have unusual anatomical features that confuse currently available diagnostic software, and they are mistakenly classified as abnormal[18]. Myopia is a very good example of this problem, as it is commonly associated with high variability in RNFL. Several studies reported that the average RNFL becomes thinner as the degree of myopia increases[22-24]. Moreover, RNFL thickness frequently varies by sector in patients with myopia, as their temporal RNFL tends to be much thicker[25,26]. Thus, caution should be taken while observing RNFL thickness in eyes with various cpRNFL abnormalities and pathologies, such as myopia, as normative data provided by OCT may be unreliable in these cases.

Glaucoma evaluation by macular imaging was first suggested by Zeimer *et al*[27]. The macula has several physiological and anatomical advantages. As the RNFL is comprised of RGC axons, assessing the RGC may be a more direct way to measure ocular damage due to glaucoma than measurement of the cpRNFL thickness. The macula is the only place where more than one RGC body is found in the ganglion cell layer of the retina and because the body of the cell is much larger than the soma, it might be easier to detect glaucoma related cellular damage[27,28]. Additionally, more than half of all the RGC in the retina are in the macula. Thus, macular

Table 1 Properties of the various spectral domain optical coherence tomography instruments

	Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin CA, United States)	RTVue (Optovue, Inc., Fremont, CA, United States)	Spectralis (Heidelberg Engineering, Heidelberg, Germany)	3D OCT 2000 (Topcon Corporation, Tokyo, Japan)
Macular layer measured	GCIP	GCC	The entire retina (from =BM to ILM)	Macular RNFL GCIP (GCL+) GCC (GCL++)
Maps provided	Thickness map, deviation map and sectors	Thickness map, deviation map and significance map	Thickness map, asymmetry map, hemisphere asymmetry map and mean thickness map	Thickness map, significance map, average thickness asymmetry map
Grid dimensions (mm)	6 × 6	7 × 7	8 × 8	6 × 6

OCT: Optical coherence tomography; GCIP: Combined retinal ganglion cell (RGC) and inner plexiform layer (IPL); RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex = macular RNFL + GCIP; BM: Bruchs membrane; ILM: Internal limiting membrane.

scanning allows most of the RGC to be sampled. In general, the shape of the RGC layer in the macular area is more consistent among healthy individuals than the RNFL in the ONH area. The macular RGC might provide a more sensitive measure than the cpRNFL because variations in this layer are likelier be result from pathological changes rather than normal variations[29].

MATERIALS AND METHODS

A systematic review was performed by searching PubMed, Medline, and Web of Science for articles published in English through July 2014 describing the various macular SD-OCT scanning strategies developed for glaucoma assessment. The search included keywords corresponding to the index test macular/RGC/ganglion cell complex (GCC) SD-OCT, the target condition (glaucoma), and diagnostic performance. Studies were included if they met the following criteria: (1) the study assessed diagnostic performance of macular/RGC/GCC SD-OCT in glaucoma patients; (2) the study evaluated early detection of glaucoma; and (3) the study assessed glaucoma progression. Relevant references used in included studies were also evaluated.

RESULTS

Using RGC/GCC OCT to assess glaucoma is a relatively new concept. Systematic review of the literature revealed an increasing number of papers dealing with this subject. SD-OCT has enabled measurements of the RGC in the macula and the retinal GCC, including the RNFL[30,31]. GCC thickness is defined by the distance from the internal limiting membrane to the outer boundary of the inner plexiform layer (IPL), which comprises the inner 3 layers of the retina (RNFL, ganglion cell layer and inner plexiform layer). Glaucoma affects all of these three layers[32]. Another way to evaluate glaucomatous macular damage is to measure the entire retinal thickness rather than ganglion cell layer alone, as is done by the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). Kita *et al*[33] introduced a new parameter, the ratio of macular GCC thickness divided by the corresponding total retinal thickness (G/T). In a study conducted on a Japanese population to differentiate between healthy eyes and those with open angle glaucoma, a decreased G/T ratio was found in the early stages of glaucoma. However, Holló *et al*[34] showed that the diagnostic accuracy of the G/T ratio in Europeans was consistently lower than measurements of RNFL thickness and GCC parameters provided by several software.

Most commonly used SD-OCT instruments for glaucoma assessment

Various macular scanning strategies were developed for glaucoma assessment using SD-OCT. The most commonly used SD-OCT instruments are Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, United States), RTVue (Optovue, Inc., Fremont, CA, United States), Spectralis (Heidelberg Engineering, Heidelberg, Germany) and 3D OCT 2000 (Topcon Corporation, Tokyo, Japan).

The macular scanning methodology for glaucoma assessment employed by each of the devices is explained below. Table 1 compares the properties of the various SD-OCT instruments.

Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, United States): The Cirrus HD-OCT evaluates the thickness of the ganglion cell and IPL combined (Figure 1A), using the Macular Cube 200 × 200 or 512 × 128 scan patterns. The scan generates data in a 6 mm × 6 mm grid that consists of 200 frames of horizontal linear B-scans with 200 A-scan lines per B-scan. The segmentation software calculates the thickness of the macular ganglion cell-inner plexiform layer from an elliptical annulus centered on the fovea (thickness map) (Figure 1B) and calculates the thicknesses of the combined ganglion cell and IPL. The results are compared to normative data (Deviation map) (Figure 1C). The ganglion cell analysis segmentation algorithm divides the elliptical annulus of the Thickness Map into 6 equal sectors expressed in micrometers. Each spoke represents the average number of pixels along that spoke that lie within the measurement annulus (Figure 1D)[29,35-38].

RTVue (Optovue, Inc., Fremont, CA, United States): The RTVue measures the GCC by scanning 1

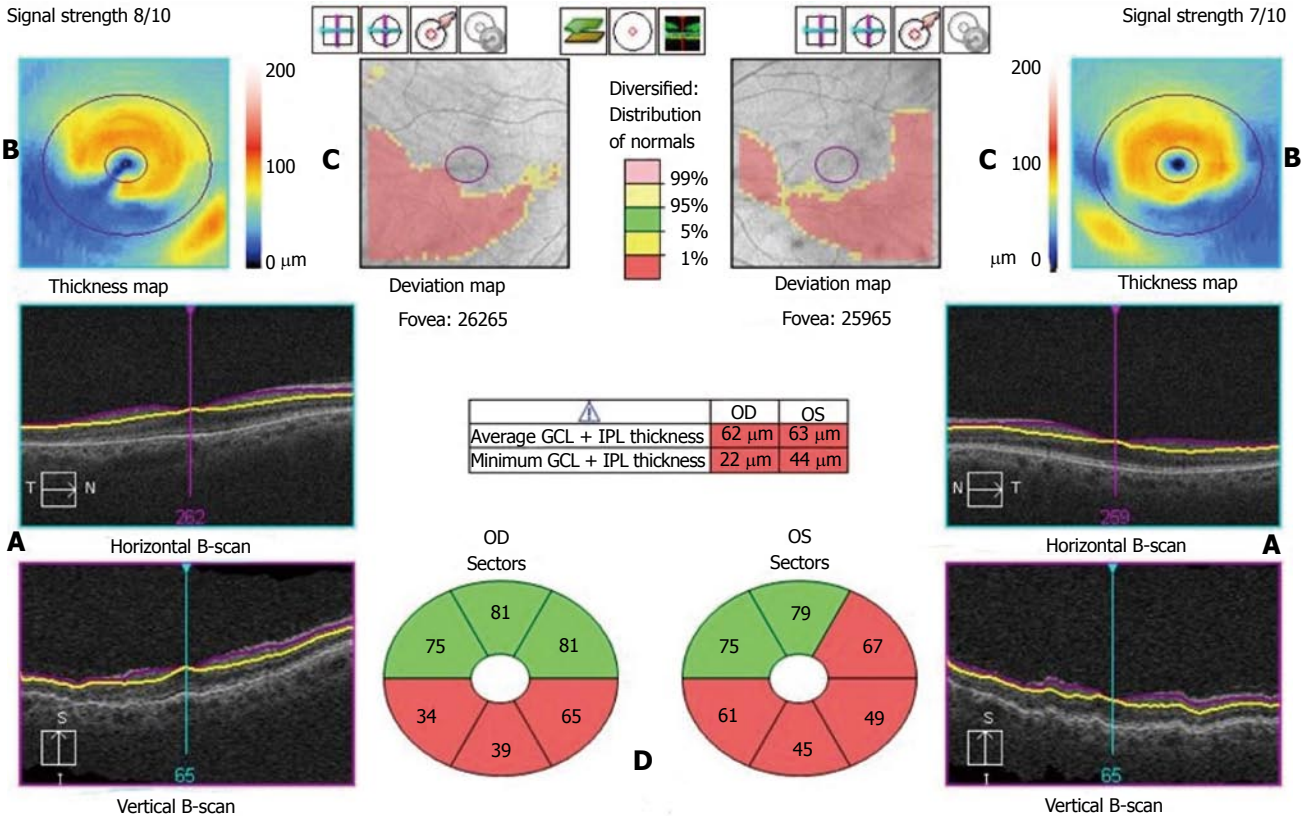

Figure 1 Cirrus HD-optical coherence tomography. A: Segmentation. Horizontal and vertical B-scans. The purple line represents the inner boundary of the ganglion cell layer and the yellow line represents the outer boundary of the inner plexiform layer; B: Thickness map. Calculation of the ganglion cell layer (GCL) + inner plexiform layer (IPL) thickness data from an elliptical annulus, 6 mm × 6 mm grid, centered on the fovea; C: Deviation map. Comparison of the GCL + IPL thickness results to a normative database; D: Sectors. Ganglion cell analysis segmentation algorithm that divides the elliptical annulus of the thickness map into 6 equal sectors expressed in micrometers. Each spoke represents the average of the pixels along that spoke that lie within the measurement annulus.

horizontal line and 15 vertical lines at 0.5 mm intervals covering a 7 mm^2 region centered on the fovea. It obtains 14928 A-scans within 0.6 s. The OCT scans are processed to provide a map of the thickness of the GCC (Figure 2A). It also provides pattern-based parameters of focal loss volume (FLV) and global loss volume (GLV). GLV corresponds to the total deviation map and FLV to the pattern deviation map that is used with visual field tests[18]. A deviation map is calculated by comparing the thickness map to the normative databases (Figure 2B)[39,40]. RTVue also provides a significance map that illustrates the areas where there is a statistically significant change from normal (Figure 2C).

Spectralis (Heidelberg Engineering, Heidelberg, Germany): The Spectralis OCT measures the entire retinal thickness rather than ganglion cell layer. It uses 61 lines (30° × 25° OCT volume scan) to measure the retinal thickness in the posterior pole for each eye in a central 20° area. A color-coded thickness map for an 8 x 8 grid centered on the foveal pit is shown (Figure 3A). The grid is symmetrical to the fovea-to-disc axis of each eye. The Spectralis examines asymmetry between the eyes (Figure 3B). It also displays the asymmetry between the superior and the inferior hemisphere of each eye (hemisphere asymmetry) (Figure 3C)[41,42]. It also provides a mean thickness map (Figure 3D).

3D OCT 2000 (Topcon, Inc., Tokyo, Japan): The Topcon 3D OCT 2000 measures the RNFL thickness, the RGC with the IPL (GCIP), and the GCC. It uses raster scanning of a 7 mm^2 area that is centered on the fovea with a scan density of 128 (horizontal) × 512 (vertical) scans (Figure 4A). The boundaries of the anatomical layers are determined by the program software (version 8.00; Topcon, Inc., Tokyo, Japan) using a validated, automated segmentation algorithm. The macular inner retinal layers (MIRL) analysis software detects the center of the fovea at the macular cube automatically, and selects a 6 mm × 6 mm region centered at the foveal center. The software divides the macular square into a 6 × 6 grid containing 100 cells of 0.6 mm × 0.6 mm, to assess regional abnormalities in MIRL thickness. Average regional thickness of GCC, GCIP and RNFL in each cell is calculated and compared to the normative database of the device[43,44] (Figure 4B).

Table 2 summarizes the characteristics of the major studies reviewed in this paper.

DISCUSSION

Comparing results between different SD-OCT devices

The literature comparing results between different SD-OCT devices is relatively sparse. Previous studies revealed that cpRNFL measurements from healthy

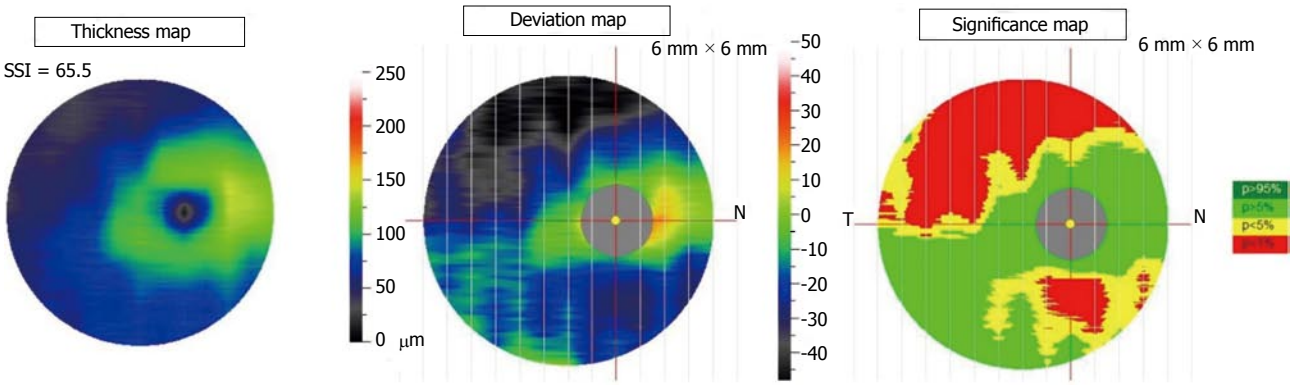

Figure 2 RTVue. A: Thickness map. The thickness map is color coded where thicker regions of the ganglion cell complex are displayed in hot colors (yellow and orange), and thinner areas are displayed in cooler colors (blue and green); B: Deviation map. Calculated based on comparing the thickness map to the normative databases. The deviation map shows the percent loss from normal as determined by the normative database; C: Significance map. Shows regions where the change from normal reaches statistical significance. The significance map is color-coded where green represents values within the normal range (P = 0.05-0.95), yellow indicates borderline results (P < 0.05), and red represents outside normal limits (P < 0.01).

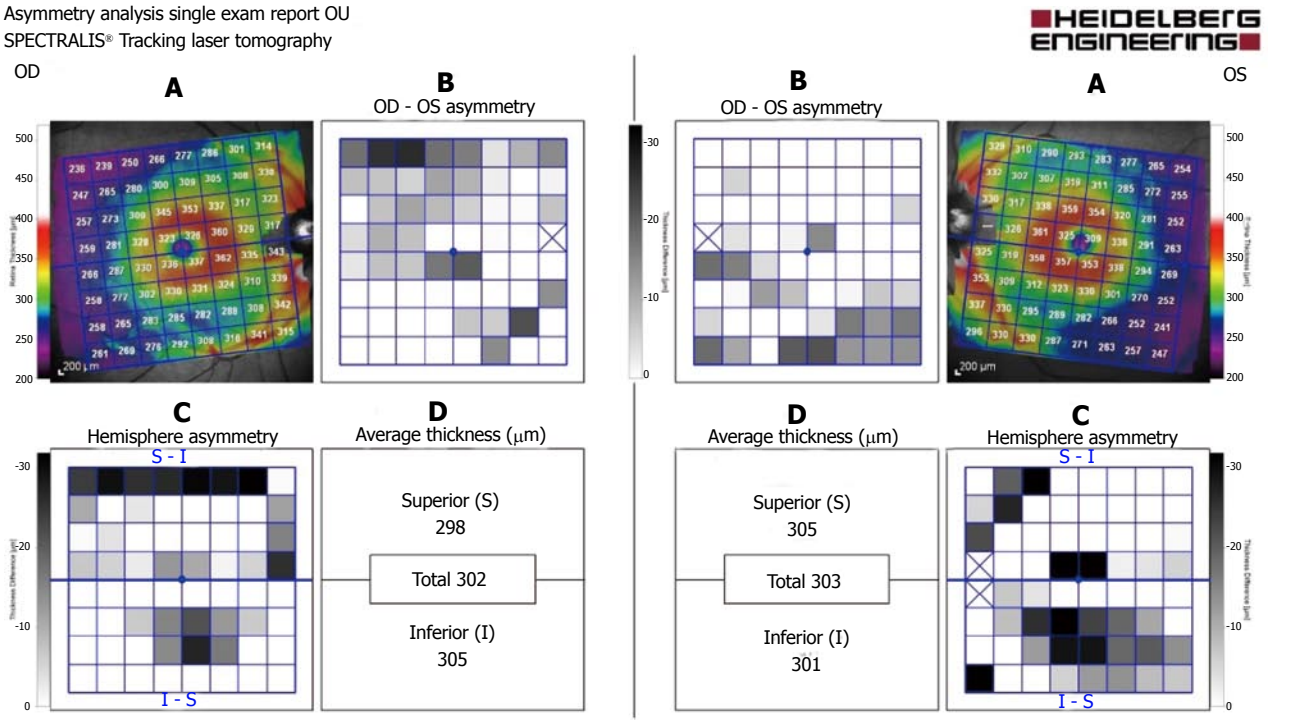

Figure 3 Spectralis. A: Thickness map - the entire retinal thickness in the posterior pole displayed as a color coded thickness map for an 8 × 8 grid centered on the foveal pit positioned symmetrically to the fovea-disc axis; B: Asymmetry map - examination by grid of the asymmetry between the thicknesses in the corresponding cell of the fellow eye. Asymmetry color scale - darker grey indicates larger differences. The closer the value is to zero (white color), the better the symmetry; C: Hemisphere analysis - displays the asymmetry between the superior and the inferior hemisphere of each eye. The fovea-disc axis is the horizontal symmetry line. The lower half compares the inferior to the superior; D: Mean thickness - represents the mean retinal thickness for the superior and inferior hemisphere, as well as the total mean thickness over the entire 8 × 8 grid.

controls using several devices varied and could not be interchanged[45,46]. Nonetheless, the diagnostic performance of most devices was similar when measuring cpRNFL thickness for glaucoma detection[47]. The Cirrus OCT and 3D OCT devices demonstrated similar accuracy when detecting a localized RNFL defect[48]. Furthermore, review of the literature revealed only a few papers that compared RGC/GCC SD-OCT measurements from different OCT devices in glaucoma patients. Kim *et al*[48] compared the GCC parameters between Cirrus OCT and 3D OCT. Among the macular GCC parameters of the 3D OCT device, inferior macular RNFL thickness had the highest sensitivity (81.2% at a specificity of 80%) and the largest area under the curve (AUC) (0.89)[48].

Akashi *et al*[49] compared the macular analysis results of the Cirrus, RTVue and 3D OCT in glaucoma patients. They found that the use of average GCC thickness for diagnosing glaucoma stages did not differ significantly among the three SD-OCT instruments.

Table 2 Summary of major studies investigating macular spectral domain optical coherence tomography for glaucoma assessment

Ref.	SD-OCT instrument	Patients	Type of glaucoma assessment	Main outcomes
Tan *et al*[39]	RTVue	310 eyes: 125 normal, 76 PPG, 109 PG	Glaucoma detection	GCC thickness had significantly higher diagnostic power than macular retinal thickness in differentiating between PPG and normal eyes
Kim *et al*[43]	3D OCT 2000	204 eyes: 64 normal, 68 PPG, 72 early PG	Glaucoma detection	GCC thickness steadily decreased from normal to PPG to early glaucoma. GCIP and GCC, but not mNFL were significantly different between PPG and controls and had similar discrimination ability as cpRNFL analysis
Lee *et al*[44]	3D OCT 2000	63 early PG eyes, 33 with and 30 without paracentral VF defects	Assessment of paracentral VF defects	Regional structural assessment of MIRL was a better indicator of paracentral scotoma than cpRNFL measurements (AROC 0.77 *vs* 0.644, respectively)
Akashi *et al*[49]	Cirrus, RTVue, 3D OCT 2000	232 eyes: 87 normal, 145 PG	Glaucoma detection ability in different SD-OCT instruments	Diagnosis of glaucoma with average GCC thicknesses was similar between the three SD-OCT instruments. RTVue exhibited better diagnostic abilities than Cirrus and 3D OCT 2000 for superior GCC thickness
Rolle *et al*[50]	RTVue	271 eyes: 163 with positive family history of POAG, 108 eyes without	Glaucoma detection	RNFL superior, GCC average, GCC superior and GCC inferior were significantly thinner and the GLV was higher in healthy eyes with a positive family history of POAG than in normal eyes without history
Kim *et al*[51]	Spectralis	106 PG eyes	Assessment of macular thickness and visual field defects	A significant relationship between VFS and MRT values was found and was strongest in the arcuate region. About 17% structural loss was necessary to detect functional loss
Inuzuka *et al*[52]	Cirrus	67 PG eyes	Glaucoma detection	GCC thickness of the inner or outer sector of the parafovea decreased as the corresponding hemifield defect increased. GCC thickness changes in apparently normal hemifield correlated with progression of the glaucomatous defects
Seong *et al*[53]	RTVue	167 eyes: 65 normal, 102 NTG	NTG assessment	MIRL thickness was strongly correlated and glaucoma discrimination ability was comparable with cpRNFL thickness in early VF defects. cpRNFL had better diagnostic ability than MIRL in eyes with advanced or peripheral VF defects
Na *et al*[55]	RTVue	173 eyes: 68 normal, 105 PPG	Glaucoma detection	PPG patients had significantly reduced GCC thickness in all sectors compared to healthy subjects. Superior GCC thickness average was best for detecting localized RNFL defects
Rao *et al*[56]	RTVue	106 eyes: 34 PPG, 72 with large physiologic optic disc cupping	Glaucoma detection	GCC parameters had moderate diagnostic ability to differentiate PPG from large physiologic cups. Inferior quadrant GCC thickness had the best AROC (0.75)
Iverson *et al*[57]	RTVue	97 eyes: 23 normal, 74 PPG	Glaucoma detection	GCC thickness had high specificity (91%) in normal eyes and moderate specificity (77%) in glaucoma suspects. About half of GCC measurements classified as outside normal limits were not replicable
Mwanza *et al*[58]	Cirrus	99 eyes: 49 normal, 50 early PG	Glaucoma detection	GCIP parameters were significantly thinner in the glaucoma compared to the control group. Diagnosis based on at least 1 abnormal GCIP parameter yielded 88% sensitivity and 81.6% specificity
Kim *et al*[60]	RTVue	186 PG eyes	Structural-functional relationship	All GCC parameters significantly correlated with best corrected visual acuity in severe, but not in early-to-moderate glaucoma patients
Leung *et al*[62]	Cirrus	222 eyes: 72 normal, 150 PG	Impact of age on glaucoma progression evaluation	Age-related change in macular measurements affected analysis of glaucoma progression. This was more substantial in macular than in cpRNFL progression
Sung *et al*[65]	Cirrus	98 advanced PG eyes	Glaucoma progression detection	Difference in the rate of change of average macular thickness was significant between progressors and non-progressors, but not in average cpRNFL thickness
Na *et al*[66]	Cirrus	279 PG eyes	Glaucoma progression detection	Differences in the rate of change of average macular and cpRNFL thickness were significant between progressors and non-progressors
Naghizadeh *et al*[67]	RTVue	68 eyes: 17 normal, 51 PG	Glaucoma progression detection	GLV and FLV detected structural progression even with mild functional progression. Progression rates were significantly different between progressing and stable eyes
Anraku *et al*[68]	RTVue	56 PG eyes	Glaucoma progression detection	Baseline GCC (average and inferior hemifield) were significantly thinner in fast progressors compared to slow progressors

SD-OCT: Spectral-domain optical coherence tomography; PPG: Pre-perimetric glaucoma; PG: Perimetric glaucoma; GCC: Ganglion cell complex; GCIP: Combined retinal ganglion cell and inner plexiform layer; mNFL: Macular nerve fiber layer; cpRNFL: Circumpapillary retinal nerve fiber layer; VF: Visual fields; MIRL: Macular inner retinal layers; AROC: Area under the receiver operating characteristics curve; POAG: Primary open-angle glaucoma; GLV: Global loss volume; VFS: Visual field sensitivity; MRT: Mean retinal thickness; NTG: Normal tension glaucoma; FLV: Focal loss volume.

However, the RTVue provided better measurement of the superior hemi-field GCC thickness than did Cirrus and 3D-OCT.

Early detection of glaucoma using macular SD-OCT

Diagnosing the early signs of the disease can be challenging and macular analysis with SD-OCT for this

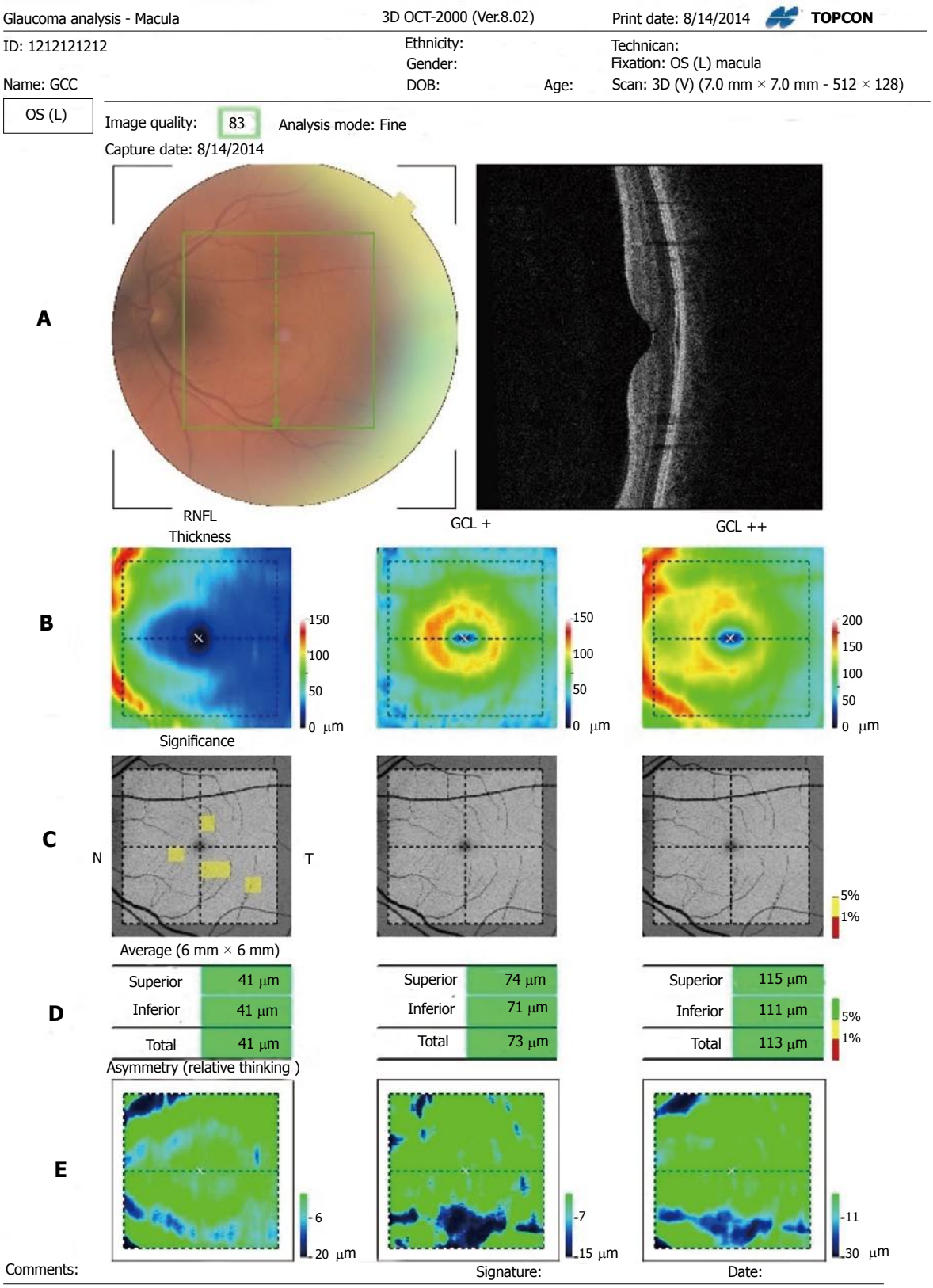

Figure 4 Three dimensions optical coherence tomography 2000. A: Segmentation: 7 mm^2 area centered on the fovea with a scan density of 512 vertical × 128 horizontal scans; B: Thickness map. Average regional thickness is calculated for RNFL, GCL+ (GCL + IPL), GCL++ (RNFL + GCL + IPL). Each cell is calculated and compared to the normative database of the device; C: Significance map. From left to right, 10 × 10 grid comparison maps covering 6 mm × 6 mm area of RNFL, GCL+ and GCL++ are shown. The comparison result is displayed with the color in the legend on the right. The background image is red free image; D: Average thickness. From left to right, three average thicknesses of RNFL, GCL+ and GCL++. The top is "Superior" which means average in the upper half area, the middle is "Inferior" which means average in the lower half area, and the bottom is "Total' which means average in the total area. Each average thickness is compared to the normative data and displayed according to color; E: Asymmetry map. From left to right, subtraction thickness maps covering 6 mm × 6 mm area of RNFL, GCL+ and GCL++ are shown. The subtraction is performed between two points which symmetrically lie with respect to the center horizontal line. In the upper half, the value in each point is calculated such that thickness of the point is subtracted from the thickness of the corresponding line-symmetry point below and vice versa. Blue indicates that the thickness of the point is thinner than that of the corresponding point. RNFL: Retinal nerve fiber layer; GCL: Ganglion cell layer; IPL: Inner plexiform layer.

purpose has recently received much attention. Tan *et al*[39] measured macular retinal thickness and GCC thickness with the RTVue OCT. They reported that the mean GCC had significantly higher diagnostic power than the macular retinal thickness for both SD-OCT and TD-OCT for discriminating between normal eyes and those with perimetric glaucoma. They also found that the diagnostic powers of the best GCC parameters were equal to that of the mean TD-OCT RNFL.

Kim *et al*[43] compared the GCC thickness measured by 3D OCT 2000 in three groups: healthy eyes, eyes with pre-perimetric glaucoma (PPG) and eyes with early glaucoma. They found that all GCC parameters decreased from normal to PPG and from PPG to early glaucoma. The values of the GCIP and GCC parameters differed significantly among the three groups ($P < 0.001$). However, the RNFL thickness of the macula between the healthy eyes and those with PPG was not significantly different ($P > 0.05$).

Rolle *et al*[50] used RTVue OCT to study early structural changes of RNFL and GCC in patients with a family history of primary open angle glaucoma (POAG). They included 163 eyes of first and second degree relatives (85 healthy, 40 with ocular hypertension and 38 with PPG) and 108 eyes of subjects with no family history (60 healthy and 48 PPG). They found that RNFL superior, GCC average, GCC superior, and GCC inferior were thinner ($P < 0.05$) in healthy eyes of patients with a family history of glaucoma than in normal eyes with no such history. They also showed that subjects with a glaucomatous sibling had significantly thinner RNFL and GCC than those with a single parent affected by the disease. These findings highlight the central role of SD-OCT in identifying individuals with early anatomical damage from glaucoma, even in eyes that appear normal.

The correlation between early glaucomatous visual field (VF) defects and macular ganglion cell layer assessment by OCT was investigated. Kim *et al*[51] evaluated the point-wise relationships between visual field sensitivity (VFS), measured by standard automated perimetry (SAP) and macular thickness, as determined by Spectralis-OCT, in glaucoma patients. They examined the correlation between the retinal sensitivities of 16 central test points from the SAP (Humphrey field analyzer) and Spectralis macular volume scans. They measured the macular thickness in 4 square cells in an 8 × 8 posterior pole retinal thickness map. The values were averaged for a mean retinal thickness (MRT) value, which corresponded to the 16 central test points in the SAP. A significant relationship between the MRT values and the corresponding VFS of each 16 central test point was found. They also showed that the level of the relationship varied among different sectors of the macula, showing the most significant relationship in the arcuate region. The study revealed that substantial structural loss (approximately 17%) appears to be necessary for detection of functional loss, using SD-OCT. Kim *et al*[51] concluded that from a clinical point of view, structural evaluation may be a more sensitive measure of ocular health in early stage glaucoma, whereas the functional evaluation may be a more sensitive and accurate measure of glaucoma progression at moderate-to-advanced stages. Inuzuka *et al*[52] examined the relationship between GCC thickness and its corresponding superior or inferior visual hemifield defects. They found that the thickness of the GCC at the inner and outer sectors of the parafovea decreased significantly as the corresponding hemifield defect increased. They also demonstrated that the GCC thickness correlated with changes in the corresponding hemifield that seemed normal. Their findings suggest that in glaucoma patients, changes in the GCC thickness occur before the VF worsens, even when the hemifield appears normal. This correlated with the severity of the disease. Thus, macular GCC thickness is an important indicator for glaucoma risk and may be a useful parameter for monitoring changes in patients with early or pre-perimetric glaucoma.

There is an increasing body of evidence to support the hypothesis that MIRL parameters are comparable to those of cpRNFL thickness in terms of the ability to diagnose glaucoma early. This is especially useful when cpRNFL measurements are not reliable, such as in eyes with extremely small or large optic discs, in tilted optic discs or peripapillary atrophy. Seong *et al*[53] used the RTVue OCT to compare the ability of MIRL thickness and cpRNFL thickness measurements to detect glaucoma. They showed that MIRL thickness was strongly correlated with cpRNFL thickness, and that MIRL thickness was able to discern glaucoma similar to cpRNFL thickness with early VF defects. However, cpRNFL measurement was better at diagnosing glaucoma than MIRL measurements in eyes with advanced or peripheral VF defects. Similar correlations between VF mean sensitivity, GCC, and cpRNFL thickness in glaucomatous eyes were reported by Cho *et al*[54]. Na *et al*[55] showed that pre-perimetric glaucoma patients with localized RNFL defects observed in red-free fundus photography had significantly thinner GCC measured by RTVue OCT, in all sectors compared to healthy individuals. The superior average GCC thickness was the best GCC parameter for detecting localized RNFL defects. It had similar area under receiver operating characteristic curve (AROC) values (0.84) to that of cpRNFL average thickness (0.89). Lee at al compared MIRL and cpRNFL measurements in discriminating between eyes with and without paracentral scotoma[44]. They included 63 eyes with early glaucoma with (33 eyes) or without (30 eyes) paracentral VF defects. Differences between the groups were significant in all of the MIRL parameters, but only in some cpRNFL parameters. The AROC for discriminating between groups was better for MIRL (0.77) than for cpRNFL (0.644) parameters. This study suggested that regional structural assessment of MIRL was a stronger indicator of scotoma in the paracentral area than cpRNFL measurements. On the other

hand, using various scanning protocols of the RTVue OCT, including GCC parameters, Rao *et al*[56] found only moderate diagnostic abilities in differentiating PPG eyes from eyes with large physiologic cups. The GCC parameter with best AUC was inferior quadrant GCC thickness (0.75). Including subjects with large physiologic cups as the control group in this study might have obscured the differences between normal and abnormal eyes.

High specificity of macular analysis is needed to avoid false positive identification of glaucoma among healthy eyes. Iverson *et al*[57] conducted a prospective, longitudinal study and found a high specificity (91%) for GCC thickness parameters in normal eyes, but only moderate specificity (77%) in glaucoma suspects, during the course of 43 mo of follow-up. Approximately half of the GCC measurements classified as outside normal limits were not replicable on subsequent scans. Mwanza *et al*[58] examined the diagnostic performance of GCIP thickness (Cirrus HD-OCT) between early glaucoma patients and normal controls. GCIP parameters were significantly thinner in the glaucoma group compared with controls. The best discriminant was the minimum, with 82% sensitivity and 87.8% specificity. Its performance was similar to that of the best RNFL and ONH parameters. The diagnosis was based on at least 1 abnormal GCIP parameter and yielded sensitivity and specificity values of 88% and 81.6%, respectively. Thus, confirmation of suspected SD-OCT abnormalities is essential for differentiating long-term variability from reproducible loss.

Macular SD-OCT has also a role in advanced glaucoma patients, although the evidence is sparse. Delbarre *et al*[59] used the Cirrus HD-OCT to evaluate the diagnostic ability of segmentation of the various internal macular layers compared to cpRNFL with the various stages of glaucoma disease: early, moderate and advanced. For the entire study population, the minimum GCIPL index provided greater diagnostic ability than the other parameters. There was no statistically significant difference with the cpRNFL parameter in the early POAG group, whereas in the advanced POAG group, minimum GCILP and GCC gave the largest AUC indices. Kim *et al*[60] assessed the relationship between visual acuity and mGCC thickness, as measured by RTVue, in open-angle glaucoma patients[60]. They noted significant correlations only in eyes with severe glaucoma. In the severe glaucoma group all GCC parameters significantly correlated with best corrected visual acuity, however no correlation was found in the early-to-moderate disease group.

Detection of glaucoma progression with macular SD-OCT

The average cpRNFL thickness was evaluated in the first study that reported using OCT for glaucoma progression analysis[61]. Clinicians were able to evaluate disease progression using specially designed statistical software. Guided Progression Analysis first became available in 2008, with the introduction of time-domain OCT (version 5.0, Stratus OCT, Carl Zeiss Meditec). The use of eye tracking (Spectralis OCT, Heidelberg Engineering) and cpRNFL thickness profiles from the same location in RNFL thickness maps (Cirrus HD-OCT, Carl Zeiss Meditec) are some of the strategies used to enhance the ability to detect changes with SD-OCT.

The macula has the highest density of ganglion cells in the retina. Measurements of the macular nerve fibers and ganglion cell and inner plexiform layer thicknesses are useful for monitoring glaucoma progression[62]. However, most OCT progression studies conducted to date were limited to cpRNFL measurements; few evaluated measurements of macular thickness.

Both time-domain and SD-OCT instruments have been used to obtain macular measurements for the detection of glaucomatous damage[63]. Repeatability of measurements is very important when evaluating progression. Mwanza *et al*[29] found higher reproducibility of macular ganglion cell layer thickness measurements with the SD-OCT than with the TD-OCT. Although the TD-OCT did not show significant differences in the rate of change of average macular thickness (an average of six radial scan lines, each 6 mm long) between eyes with and without evidence of progression in the VF and/or optic disc stereophotographs (defined as progressors and nonprogressors, respectively)[64], a study that used the SD-OCT had different results. Using similar definitions of progressors and non-progressors, Sung *et al*[65] followed 98 patients with advanced glaucoma for a mean of 2.2 years and reported a significant difference in the rate of change of average macular thickness, but not in average cpRNFL thickness, between the two groups. However, in a study evaluating 162 patients with mild glaucoma followed for the same period, significant differences in the rates of change of cpRNFL and macular thicknesses between progressors and nonprogressors were found[66]. In terms of progression as determined by optic disc/RNFL photographic or VF assessment, the thickness of the ganglion cell layer had similar sensitivity to RNFL and to total macular thickness. The enhanced measurement reproducibility and denser scanning afforded by SD-OCT may increase detection of structural progression. However, additional studies confirming this hypothesis have yet to be published.

As mentioned above, the RTVue GCC map includes FLV and GLV patterns, based on parameters. Naghizadeh *et al*[67] found that compared to ONH, RNFL thickness, or average GCC parameters, GLV and FLV provide better detection of early structural changes due to glaucoma progression. They reported that these parameters detected structural progression even with mild functional progression and that both parameters demonstrated different progression rates between stable and progressing eyes.

Anraku *et al*[68] investigated the functional impact of the baseline mGCC thickness. They assessed the association of the baseline mGCC thickness with the progression of VF loss in 56 POAG patients[68] who

were followed for more than 2 years after baseline OCT measurements. They found that the baseline mGCC thickness (average and inferior hemifield) was significantly thinner in the fast progressors than in the slow progressors. In a multivariate analysis, only mGCC thickness of the inferior hemifield was associated with disease progression (P = 0.007). They concluded that baseline mGCC thickness can be predictive of progressive VF loss in POAG.

However, using OCT parameters to track disease progress is somewhat limited. Some changes to the optic disc, RNFL and macular thicknesses detected by the OCT may not be due to glaucoma[63]. Prospective studies have reported age-related RNFL and thinning of the macula as additional causes[62].

Detecting a decrease in macular thickness is not necessarily a sign of glaucoma progression. A prospective study followed 150 eyes in 90 glaucoma patients 3 times a year for an average of 3.8 years. Trend analyses showed progression of the inner macular thickness in 50% and in total macular thickness, in 30% of eyes[62]. After considering changes due to age, progression decreased to 20.0% and 16.0% for inner retinal thickness and total macular thickness, respectively. These findings underscore the affects of changes due to aging on macular and RNFL measurements.

In cases of advanced optic neuropathy, OCT also has limitations related to detecting RNFL thinning[63]. Changes in RNFL thickness are associated with initial measurements (the rate of decrease in RNFL thickness is increased when the eye has a thicker RNFL)[62]. RNFL thickness is not less than 30 μm even when the eye has end-stage optic neuropathy and no light perception[69].

Measurements of OCT are related to the signal-to-noise ratio (or signal strength) of OCT images[56,70,71]. The signal strength of OCT images may decrease over time if cataract, vitreous opacities or other entities that may affect the opacity of the media. Rao *et al*[71] investigated the relationship between scan quality and diagnostic accuracy with SD-OCT using the RTVue OCT in glaucoma patients. The diagnostic ability was dependent on the scan quality even when the signal strength index (SSI) values were within the manufacturer-recommended limits. Scan quality had a greater effect on the diagnostic accuracy of ONH and cpRNFL than on GCC parameters. The sensitivity of all SD-OCT parameters, including GCC, for diagnosing glaucoma increased as the SSI increased. Thus, when interpreting a diagnosis of glaucoma and disease progression, the possible effect of the signal-to-noise ratio of the image series should always be considered.

Changes in the GCC demonstrated by OCT may also reflect pathologies other than glaucoma. The technology was found to be beneficial for detecting toxic effects of oral isotretinoin therapy[72] and for demonstrating macular retinopathy related to sickle cell anemia[73]. GCC OCT was used to detect optic chiasmal compression neuropathy[74], early macular retinal ganglion cell loss related to dominant optic atrophy[75] and was also used in migraine patients with aura[76]. Bayhan *et al*[77] used it to follow patients with Parkinson's disease, whereas Narayanan *et al*[78] found it beneficial in multiple sclerosis especially with prolonged disease duration and in relapsing remitting eyes.

Future research directions

OCT is a relatively new, evolving technology. It continue to undergo improvements that will enhance our ability to understand the structural pathogenesis of glaucoma and to offer more objective and accurate detection of structural glaucomatous damage and changes over time.

A variety of OCT devices are used to capture the retinal layers. Finding a tool that allows comparison between the results of different GCC OCT devices may be beneficial. We should aspire to develop an algorithm that allows combining the visual field test points with the GCC sectors demonstrated by OCT in order to better investigate the structural-functional aspects of glaucoma progression.

A normative database that incorporates age, sex, axial length and population origin will be required to take full advantage of this technology.

An increasing body of evidence supports using RGC/GCC macular GCC thickness as an indicator for early glaucoma and a valuable tool for monitoring disease progression.

COMMENTS

Background

Optical coherence tomography (OCT) has become a well-established tool for diagnosing and monitoring glaucoma. Limitations in optic nerve head assessment with OCT have driven investigators to look for novel OCT scanning strategies for glaucoma evaluation. Spectral domain (SD) OCT has enabled measurements of the retinal ganglion cells (RGC) in the macula and the retinal ganglion cell complex (GCC), including the retinal nerve fiber layer (RNFL), which are primarily affected in glaucoma and can be directly assessed by this method. Using RGC/GCC SD-OCT in glaucoma is a relatively new concept and the aim of this study was to systematically review the current literature published on this subject.

Research frontiers

New macular segmentation strategies using SD-OCT were developed in recent years for glaucoma assessment, focusing on the measurement of RGC and GCC thickness. Several SD-OCT instruments, including Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, United States), RTVue (Optovue, Inc., Fremont, CA, United States), Spectralis (Heidelberg Engineering, Heidelberg, Germany) and 3D OCT 2000 (Topcon Corporation, Tokyo, Japan), incorporate sophisticated glaucoma evaluation tools based on these parameters.

Innovations and breakthroughs

To the best of our knowledge, this is the first systematic review of the current data regarding the use of macular RGC/GCC SD-OCT for glaucoma assessment and no published paper thus far has summarized the current data in this field.

Applications

This systematic review may support clinicians to use macular RGC/GCC SD-OCT measurements as a routine adjunctive test to detect early glaucoma and to monitor glaucoma progression in established glaucoma patients.

Terminology

Glaucoma is an optic neuropathy characterized by loss of RGC, thinning of the RNFL and the neuroretinal rim, and increased cupping. RGC layer is an inner retinal layer which is thicker at the macula. GCC thickness is defined by

the distance from the internal limiting membrane, the inner most retinal layer, to the outer boundary of the inner plexiform layer (IPL), which comprises the inner 3 layers of the retina (retinal nerve fiber layer, ganglion cell layer and IPL. Glaucoma affects all of these three layers. OCT is a micron-level, diagnostic method that uses 800-840 nm wavelength infrared light to provide high-resolution, non-invasive neural imaging.

Peer-review

This manuscript is very good and well summarized about macular GCC analysis by various kinds of SD-OCT.

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EDITORIAL

Pharmacologic vitreolysis: New strategy for treatment of anomalous vitreo-macular adhesion

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Abstract

Persistent anomalous vitreo-macular adhesion (VMA) is a well-known factor, associated with a variety of sight threatening diseases - including macular hole, vitreo-macular traction syndrome, cystoid and diabetic macular edema, exudative age- related macular degeneration, myopic traction maculopathy and others. With the advent of optical coherence tomography our understanding of these pathologies and the ability of their early diagnosis has gone much far in the past two decades. The release of macular traction has been of exclusive surgical capability. Notwithstanding good results, vitrectomy is hampered by the inability of complete vitreo-retinal separation (*i.e.*, smooth, bare internal limiting membrane), compulsory postoperative positioning in macular hole cases, surgical complications, and high costs. With aim to offer less invasive and safe treatment modality for anomalous VMA, investigators have made enormous progress in the past decade. Leading among the studied nonsurgical measures is the intravitreal application of pharmacologic agents for the induction of vitreo-retinal separation and vitreous liquefaction, a method termed pharmacologic vitreolysis. Several vitreolytic agents have been studied to date, the most potent among them proved to be plasmin. Recently, ocriplasmin (formerly known as microplasmin) - a more stable than plasmin recombinant product, proved to be safe and efficient in releasing VMA in large studies, and consequently received FDA approval. It's role in clinical practice is now in the process of being determined. This paper aims to review and summarize the current knowledge and status of investigation on this new approach for the treatment of VMA.

Key words: Pharmacologic vitreolysis; Vitreo-macular adhesion; Posterior vitreous detachment; Macular hole; Microplasmin

Core tip: Persistent anomalous vitreo-macular adhesion (VMA) is a well-known factor, associated with a variety of sight threatening diseases (macular hole, vitreo-macular traction syndrome, macular edema, exudative age-related macular degeneration). The release of

traction has been of exclusive surgical capability. Notwithstanding good results, vitrectomy is hampered by the inability of complete vitreo-retinal separation and surgical complications. With aim to overcome limitations of surgery, investigators have made enormous progress with the advent of pharmacologic vitreolysis - a method for releasing VMA by intravitreal drug delivery. This paper aims to summarize the current knowledge and status of investigation on this new treatment approach.

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INTRODUCTION

With the advent of optical coherence tomography (OCT) - a sophisticated modality for retinal imaging, ophthalmologists obtained more knowledge on the important role of the posterior vitreous in a variety of retinal diseases. In the development of physiologic, or age-related, posterior vitreous detachment (PVD) two processes (liquefaction - synchysis, and fibrillar collapse - syneresis) take place simultaneously and interact, thus resulting in vitreo-retinal separation[1-3]. With time areas of liquefaction increase, the collagen meshwork fibrils form thick fibers (synergetic debris), and after separation from the internal limiting membrane (ILM) the posterior hyloid collapses anteriorly[1-3]. While previously we believed the process of PVD to be an acute one, recent OCT studies have shown that it is a gradual one and may take ears. Usually PVD starts as a shallow separation of the hyaloid from the retina in the perifoveal area and expands gradually until the last detachment from the optic disc margin. The results of this last separation are acute symptoms and the sign of Weiss ring (complete PVD) [4,5]. In some subset of eyes this physiologic process of complete PVD is hampered by firm vitreo-retinal adhesions to different sites - optic disc margin, fovea, or focal areas in retinal periphery. If this is the case, the dynamic traction of the posterior hyaloid exerted upon retina at points of adhesion gives rise to various complications, such as vitreous hemorrhages, macular hole, vitreo-macular traction syndrome (VMT), vitreo-papillary traction syndrome, retinal tears and retinal detachment. It has been documented that persistent vitreo-macular adhesion (VMA) may aggravate macular edema and retinal pathology in various conditions such as diabetic retinopathy (DR), retinal vein occlusions, neovascular age-related macular degeneration (AMD), uveitis, myopic maculopathy, and others[6-8]. Persistent vitreo-retinal adhesions may serve as scaffold for vitreo-retinal neovascular proliferations in DR and retinal vein occlusions. Sebag and associates have revealed the role of vitreoschisis (vitreous cleavage with residual vitreous cortical layer on retinal surface) for the pathogenesis of macular holes and epiretinal membranes (ERM)[3].

The therapeutic option in all these pathologic vitreo-retinal entities for many years has been vitreo-retinal surgery. Notwithstanding good results[9,10], vitrectomy is hampered by the inability of complete vitreo-retinal separation (*i.e.,* "smooth", "cell-free" ILM, ILM)[11], compulsory postoperative positioning for macular hole cases, surgical complications, and high costs. Some studies draw our attention that after vitrectomy, despite meticulous PVD induction and thorough aspiration, or posterior hyloid peeling, some cortical vitreous fibers may still remain and adhere to the retinal surface, and thus give rise to fibrocellular proliferation and formation of postoperative ERM[12]. Gandorfer and coauthors have documented by electron microscopy and immunocystochemistry that in 2/3 of vitrectomy cases with ERM removal, cortical vitreous cells remain on the ILM, which subsequently lead to recurrence of ERM[11]. To achieve a "cleaner" retinal surface, surgeons may peel the ILM in every case, but this increases the risks of some complications, such as nerve fiber layer damage, retinal haemorrhages or breaks, and paracentral scotomas. With aim to overcome limitations of vitrectomy, investigators have explored as alternative different methods for achieving complete PVD and "smooth" ILM. Leading among the studied nonsurgical techniques is the application of different pharmacologic agents in the vitreous for inducing vitreo-retinal separation and vitreous liquefaction. This method was termed pharmacologic vitreolysis by Sebag[13]. As a result of a huge work in this field of ophthalmology by many investigators, such as Sebag, Gandorfer, de Smet, Stalmans and others, we have now a better understanding of vitreo-macular pathology and recently obtained pharmacologic vitreolysis in the treatment armamentarium for anomalous VMA in our clinical practice. The early interest of vitreolysis was concentrated on the use of vitreolytic agents in difficult cases for obtaining cleaner vitreo-retinal separation (pharmacology assisted vitrectomy)[13,14]. Realizing the potential of vitreolysis, investigators have then begun to explore the use of vitreolytic substances as stand-alone drug deliver therapy for the treatment of anomalous VMA related diseases[15,16]. This paper aims to review and summarize the current knowledge and status of investigation on this new treatment approach.

VITREOLYTIC AGENTS

Pharmacologic vitreolytic substancies can be categorized according to the mechanism of action as "enzymatic" (plasmin, microplasmin, tissue plasminogen activator, nattokinase, chondroitinase, dispase, and hyaluronidase) and "non-enzymatic"(Vitreosolve and RGD peptides - arginine-glycine-aspartate peptides). Sebag[17,18] offers a more useful classification, based on their biological effect - "liquefactants" (able to induce liquefaction),

"interfactatns" (able to disrupt vitreo-retinal adhesions) or having both effects. Sole liquefactants are collagenase and hyaluronidase, sole interfactants are RDG peptides and dispase, and having both effects - chondroitinase, nattokinase, plasmin, microplasmin, tissue plasminogen activator, and Vitreosolve.

It must be stressed, that for the induction of safe PVD with complete vitreo-retinal separation, it's fundamental to achieve both effects. If liquefaction occurs without adequate vitreo-retinal interface disruption, this will result in worsening of the existent tractional pathology[17 18].

Collagenase

Collagenase is a bacterial protease, purified from Clostridium histolyticum and it selectively cleaves collagen type Ⅱ which comprises the fibrillar meshwork of the vitreous body[19]. It acts as a sole liquefactant. In animal models collagenase succeeded to liquefy the vitreous, but was noted to have adverse effects - ILM damage, disruption of retinal architecture, and retinal toxicity proved by histological and electrophysiological examination[20]. In recent studies of collagenase-assisted pars plana vitrectomy some complications have been noted - vascular digestion of proliferative membranes and retinal hemorrhages[21].

Hyaluronidase

Hyaluronidase represents an endoglycosidase which is able to dissolve hyaluronan - a molecule that comprises the glycosaminoglycan meshwork of the vitreous body. Hyaluronidase is a pure liquefactant and its' effect was demonstrated *in vitro*[22] and *in vivo*[23], and recently in a phase Ⅲ trial (Vitrase) in the management of hemophthalmus[24]. As it has no effect on vitreo-retinal adhesions, if applied alone may worsen existing VMA-related pathologies.

Dispase

Dispase represents a protease molecule which cleaves collagen Ⅳ and fibronectin, and thus attenuates attachments between the hyaloid and the ILM. In experimental *in vivo* animal studies some harmful effects were reported - retinal toxicity with disruption of ganglion cells and photoreceptor layers, retinal and vitreous hemorrhages, cataract and lens subluxation[23].

RGD peptides

Integrins are receptor molecules on the cell surface which take part in the cellular - extracellular matrix signaling and adhesion. They are bound to the ILM by a specific sequence of amino acids - RGD (arginine-glycine-aspartate). Synthetic RDG peptides compete for integrin-biding sites and thus disrupt the integrin-extracellular matrix interaction and loose vitreo-retinal adhesions[25]. RGD peptides are non-enzymatic and are considered as pure interfactants. In a rabbit model RGD peptides facilitated the induction of PVD during vitrectomy, and no toxicity was noted[26]. No further investigations are reported.

Vitreosolve

Vitreosolve® (Vitreoretinal Technologies Inc, United States) is a non-enzymatic urea-based molecule that is considered to have both liquefatant and interfactant vitreolytic effects. It currently undergoes Phase Ⅱ/Ⅲ study in patients with non-proliferative DR without PVD. Preliminary results demonstrate good ability at achieving complete PVD. Final results are being expected.

Chondroitinase

Chondroitinase is a protease which catalyzes depolymerization of chondroitin sulfate, hyaluronan, and dermatan sulfate. It has both liquefactant and interfactant properties. The results from pre-clinical studies are mixed. One group found no significant effect on inducing PVD[20], while another group reported complete vitreo-retinal disinsertion in a monkey model[27]. High doses demonstrate some toxicity, while lower doses were unable to achieve significant rates of spontaneous PVD, or bare ILM after viteo-retinal separation[28].

Nattokinase

Nattokinase is a serine protease produced by Bacillus subtilis and is derived from fermented soybean. It is known to have fibrinolytic effect and is under investigation in cardiovascular and thrombotic therapy. It is considered to enhance the activation of plasmin by increasing the synthesis of tissue plasminogen activator (tPA), thus it has both liquefactant and interfactant properties[29]. In a rabbit model nattokianse showed good vitreolytic property with leaving smooth ILM, but only in the highest intravitreal doses tested. These doses, however showed also adverse actions, such as alterations in retinal structure, intraretinal hemorrhages, and toxicity confirmed by electroretinography[30].

Plasmin

Plasmin represents a serine protease which lyses laminin, fibrin, and fibronectin, and also acts through increasing the levels of other proteases that disrupt extracellular matrix structures. Its' primary action is to weaken vitreo-retinal adhesion, and to a less extent provoke liquefaction[31,32]. Plasmin was the most widely studied vitreolytic agent, and in many pre-clinical studies has shown good properties in achieving complete PVD with bare ILM (in a dose-dependent manner), and its' safety profile was excellent[33-37].

However, plasmin is extremely unstable. The application of plasmin in clinical practice requires activation of plasminogen (its' proenzyme) with plasminogen activators immediately prior to use. As there is no commercially available plasminogen, investigators rely on a very expensive and time-consuming process of generation of autologous human plasminogen derived

from patients' own plasma and purified *via* affinity chromatography[37]. Numerous studies using the described technique in difficult vitrectomy cases with plasmin-assisted PVD, such as retinopathy of prematurity (stage 5) [38], tractional DME, complicated proliferative DR[39], complicated X-linked retinoschisis[40] report ease in PVD induction, improved final anatomic outcomes, and no enzyme-related complications[37-40]. However, this method is quite expensive, time-consuming and inapplicable in daily clinical setting.

Plasminogen activators (tPA and urokinase)

Plasminogen activators have fibrinolytic properties and are approved for non-ophthalmic vascular disorders (stroke, symptomatic coronary artery). They exert their effect through plasmin, thus having potent viteolytic properties. Their advantages are commercial availability, safety in terms of microbal contamination (recombinant molecule), established ocular safety in some other ophthalmological conditions (post-surgical fibrin lysis, submacular hemorrhage, acute retinal vein occlusion) [41,42]. Pre-clinical studies on plasminogen activators for inducing PVD show promising efficacy and safety results[43,44]. The difficulty in applying plasminogen activators in clinical practice comes from the inability to achieve sufficient quantities of intraocular plasminogen (which can be achieved by blood-retinal barrier brake down, *i.e.,* cryopexy), or exogenous administration. Thus dosing would be imprecise.

Ocriplasmin (microplasmin)

Ocriplasmin (formerly known as microplasmin) represents a recombinant protein which contains the catalytic domain of plasmin, and so having the properties of human plasmin[45]. Microplasmin was developed for intravenous administration for the treatment of systemic thromboembolic disease. Its' effects after intravitreal application are specific for vitreous and less active on ocular structures, such as vessels, lens, lamina cribrosa, and ciliary body[46]. It has numerous advantages over plasmin, autologus plasminogen, and tPA: it is more stable than plasmin, commercially available, allows accurate dosing, generated by recombinant technique it assures sterility, the smaller size (22 kDa of microplasmin versus 88 kDa of plasmin) facilitates its' permeability in tissues. Pre-clinical studies have demonstrated a dose- and time-dependant efficacy in achieving complete PVD with clean, bare ILM[32,33,46]. It showed no histological or functional toxicity, except a- and b-wave depression in electroretinography in cases, treated with the highest dose (250 μg)[47].

The most potent and safe vitreolytic agent among all tested proved to be microplasmin, thus it underwent exploration in a series of clinical trials sponsored by ThromboGenics and collectively entitled the Microplasmin Intravitreal Injections (MIVI) trials - 14 listed in the clinical trials registry. The majority has been completed and ocriplasmin (Jetrea, ThromboGenics Inc) received FDA approval (on 17th October 2012) for nonsurgical treatment of symptomatic VMA.

MIVI Ⅰ was an uncontrolled Phase Ⅰ/Ⅱa clinical trial that aimed to assess the safety profile and efficacy of ocriplasmin, applied intravitreally in different concentrations (25, 50, 75, and 125 μg) and increasing exposure times (2 h, 24 h and 7 d). Subjects of the trial were patients scheduled for surgery (with DME, VMT syndrome, macular hole)[48]. The incidence of spontaneous PVD as well as the ease of PVD induction during vitrectomy was found to be dependent on the dose and time exposure. However, less than 50% of eyes in every subgroup developed spontaneous PVD. Except one case of retinal detachment, there was no safety concern described[48]. The results from this initial trial have demonstrated the good safety profile of ocriplasmin and confirmed that it's capable in inducing PVD in some cases.

MIVI Ⅱt (traction) was a prospective and sham-controlled Phase Ⅱ clinical trial for assessment of the efficacy of ocriplasmin alone for the treatment of symptomatic VMA and macular holes. Four cohorts were examined in randomization 4:1 to ocriplasmin at doses 75, 125, 175 μg and sham[49]. The primary endpoint of non-surgical release of VMA at day 28 after injection was reached in 8%, 25%, 44% and 27% of patients in the sham, 75 μg, 125 μg, and 175 μg cohort, respectively. The greatest proportion of VMA release was noted until day 7, and repeated injections in eyes with unreleased VMA after day 28 in the 125 μg cohort did not increase the chance of PVD induction.

MIVI Ⅲ was a larger multicenter prospective placebo-controlled study designed to evaluate three doses of ocriplasmin (25, 75, and 125 μg) compared to placebo for facilitating PVD before vitrectomy[50]. The percentage of complete PVD were 10%, 14%, 21% and 31% for the placebo, 25, 75, and 125 μg ocriplasmin, respectively.

MIVI-TRUST comprises pooled data from two parallel multicenter, randomized Phase Ⅱ clinical trials (MV 006 and MV007), which had same protocol except the ratio of randomization. The aim was to compare a single dose of 125 μg ocriplasmin with sham in patients with symptomatic VMA alone and in VMA associated with macular hole[51]. The primary endpoint of VMA resolution at day 28 was achieved in 26.5% of ocriplasmin treated eyes and in 10% of placebo-injected eyes ($P < 0.001$). Non-surgical closure of macular holes resulted in 40.6% of ocriplasmin treated eyes compared to 10.6% of sham-injected eyes ($P < 0.001$). The subgroup analysis showed that resolution of VMA at day 28 was achieved more often in eyes without ERM, younger patients (< 65 years), eyes with full thickness macular hole, phakic eyes, and those with a focal VMA ⩽ 1500 μm[52]. Eyes with macular hole width ⩽ 250 μm were more likely to achieve nonsurgical macular hole closure. As safety concerns, investigators reported: similar rates of retinal holes (0.9% *vs* 1.6%) and retinal detachment (1.1% *vs* 2.7%) in the ocriplasmin and vehicle

injected eyes, respectively; decrease in visual acuity with > 3 lines in 5.6% and 3.2% in the ocriplasmin and sham injected eyes (a condition of progression of the pathology, that requires proper monitoring and timely schedule for surgical treatment); mild transient intraocular inflammation in 7.1% and 3.7% of eyes injected with ocriplasmin and sham, respectively; 2% of ocriplasmin cases reported dyschromatopsia and accompanying a-and b-wave amplitude decrease in electroretinography; potential for lens subluxation[51,52].

Studies for treatment of anomalous VMA in cases with DME (MIVI 11), ARMD (MIVI 5), as vitreolysis-assisted vitrectomy in children and infants scheduled for surgery (MIC), and in uveitic macular edema (MIME) are still undergoing and their results are being expected.

The use of ocriplasmin is now on its' way of translation to the real world clinical practice. Ophthalmologists report comparable results to those in the clinical trials[53,54], or even better in cohort of selected (best outcome expectancy) cases[55]. Singh and coauthors report overall response rate of 47.1% (8/17 eyes), in patients meeting three of four positive predictors criteria (*e.g.,* focal VMA ⩽ 1500 μm, no ERM, and phakic lens status) they report successful VMA release in 50.0% (7/14 eyes), and patients meeting all four criteria (*e.g.,* VMA diameter ⩽ 1500 μm, no ERM, younger than 65, and phakic lens status) showed a response of 75.0% (3/4 eyes)[55]. Other authors have published initial results of much lower macular hole closure rate - 12.5% (one of 8 eyes with stage 2 macular hole)[56], unsuccessful resolution of VMA (none of 7 treated eyes)[57], and enlargement of macular hole with worsening of visual acuity[58]. With view of previous good results and the latter disappointing ones, a careful selection of candidates for ocriplasmin treatment as well as watchful observation after treatment should be done. It is important to discuss with the patient that in rare cases macular hole progression may result with worsening of the condition. On the whole, investigators that are involved in the development of ocriplasmin treatment, advise that candidates for ocriplasmin injections should be scheduled for surgery, thus if drug delivery does not succeed within 4 wk, surgery would be performed without delay.

In terms of adverse effects ophthalmologists report their clinical observations of vision loss[59,60], dyschromatopsia, subretinal fluid accumulation predominantly in cases with release of VMA[61], cystoid macular edema development[62], spectral OCT detection of disturbances in the neuroreceptor ellipsoid zone[60-64], as well as documented by electroretinography a decrease in the a-and b-waves[63,64]. These effects seem to be short (months)[59] or long lasting (years)[60], but transient. These documented observations raise the concern about the enzymatic effect on photoreceptors and pigment epithelial cells. Further investigations are needed to elucidate the precise mechanisms by which ocriplasmin exerts these retinal microstructure alterations.

CONCLUSION

Though great progress has been done in the research process, the development of non-surgical treatment for anomalous VMA related diseases is very much an ongoing work. From the various agents, tested for the needs of pharmacologic vitreolysis, microplasmin has shown the greatest potential for safe and complete PVD. Randomized controlled clinical trials documented efficacy, but in less than 50% of cases. In selected cases (smaller than 250 μm macular holes, without ERM, focal VMA ⩽ 1500 μm, younger than 65, and phakic lens status) the prognosis is documented to be better, thus they represent best candidates for ocriplasmin treatment. Safety results seem satisfactory, though caution regarding some possible complications is advisable. The clinical role of ocriplasmin in cases with macular traction and persistent DME, uveitic edema, exudative AMD and others is still under investigation.

Future perspectives in this field of research would cover exploration of non-enzymatic agents that would offer vitreolysis without collateral damage of adjacent structures. Some investigators believe that the most promising concept would be to use a mixture of specific agents at much lower doses, previously found to have some toxicity, as a combination therapy may allow the use of lower and safer doses to increase the success rate of VMA release.

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EDITORIAL

Approved pharmacotherapy for macular edema secondary to branch retinal vein occlusion: A review of randomized controlled trials in dexamethasone implants, ranibizumab, and aflibercept

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Abstract

There are three approved pharmacotherapies for treating macular edema secondary to branch retinal vein occlusion (BRVO), including corticosteroids (dexamethasone implants) and anti-vascular endothelial growth factor (VEGF) (ranibizumab and aflibercept). They all show superior ability to improve vision and reduce macular thickness, comparing with sham injections or macular grid laser treatment. There is no severe ocular or systemic adverse reaction reported in studies associated with anti-VEGF for macular edema after BRVO. Intraocular pressure elevation and cataract aggravation should be addressed after intravitreal dexamethasone implants. Single intravitreal dexamethasone implant had effective duration as long as four to six months. Intravitreal anti-VEGF requires six monthly injections as loading doses, and then PRN regimen needed according to functional and anatomical changes. Ozurdex and ranibizumab reduce not only macular edema, but also the probability of retinal ischemia and neovascularization in patient s with BRVO. Prompt treatment with these agents can lead to a better outcome.

Key words: Branch retinal vein occlusion; Intravitreal injection; Aflibercept; Ranibizumab; Macular edema; Ozurdex

Core tip: There are three approved pharmacotherapies

for treating macular edema secondary to branch retinal vein occlusion (BRVO), including corticosteroids (dexamethasone implants) and anti-vascular endothelial growth factor (VEGF) (ranibizumab and aflibercept). They all show superior ability to improve vision and reduce macular thickness, comparing with sham injections or macular grid laser treatment. There is no severe ocular or systemic adverse reaction reported in studies associated with anti-VEGF for macular edema after BRVO. Intraocular pressure elevation and cataract aggravation should be addressed after intravitreal dexamethasone implants. Single intravitreal dexamethasone implant had longer effective duration than two anti-VEGFs.

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Branch retinal vein occlusion (BRVO) is a common sight-threatening retinal vascular disorder, in which macular edema is the main cause of visual impairment[1]. The pathophysiology of macular edema involves both the presence of inflammation and angiogenic stimulant regarding vascular endothelial growth factor (VEGF)[2,3]. Intravitreal injections of anti-VEGF, including ranibizumab[4-7], bevacizumab[8], pegaptanib[9], aflibercept[10] are proven to be effective for treating macular edema resulting from BRVO. Intravitreal injections of corticosteroids, potent anti-inflammatory agents, such as dexamethasone implants[11-13] and triamcinolone acetonide[14], have been shown to be beneficial to macular edema associated with BRVO. The Food and Drug Administration of United States and European Medicines Agency have approved intravitreal injections of dexamethasone implants, ranibizumab, and aflibercept for treating macular edema secondary to BRVO. Herein the clinical outcome of the randomized controlled studies in these approved pharmacotherapies will be reviewed.

Ozurdex™ (Pharm Allergan Inc., Irvine California) was the first intraocular implant that could slowly release dexamethasone. Ozurdex showed an anti-edematous effect as early as 7 d after implantation[14]. The effect can persist as long as four to six months after single injection[11,12]. The GENEVA study, a randomized controlled trial, collected 291 eyes with BRVO receiving Ozurdex 0.7 mg, 260 eyes in Ozurdex 0.35 mg, and 279 eyes in sham injections[11]. Following single intravitreal injection of Ozurdex 0.7 or 0.35 mg, maximal response was found two months after the injection with visual improvement in nearly ten letters, significantly better than five-letter gain in the sham group. The central retinal thickness also showed significant decrease in the treatment group than in the sham group 90 d after Ozurdex implantation. The effect of Ozurdex diminished six months after the injection. The same response for macular edema was noted after repeated injections of Ozurdex during 12-mo follow-up[12]. Over 12 mo, cataract progression occurred in nearly one third of phakic eyes, and a 10-mmHg intraocular pressure increase from baseline was observed in 15.4% of all patients receiving two injections of Ozurdex 0.7 mg. The intraocular pressure increases were usually transient and controlled with medication or observation. A laser or surgical procedure to reduce intraocular pressure was required for only 14 study eyes. IOP required specific time for clinical monitoring[15]. The dexamethasone implants were reported migration into the anterior chamber, causing permanent corneal edema[16]. Absence of lens capsule and prior vitrectomy were risk factors for Ozurdex anterior migration[16]. In eyes with BRVO in the GENEVA study, longer macular edema duration at the time of first Ozurdex treatment was associated with a significantly lower likelihood of achieving clinically meaningful improvements in vision or macular thickness 6 or 12 mo after treatment[17]. This suggests that prompt Ozurdex treatment may be associated with improved clinical outcomes[17]. The proportion of BRVO eyes with active neovascularization increased from baseline to day 180 in the sham group, but stayed relatively constant in the Ozurdex-treated group in the GENEVA study[18]. It is hypothesized that corticosteroids are associated with the down-regulation of the VEGF and inhibition of ocular neovascularization.

The SHASTA study was a multicenter retrospective study collected 157 patients with macular edema secondary to BRVO[19]. The patients received intravitreal Ozurdex 0.7 mg injection as monotherapy or with adjunctive treatments. Mean reinjection interval was 5.6 mo. Two third of the patients achieved more than 2-line visual improvement in the peak response. Intraocular pressure increase more than 10 mmHg occurred in one third of patients, but only 1.7% of patients required incisional glaucoma surgery. Another randomized multicenter study compared clinical outcome of Ozurdex monotherapy and Ozurdex combined with macular grid laser in patients with macular edema associated with BRVO[20]. The combination of Ozurdex implant and macular grid laser was synergistic for visual improvement and lengthening the time between Ozurdex injections.

Ranibizumab (Lucentis™, Genentech, Inc., South San Francisco, CA, and Novartis Pharma AG, Basel, Switzerland) is an antibody fragment with a high binding affinity towards all forms of VEGF-A, which can effectively inhibit intraocular level of VEGF-A. The BRAVO study included 397 patients with macular edema after BRVO, who were randomized 1:1:1 to receive 6 monthly intraocular injections of 0.3 mg or 0.5 mg of ranibizumab or sham injections[4]. At month 6, ranibizumab 0.3 mg or 0.5 mg resulted in a mean gain of 16.6 and 18.3 letters, significantly better than 7.3 letters in the sham group. The central foveal thickness also demonstrated significant decrease in the treatment group than in the

sham group. No significant ocular or nonocular safety events were identified. All the patients including the sham group received PRN ranibizumab injections from month 6 to month 12[5]. The mean number of intravitreal ranibizumab was nearly three injections in the treatment group between month 6 and month 12. At month 12, ranibizumab 0.3 mg or 0.5 mg resulted in a mean gain of 16.4 and 18.3 letters, significantly better than 12.1 letters in the sham group. In the HORIZON trial, 304 patients with BRVO treated with PRN ranibizumab administration according to the protocol of the BRAVO study completed 2-year follow up[6]. The mean number of intravitreal ranibizumab was 2.1 injections in the 0.5 mg ranibizumab group between month 12 and month 24[6]. At month 24, ranibizumab 0.5 mg injection caused a mean gain of 17.5 letters, which maintained the visual outcome comparing to the results at month 6 and month 12. Fewer ranibizumab injections were required to control the edematous condition from month 6 to month 24. In the RETAIN study, 34 BRVO eyes treated with ranibizumab according to the protocol of the BRAVO study completed 4-year follow up[7]. Half of the patients required frequent injections, and another half of them had edema resolution without further treatment. There was a trend that the patients with resolved macular edema had more visual improvement in 25.9 letters, compared with those with unresolved edema in visual gain of 17.1 letters. The retrospective analysis of the BRAVO study suggest that initiating ranibizumab injection immediately after diagnosis of BRVO provides greater vision gain than the patients receiving delayed treatments[21]. Another analysis of the patients with BRVO in the BRAVO study found 79.1% (0.3 mg) and 84.7% (0.5 mg) having central foveal thickness less than 250 μm 3 mo after treatment, and therefore was categorized as early ranibizumab responders[22]. The early ranibizumab responder demonstrated better visual outcome at months 6 and 12, comparing to late or incomplete responder[22]. After analysis of the data in the BRAVO trial, ranibizumab injections prevent the worsening of retinal nonperfusion area, and even promotes reperfusion of the ischemic area, comparing to the sham group[23].

Aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., and Bayer Pharma AG, Berlin, Germany) is a decoy receptor fusion protein, composed of the second domain of human VEGF receptor 1 and the third domain of VEGF receptor 2, which are fused to the Fc domain of human IgG1. Aflibercept can downregulate both VEGF-A and placental growth factor, which are synergistic for pathologic angiogenesis. The VIBRANT study, a randomized controlled trial, demonstrated the efficacy of intravitreal aflibercept 2 mg over the macular grid laser for 183 patients with macular edema associated with BRVO[10]. The authors used monthly injections for 6 mo[10]. The 6-mo results showed the aflibercept group gained mean 17.0 letters, significantly better than the laser group having only mean 6.9-letter improvement. Decrease of macular thickness was more prominent in the aflibercept group than in the laser group, without accompanying serious ocular and systemic adverse events.

Although there was no serious adverse effect reported in studies of ranibizumab and aflibercept for macular edema secondary to BRVO, some rare serious complications were found after use for other indications. Retinal pigment epithelium tears, macular ischemia, cataract progression, retinal breaks and detachment, endophthalmitis, macular hole, and intraocular inflammation were reported as ocular complications after intravitreal anti-VEGF for treating neovascular AMD[24]. Systemic adverse effects were uncommonly reported such as thromboembolic events (stroke and myocardial infarction) and gastro-intestinal bleeding[24].

In summary, there are three approved pharmacotherapy for treating macular edema secondary to BRVO, including intravitreal injections of corticosteroids (dexamethasone implants) and anti-VEGF (ranibizumab and aflibercept). They all show superior ability to improve vision and reduce macular thickness, comparing with sham injections or macular grid laser treatment. There is no severe ocular or systemic adverse reaction reported in studies associated with anti-VEGF for macular edema after BRVO. Intraocular pressure elevation and cataract aggravation should be addressed after intravitreal dexamethasone implants. Single intravitreal Ozurdex had effective duration as long as four to six months. Intravitreal anti-VEGF requires six monthly injections as loading doses, and then PRN regimen needed according to functional and anatomical changes. Ozurdex and ranibizumab reduce not only macular edema, but also the probability of retinal ischemia and neovascularization in patient s with BRVO. Prompt treatment with these agents can lead to a better outcome.

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REVIEW

Ocular renin-angiotensin system with special reference in the anterior part of the eye

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Abstract

The renin-angiotensin system (RAS) regulates blood pressure (BP) homeostasis, systemic fluid volume and electrolyte balance. The RAS cascade includes over twenty peptidases, close to twenty angiotensin peptides and at least six receptors. Out of these, angiotensin Ⅱ, angiotensin converting enzyme 1 and angiotensin Ⅱ type 1 receptor (Ang Ⅱ-ACE1-AT1R) together with angiotensin (1-7), angiotensin converting enzyme 2 and Mas receptor (Ang(1-7)-ACE2-MasR) are regarded as the main components of RAS. In addition to circulating RAS, local RA-system exists in various organs. Local RA-systems are regarded as tissue-specific regulatory system accounting for local effects and long term changes in different organs. Many of the central components such as the two main axes of RAS: Ang Ⅱ-ACE1-AT1R and Ang(1-7)-ACE2-MasR, have been identified in the human eye. Furthermore, it has been shown that systemic antihypertensive RAS- inhibiting medications lower intraocular pressure (IOP). These findings suggest the crucial role of RAS not only in the regulation of BP but also in the regulation of IOP, and RAS potentially plays a role in the development of glaucoma and antiglaucomatous drugs.

Key words: ACE1; ACE2; ACE-inhibitors; Angiotensin Ⅱ; Angiotensin (1-9); Angiotensin (1-7); Glaucoma; Intraocular pressure; Mas receptor; Renin-angiotensin system

Core tip: Many of the central components of renin-

angiotensin system (RAS) have been identified in different structures of the human eye. Recent findings suggest that local RAS accounts for long term changes in ocular tissue level. Antihypertensive drugs which inhibit RAS (ACE or AT-receptor blockade) reduce intraocular pressure suggesting their possibility as anti-glaucomatous drugs in the future. Here we describe the local intraocular RAS especially in the anterior part of eye.

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INTRODUCTION

Glaucoma is after cataract the second leading cause of vision loss worldwide. In 2020, 79.6 million people are estimated to be diagnosed with glaucoma. The majority of these patients are estimated to have open angle glaucoma[1]. Glaucoma is a neurodegenerative disorder that leads to the loss of the axons of the optic nerve and to the death of retinal ganglion cells by non-apoptotic and apoptotic mechanisms all of which in the end cause visual field defects and irreversible vision loss[2-6]. Together with age and family history, increased intraocular pressure (IOP) is one of the known major risk factors for glaucoma[2,6,7]. In subjects with increased IOP, ocular hypotensive medication prevents or delays surgery of glaucoma[8]. A 30% reduction in IOP reduces disease progress 10%-35% in glaucoma patients[9,10]. Even though risk factors and possible outcomes of glaucoma are known, the exact mechanism behind development of glaucoma is still poorly known. Interestingly, imbalances in the local ocular renin-angiotensin system (RAS) cascade have been associated to glaucoma[3].

In addition to the circulating RAS that controls blood pressure (BP) homeostasis, electrolyte balance and systemic fluid volume, tissue-specific RAS, accounting for local effects and long-term changes in tissue level, have been described. Local RA-systems have been demonstrated in different organs studied[11,12], including the human eye[2,12-14]. Systemic antihypertensive drugs which inhibit RAS can reduce IOP. Certain ACE inhibitors[15] and AT1 receptor blockers[16] have been shown to reduce IOP in both non-glaucomatous and glaucomatous patients. In animal studies Angiotensin converting enzyme (ACE) inhibitors[17,18], AT1 receptor blockers[19,20], and renin inhibitors[21] have been reported to lower IOP. These findings imply that RAS is not only important in the regulation of BP but that it is possibly also involved in the regulation of IOP[5,22]. However, the question of how RAS is involved in the regulation of IOP remains to be answered.

In this review we describe the tissue RAS cascade and concentrate on the anterior part of the eye. A survey of PubMed using the following keywords was performed to collect the literature on eye, IOP (38214, number of reports), RAS (26697), tissue RAS (4870), angiotensin (110705), angiotensin I (7879), angiotensin Ⅱ (55855), angiotensin converting enzyme (45777), angiotensin (1-9) (28), angiotensin (1-7) (1043), Mas receptor (305), angiotensin receptor (16021), eye disease (4830), glaucoma (55288), diabetic retinopathy (DR) (25958), retinopathy of prematurity (ROP) (5710) and age-related macular degeneration (10875). Combining the used keywords allowed to narrow down the literature to 185 references which were used in this review. They were selected based on the abstracts.

RAS: CIRCULATING RAS AND TISSUE RAS

History

The very first clue of the existence of RAS was found in 1898 when scientists Robert Tigerstedt and Per Bergman in Finland discovered that injecting renal homogenate from one rabbit to another causes an acute elevation of BP indicating that kidney secretes a vasopressor substance, named renin[23,24]. Due to the discovery of this hormone, RAS was first thought to be a hormone system through which the kidney influences systemic cardiovascular regulation[25]. Over 40 years later more RAS effectors were found. In 1940, groups working under Braun-Menéndez and Page reported that previously identified renin catalyzes the formation of pressor peptide, first named angiotonin or hypertensin, from a plasma protein substrate angiotensinogen[22,26,27]. Later angiotonin was renamed angiotensin[22].

In the early 1970s major components of the circulating RAS were found and its important role as a BP and fluid balance regulator was understood[23]. In addition, first antihypertensive medications were developed in the 1970s. First of these drugs was captopril, an ACE inhibitor that was designed to prevent the formation of vasoconstrictive peptide Angiotensin (Ang) Ⅱ[22,23]. In 1988, Ang Ⅱ receptor type 1 blockers (ARBs) were invented which main goal was to prevent the direct effects of Ang Ⅱ mediated through angiotensin Ⅱ type 1 receptor (AT1R)[12]. During past years many new peptides and a new angiotensin reseptor type (Mas receptor, MasR) have been identified. MasR is an important member of the RAS, and its actions are mainly opposite to those of AT1R. Mas-receptors play a role in cell proliferation and antifibrosis as well as vasodilatation and local fluid volume homeostasis. In fact, the potentials of MasR ligands, like Ang (1-7) and ACE2 in degrading vasoconstrictive Ang Ⅱ to vasodilatory peptides are regarded as a present focus of cardiovascular drug development[28-30].

Circulating RAS

When RAS was first described, it was seen as a linear cas-

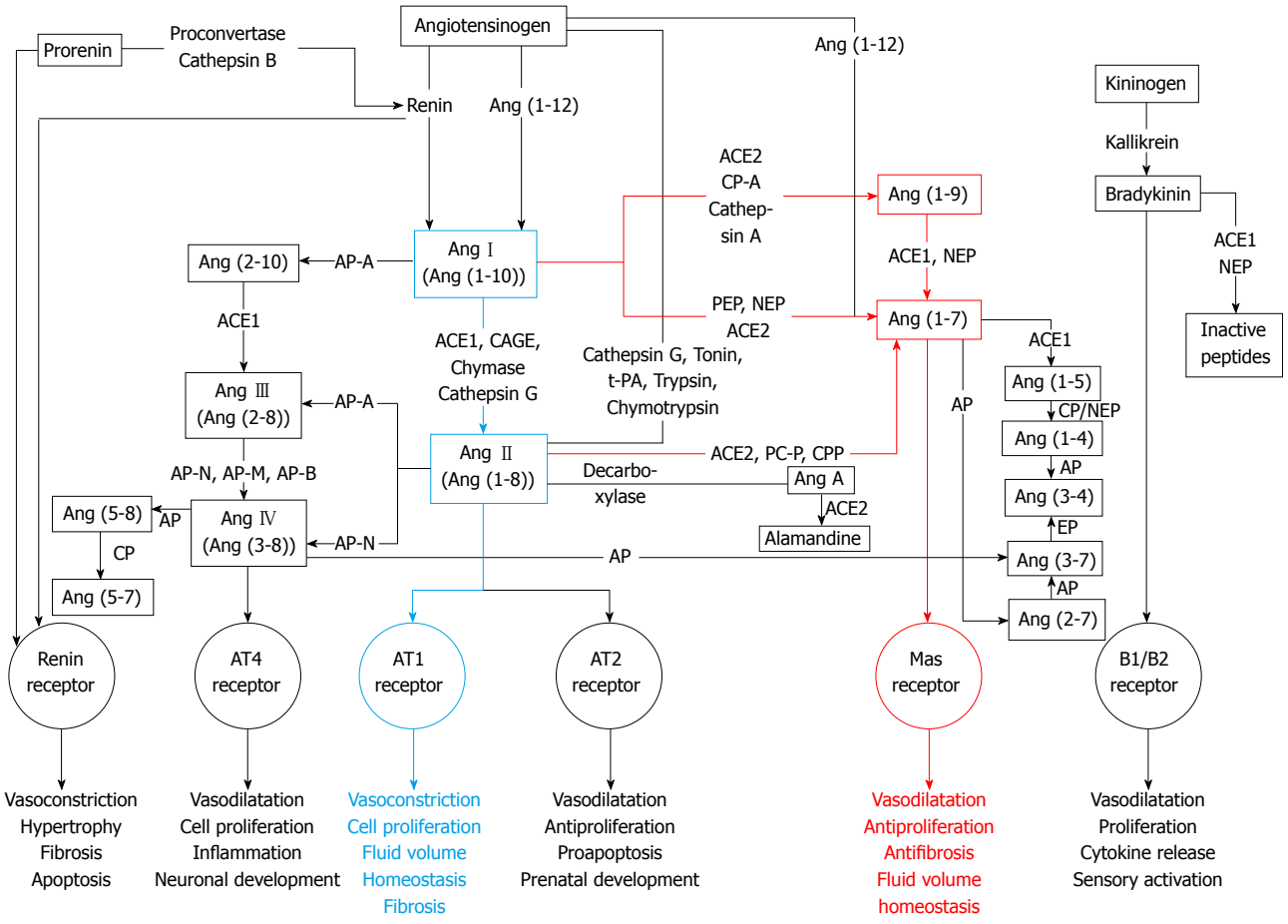

Figure 1 The renin-angiotensin system. The two main pathways of RAS: Ang II-ACE1-AT1R (blue lines) and Ang(1-7)-ACE2-MasR (red lines) are highlighted with colours. ACE(1): Angiotensin-converting enzyme (1); ACE2: Angiotensin-converting enzyme related carboxypeptidase; Ang I, II, III, IV: Angiotensin I, II, III, IV; Ang(1-10): Angiotensin (1-10); Ang(1-8): Angiotensin (1-8); Ang(2-8): Angiotensin (2-8); Ang(3-8): Angiotensin (3-8); Ang(1-9): Angiotensin (1-9); Ang(1-7): Angiotensin (1-7); Ang(1-5): Angiotensin (1-5); Ang(1-4): Angiotensin (1-4); Ang(2-7): Angiotensin (2-7); Ang(3-7): Angiotensin (3-7); Ang(3-4): Angiotensin (3-4); Ang(1-12): Angiotensin (1-12); Ang(5-8): Angiotensin (5-8); Ang(5-7): Angiotensin (5-7); Ang(2-10): Angiotensin (2-10); A: Angiotensin A; AT1R: Angiotensin II type 1 receptor; AT2R: Angiotensin II type 2 receptor; AT4R: Angiotensin II type 4 receptor; AP: Aminopeptidase (-A, -N, -M, -B); B1/B2: Bradykinin receptors; CAGE: Chymostatin-sensitive AngII generating enzyme; CP: Carboxypeptidase; EP: Endopeptidase; Mas receptor: Ang(1-7) receptor type; Nep: Neprilysin; PEP: Prolyl endopeptidase; PCP: Prolylcarboxypeptidase; tPA: Tissue-type plasminogen activator. The picture is updated from Vaajanen *et al*[160].

cade consisting of only one substrate (angiotensinogen), two proteases (renin and ACE1), two peptides (AngI and AngⅡ) and one receptor (AT1R). Today, RAS is known to consist of several enzyme pathways and to include over twenty peptidases, close to twenty angiotensin peptides and at least six receptors[31,32]. Thus, the classical linear cascade has evolved to a cascade with multiple mediators, multifunctional enzymes and multiple different receptors mediating the effects of angiotensin peptides[33-35]. The complexity of the RAS cascade known today is seen in Figure 1.

Central peptides of RAS

Angiotensinogen (AGT) is a 255 amino acids long α-glycoprotein that is synthesized in and released from liver. Renin catalyzes the reaction in which angiotensinogen is converted into AngI[22,36,37]. Mainly synthetized in the liver, angiotensinogen is also formed in heart, vessels, kidney and adipose tissue[38]. The synthesis of α-glycoprotein angiotensinogen is stimulated *e.g.* by inflammation, insulin and estrogens[36].

Angiotensin Ⅰ (Ang Ⅰ), a weak active prohormone, also known as angiotensin (1-10), is a decapeptide generated from angiotensinogen by an enzyme renin[39]. Ang Ⅰ, a weak vasoconstrictor is further cleaved to an octapeptide AngⅡ by ACE1 removing two amino acid residues (His-Leu) from the carboxy terminal of AngI[39,40]. AngⅡ can also be generated by enzymes other than ACE1 such as chymase and cathepsin G.

Angiotensin Ⅱ (AngⅡ), also known as Ang(1-8), first isolated in 1940 and characterized as a potent vasoconstrictor that elevates BP[26,27]. Then, RAS was regarded as an endocrine system in which circulating AngⅡ regulates electrolyte balance, vascular tone, thirst, water intake, aldosterone synthesis, sympathetic activity, sodium handling in the kidney, and antidiuretic vasopressin release from the posterior part of hypophysis[37]. In circulating RAS, renin formed in the kidney is the rate-limiting factor for AngⅡ formation in circulating RAS whereas in vascular tissue ACE1 and chymase are the main actors in AngⅡ generation[41].

AngⅡ exerts its main actions *via* two types of

receptors, AT1R and AT2R[36,42]. Ang Ⅱ can be generated from Ang Ⅰ by three different categories of enzymes: ACE1, a metallo dipeptidyl carboxypeptidase, secondly aprotinin-sensitive serine proteases, such as trypsin, tonin, kallikrein and cathepsin G and thirdly a group of chymostatin-sensitive serine proteases, such as human chymase[43]. Ang Ⅱ, a potent vasoconstrictor stimulates the release of vasopressin and aldosterone and thus participates sodium and water retention all of which act in concert to raise BP[37]. ACE inhibitors as antihypertensive medication block the conversion of Ang Ⅰ to Ang Ⅱ by ACE1, thus antagonizing the harmful effects of Ang Ⅱ on AT1R[36].

Angiotensin Ⅲ (AngⅢ), also known as Ang(2-8), is generated from Ang Ⅱ or from angiotensin (2-10) by aminopeptidase A and ACE1[22,23,36,37]. This heptapeptide was found in 1970s and it exerts its actions *via* AT1 and AT2 receptors. AngⅢ has higher affinity to AT2 receptors than to AT1 receptors[44]. AngⅢ induced vasoconstriction and release of aldosterone are close to those of Ang Ⅱ. AngⅢ has 40% of the vasoconstriction activity of Ang Ⅱ[22,23,37]. In some actions on AT1R the role of AngⅢ is at least equally important as that of Ang Ⅱ[23,37].

Angiotensin Ⅳ (AngⅣ), is generated from Ang Ⅱ by aminopeptidase N or from AngⅢ by several other aminopeptidases N, M and B[22,37]. This hexapeptide [Ang(3-8)] exerts its actions *via* angiotensin Ⅱ type 4 receptor (AT4R) found in kidney, lung, brain and heart[23,45,46]. However, AngⅣ can also induce its effects such as renal vasodilatation, hypertrophy and regulation of cell growth in endothelial cells, cardiac fibroblasts and vascular smooth muscle cells by interacting with AT1R[47]. Furthermore, AngⅣ is thought to have an important regulatory role in cardiovascular damage, cognition and renal metabolism and it might be involved in the vascular inflammatory response[22,37].

Angiotensin (1-9) [Ang(1-9)] is formed by cleaving one amino acid residue from the carboxyl terminus of AngI by ACE2[48] and is metabolized by ACE1 and NEP to generate Ang(1-7)[49]. Ang(1-9) can also be generated from Ang Ⅰ through the activity of carboxypeptidase A or cathepsin A[50,51]. The formation of Ang(1-9) is dependent on ACE2 activity[49,52]. The biological function of Ang(1-9) is to increase nitric oxide formation and release of arachidonic acid, enhance bradykinin activity[50] and possibly be involved in the inhibition of platelet function[53]. Ang(1-9) may decrease BP and thus protect the heart and blood vessels and reduce hypertension[54]. Ang(1-9) could mediate its actions *via* the AT2 receptors[54,55].

Angiotensin (1-7) [Ang(1-7)] was originally believed to be an inactive component of RAS. In 1988 this heptapeptide was shown to have actions opposing those of Ang Ⅱ[37]. Ang(1-7) is generated from Ang Ⅱ by ACE2 or by other known peptidases such as prolylendopeptidase and prolyl-carboxipeptidase[23,37,42,56]. Ang(1-7) can also be synthesized directly from AngI by prolylendopeptidase and from Ang(1-9) or from prohormone Ang(1-12) bypassing the synthesis of Ang Ⅱ[37,56]. Furthermore, Ang(1-7) interacts with the kallikrein-kinin system, and can be converted into Ang(1-5) or into Ang (3-7)[22]. Ang(1-7) levels are elevated by ACE inhibitors that increase AngI concentration and on the other hand prevent Ang(1-7) degradation[37].

Ang(1-7) was thought to be devoid of biological functions[37]. Nowadays Ang(1-7) is seen as a protector peptide that counterbalances many functions of Ang Ⅱ by binding to MasR which mediates vasodilating and antiproliferative functions of Ang(1-7)[23,36,55,57]. Although MasR is the main receptor of Ang(1-7), some of the functions may still originate *via* AT1R and AT2R[54,55,57,58]. In addition to the inhibition of Ang Ⅱ-induced vasoconstriction by Ang(1-7), its antiarrhythmogenic, antithrombogenic and growth-inhibitory properties suggest that Ang(1-7) acts as a physiological counterregulator within the RAS, and that Ang(1-7) could be a potential target for drug development[33-35]. In fact, Ang(1-7) has been associated to pathophysiology of several diseases such as. hypertension[59-63], chronic renal diseases[61] and diabetic nephropathy[64,65].

In addition to previously described peptides, RAS cascade includes short peptides which functions and roles in this circulating and tissue-specific regulatory system are still poorly known.

Key enzymes of RAS

Renin, ACE1 and ACE2 are seen as three key enzymes of the RAS. Renin, a specific enzyme having only one known substrate, is an aspartyl protease that cleaves its substrate angiotensinogen to form Ang Ⅰ. Renin cleaves the peptide bond between Leu10 and Val11 at the amino terminus of angiotensinogen. Renin is synthesized as a 406 amino acid residues long inactive prorenin in the juxtaglomerular apparatus of the kidney[22,36,37]. Upon demand synthesized prorenin is cleaved and activated by proconvertase or cathepsin B to generate 340 amino acid residues long catalytically active form of renin. Renin can also be synthesized in organs such as brain, heart, testis, pituitary and adrenal glands, arterial smooth muscle and eye[36]. Classically, renin is secreted by juxtaglomerular cells in response to three different stimuli: (1) decreased arterial BP; (2) decreased sodium levels in the macula densa ultrafiltrate; and (3) increased sympathetic nervous system activity[40,66,67]. Activation of prorenin can be either proteolytic or non-proteolytic. The proteolytic way is irreversible while the latter one is reversible[36].

ACE1 belongs to the M2 family of metallopeptidases containing zinc in its active site. ACE1 is a monomeric glycoprotein that has two different isoforms: somatic ACE1 (sACE1, 150-180 kDa) and germinal ACE1 (gACE1, 90-110 kDa)[36]. The somatic ACE1 is found in various epithelial and endothelial cells[68] whereas germinal ACE1 in germinal cells in the testis[36]. ACE1 is a type I integral membrane protein that consists of hydrophilic C-terminal cytoplasmic domain, hydrophobic transmembrane

domain and a heavily glycosylated N-terminal ectodomain[36]. It is distributed in many tissues and is also found in biological fluids, *e.g.*, in plasma and cerebrospinal fluid[69-71].

ACE1 has an activated water molecule complexed to Zn^{2+} in its active sites[72]. In addition, ACE1 activity depends on the presence of chloride that enhances the binding of different substrates[73]. As an exopeptidase ACE1 cleaves dipeptides from the free C-terminus of Ang Ⅰ and of the hypotensive peptide bradykinin[36,40]. ACE1 can also generate AngⅢ and Ang(1-7) and then further degrade Ang(1-7) to inactive Ang(1-5). Moreover, ACE1 acts in kallikrain-kinin system cleaving bradykinin to inactive compounds[36,40,57]. Because ACE1 participates in regulation of BP and in development of cardiovascular diseases, it is one major target for pharmacotherapy[36].

ACE2, the first known human homologue to ACE1 (42% sequence identity), was cloned in 2000[36,42,48,68,74]. ACE2 was first shown to convert AngI to Ang(1-9)[48]. Later, ACE2 was found to hydrolyze AngⅡ into Ang(1-7) with much higher efficiency (approximately 400-fold) than the hydrolysis of AngI to Ang(1-9)[36,42,49,57,75]. ACE2 is a 805 amino acid residues long (120 kDa) type Ⅰ transmembrane glycoprotein that has been found in organs such as kidney, heart, lungs, liver and brain. ACE2 has a conserved zinc metallopeptidase consensus sequence His-Glu-X-X-His, in wich X stands for any amino acid (HEXXH) in its active site and its activity is regulated by chloride ions[36]. Contrary to ACE1, primarily dipeptidylcarboxypeptidase, ACE2 functions as a monocarboxypeptidase cleaving a single amino acid residue (Phe) from AngⅡ to generate Ang(1-7). Thus, it negatively regulates the activated RAS and ACE1 activity by degrading AngⅡ and increasing Ang(1-7) formation[36,74]. ACE2 is not blocked by conventional ACE inhibitors[58].

ACE2 together with Ang(1-7) and MasR have become the focus of recent research regarding RAS[42,58]. ACE2 is seen as the key player maintaining the balance between the two main pathways of RAS: ACE1-AngⅡ-AT1R and ACE2-Ang(1-7)-MasR[36]. Chronic and long lasting imbalance of these two enzymatic pathways may lead to pathophysiology of the renal, pulmonary, cardiovascular and central nervous system[76].

In addition to previously mentioned enzymes, there are several different peptidases and proteases that act on longer angiotensin peptides thus cleaving them into shorter peptides. For example, AngⅡ can be generated from Ang Ⅰ by four different enzymes: ACE1, CAGE, chymase and cathepsin G[43]. Alternative enzymes acting on different angiotensin peptides are shown in Figure 1.

Alternative pathways for angiotensin II biosynthesis

A number of studies have shown alternative pathways for AngⅡ generation[77-79] being important in physiological and pathophysiological conditions[41,80]. AngⅡ-forming enzymes can be divided into three categories: metallodipeptidyl carboxypeptidase known as ACE1, aprotinin-sensitive serine proteases such as tonin[81], cathepsin G[82], kallikrein[83], trypsin[84] and chymostatin-sensitive serine proteases such as human chymase[85,86] (Figure 1).

Main receptors of RAS

Human (pro)renin receptor [(P)RR] is a 350 amino acid residues long single transmembrane-domain protein containing unglycosylated N-terminal domain responsible for renin and prorenin binding and the short cytoplasmic tail that is involved in the intracellular signalling[36,87]. Compared to the binding of free renin, the binding of renin to (P)RR is 3- to 5-fold more catalytically efficient, thus cleaving AGT to AngI more effectively[36,37].

Four heptahelical G-protein-coupled receptors of RAS: AT1R, AT2R, AT4R and MasR, mediate the effects of angiotensins causing vasodilatation and vasoconstriction[55,88]. AT1 and AT2 receptors are mainly responsible for mediating the effects of AngⅡ, whereas AT4 receptor is target of AngⅣ generated by degradation of AngⅡ[23,37]. A break-down product of Ang(1-7), namely Ang(3-7), can also bind to AT4R. AT4 receptors are located in the brain, lungs, heart, kidneys and liver and they are related to cognitive functions and proliferative effects[43,45,46].

Although AT1 and AT2 subtypes bind Ang Ⅱ in a similar manner, they differ in tissue-specific expression and genomic structure (only about 30% sequence homology) as well as in localization and regulation. AT1 receptors can be activated by Ang Ⅱ but other peptides, such as Ang Ⅲ, Ang Ⅳ and Ang(1-7), can also stimulate AT1R but with lower binding affinity[43]. AT1 and AT2 receptors mediate opposite effects of Ang Ⅱ, the former having negative cardiovascular effects, such as vasoconstriction and aldosterone release, and the latter having positive cardiovascular effects[12]. Whereas the role and function of AT1R is quite well established, the function of AT2R is not as clearly defined[55]. AT2 receptors, which are activated by Ang Ⅱ and also by Ang(1-7), may exert the antiproliferative, proapoptotic, vasodilatory and antihypertensive effects[43,89]. AT2 receptors are known to be involved in differentiation, regulation of growth and regeneration of neuronal tissue, and they are also known to play an important role in prenatal development. AT2 receptors can also inhibit AT1R signaling by directly binding into it. Thus they are considered to be cardiovascular protective receptors[12].

MasR was first discovered in year 1986 by Young *et al*[90] as proto-oncogene. Two years later high MasR levels were reported in the rat central nervous system by the same research group[91]. Later Kitaoka *et al*[92] described MasR expression in the eyes of rhesus macaque. It was early found in the mouse kidney and described as a factor involved in tumorigenesis[93]. Subsequently it is also found in other organs such as in heart, vessels, testis, kidney and brain[94] and very recently in the

human eye[95]. MasR is a G protein coupled receptor that has seven transmembrane domains[93]. This receptor acts antagonistically to the AT1R, mediating number of positive cardiovascular effects, such as vasodilation and antiproliferative effects, of its ligand Ang(1-7)[43]. MasR is part of the counterregulatory arm of RAS (ACE2-Ang(1-7)-MasR) thus balancing the effects of ACE1-Ang Ⅱ-AT1R pathway[34,35].

Tissue RAS

In addition to circulatory RAS, various organs have their own local RA-systems accounting for long-term changes and local effects including proliferation, growth and protein synthesis at tissue level[12,23,41]. The first clues of the existence of local RA-systems came in 1971 when Ganten *et al*[96] demonstrated that RAS components could be produced locally in organs and tissues. This proves that RAS is not only a circulating hormonal system, as thought earlier, but also a tissue-specific regulatory system[23]. Heart, liver, brain, kidney, lungs, intestine and even the human eye have their own local RA-systems[2,12,37].

Local RAS includes all components necessary for independent production of different components of RAS, such as Ang Ⅱ, angiotensinogen, ACE1, AT1R and AT2R[2,12,37]. Thus, RAS is not only an endocrine and circulating, but also a local paracrine and intracrine system regulating more functions than was previously thought[12,41]. Even though many of the local RA-systems operate independently from the circulatory RAS, in heart and kidney, tissue-RAS operates in close interaction with the systemic RAS thus complementing each other's functions[37]. Based on the origin of Ang Ⅱ, local RAS can be divided into extrinsic and intrinsic system, the former getting its Ang Ⅱ from the circulation and the latter obtaining its Ang Ⅱ through local biosynthesis[18].

LOCAL OCULAR RAS

RAS expression

Local RAS has also been identified in the human eye. Researchers have localized all of the central components of RAS, including its receptors, to the structures of the eye in variety of species[2,5]. Moreover, all components of the two main axes of RAS: Ang Ⅱ-ACE1-AT1R and Ang(1-7)-ACE2-MasR have been identified in the ocular structures of different species. When human eye is considered, the components of the two main axes are found in retinal structures and in non-retinal structures of the human eye[2,95,97]. Our research group has very recently succeeded to determine Ang (1-7) and ACE2 in the human aqueous humor[97]. Tables 1 and 2 summarize the localization of RAS peptides and enzymes in non-retinal ocular structures of the human eye. Tables 3 and 4 summarize the localization of RAS receptors in non-retinal ocular structures of the human eye. Although, essential components of RAS haven been identified in the human eye, the importance and functions of intraocular RAS are still unknown. However, intraocular RAS has been the focus of growing interest in recent years due to its possible role in the regulation of IOP through its effects on aqueous humor formation and drainage[5,12]. Furthermore, intraocular RAS activity has been linked to the development of glaucoma through its effect on IOP[2].

Concerning intraocular local RAS, there has been debate whether intraocular angiotensins originate from local production or from the blood compartment[14]. It has been shown that neither Ang Ⅰ, Ang Ⅱ nor angiotensinogen are able to pass the blood-brain barrier which is similar to blood-retina barrier in the eye[14,121,122]. Circulating angiotensins cannot reach the vitreous fluid when blood-retina barrier is intact[14]. However, if disrupted their entering the eye through blood-retina barrier becomes possible[99]. In porcine ocular tissues Ang Ⅰ and Ang Ⅱ levels are 5 to 100-fold over those found from admixture with blood or diffusion from blood[14]. In rabbit and pig ACE1 activity has been shown to be higher in ocular tissues than in plasma[101,108]. The local intraocular RAS is estimated to have a role in the regulation of IOP affecting the formation of aqueous humor and the drainage. It has been shown that systemic antihypertensive RAS-inhibiting medications lower IOP. Certain ACE inhibitors[15] and AT1 receptor blockers[16] have proved to lower IOP in both non-glaucomatous and glaucomatous patients. In animal studies, ACE inhibitors[17,18], AT1 receptor blockers[19,20] and renin inhibitors[21] have been reported to reduce IOP. It has also been suggested that Ang Ⅱ can increase aqueous humor secretion *via* AT1 receptor[123].

Aqueous humour dynamics and IOP

Aqueous humor formation: Intraocular pressure (IOP) can be described as a net sum of homeostatic balance between aqueous humor formation and outflow[124,125]. In the healthy human eye, the flow of aqueous humor against the resistance generates an IOP of about 15 mmHg[126]. Maintaining the optimal physiological IOP is fundamental to keep the optical and refractive properties of the eye, including the right shape of the eye[125,127]. The circulating fluid nourishes unvascularized eye structures such as the cornea and the lens. The normal aqueous humor formation rate is 2.5-2.8 μL/min and the entire volume is replaced every 100 min[5]. This is reduced during sleep, with ageing, and in some systemic diseases like diabetes[128]. Currently IOP is the main risk factor for glaucoma that is amenable to treatment[129].

The ciliary body epithelial lis responsible for the production of aqueous humor[124] which is secreted mainly by active ionic transport across the epithelium against a concentration gradient[118]. Active secretion requires energy, produced in hydrolysis of adenosine triphosphate (ATP) by Na^+/K^+ ATPase. Active transport of Na^+ into the posterior chamber by the non-pigmented ciliary epithelial cells induces also water movement from the stromal pool into the posterior chamber. Active transport of Cl^- and HCO_3^- occurs to a lesser extent[130]. In addition to the active secretion two other physiological

Table 1 Renin-angiotensin system components in tears, lacrimal gland, bulbar conjunctiva, cornea, trabecular meshwork, aqueous humor and iris

RAS component	Tears lacrimal gland	Bulbar conjunctiva	Cornea	Trabecular meshwork	Aqueous humor	Iris
Prorenin		White *et al*[98]	White *et al*[98]		Danser *et al*[99]	White *et al*[98]
Renin		White *et al*[98]	White *et al*[98]			White *et al*[98]
AGT		White *et al*[98]	White *et al*[98]		Chowdhury *et al*[100]	White *et al*[98]
ACE1	Vita *et al*[102]	Savaskan *et al*[13]	Savaskan *et al*[13]	Savaskan *et al*[13]	Vita *et al*[102]	Ferrari-Dileo *et al*[107]
	Sharma *et al*[103]				Weinreb *et al*[105]	
	Immonen *et al*[104]	White *et al*[98]	White *et al*[98]		Aydin *et al*[106]	White *et al*[98]
					Holappa *et al*[97]	
ACE2					Holappa *et al*[97]	
Ang I					Danser *et al*[14]	Danser *et al*[14]
						Osusky *et al*[109]
Ang II		Savaskan *et al*[13]	Savaskan *et al*[13]	Osusky *et al*[109]	Danser *et al*[14]	Danser *et al*[14]
				Savaskan *et al*[13]	Osusky *et al*[109]	Senanayake *et al*[110]
Ang(1–7)				Vaajanen *et al*[95]	Holappa *et al*[97]	

Table modified and updated from the table published by Giese et Speth, 2014. ACE1, -2: Angiotensin converting enzyme 1, -2; AGT: Angiotensinogen; Ang Ⅰ, -Ⅱ: Angiotensin Ⅰ, -Ⅱ; Ang(1–7): Angiotensin (1–7); RAS: Renin-angiotensin system.

Table 2 Renin-angiotensin system components in ciliary body, non-pigmented ciliary epithelium, lens, vitreous, optic nerve head and sclera

RAS component	Ciliary body/non-pigmented ciliary epithelium		Lens	Vitreous	Optic nerve head	Sclera
Prorenin	Sramek *et al*[111]	White *et al*[98]		Danser *et al*[99]		White *et al*[98]
	Danser *et al*[99]			Wallow *et al*[112]		
	Wallow *et al*[112]					
	Berka *et al*[113]					
Renin	Berka *et al*[113]	White *et al*[98]				White *et al*[98]
AGT	Sramek *et al*[114]			Sramek *et al*[114]		
ACE1	Igic *et al*[115]	Savaskan *et al*[13]		Ferrari-Dileo *et al*[107]	Ferrari-Dileo *et al*[107]	White *et al*[98]
	Ferrari-Dileo *et al*[107]	White *et al*[98]		Nakanishi *et al*[116]		
	Sramek *et al*[114]			Ishizaki *et al*[117]		
				Aydin *et al*[106]		
ACE2						
Ang I	Danser *et al*[14]					
Ang II	Danser *et al*[14]	Senanayake *et al*[110]		Senanayake *et al*[110]	Savaskan *et al*[13]	
	Savaskan *et al*[13]					
Ang(1–7)	Vaajanen *et al*[95]	Vaajanen *et al*[95]				

Table modified and updated from the table published by Giese et Speth, 2014. ACE1, -2: Angiotensin converting enzyme 1, -2; AGT: Angiotensinogen; Ang Ⅰ, -Ⅱ: Angiotensin Ⅰ, -Ⅱ; Ang(1–7): Angiotensin (1–7); RAS: Renin-angiotensin system.

processes exist in the fluid formation: diffusion from the blood compartment and ultrafiltration. They are passive and require no cellular activity[131]. The whole ciliary body system and its aqueous humor formation should be regarded as a multifunctional and interactive process. Aqueous humor is a mixture of organic solutes, electrolytes, growth factors, cytokines and proteins[132-136]. After the production it is secreted into the posterior chamber from where it flows between the lens and iris into the anterior chamber[132,137,138].

Aqueous humor outflow: *Via* anterior chamber and through the trabecular meshwork and the canal of Schlemm, aqueous humor escapes the eye into the venous blood system[124]. It can leave the eye through three different main routes: the trabecular, the uveoscleral or the uveolymphatic pathways[129]. Trabecular outflow is the main route of drainage accounting for 90% of all aqueous humor outflow, and it is pressure-dependent[5,129,139]. The fluid outflow through the trabecular meshwork is affected by adhesions of trabecular meshwork cells and by the state of the actin cytoskeleton[140].

Outflow, where aqueous humor drains through the ciliary muscle and exits through the supraciliary space and across the anterior or posterior sclera into choroidal vessels, is called the uveoscleral outflow[141] which is independent of IOP and particularly impacted by age[139]. A third outflow route is suggested to exist: channels in the stroma of the ciliary body and interstitial spaces between ciliary muscle bundles. It may function as a backup outflow system[142]. The relevance of this pathway remains to be determined. The other alternative, minor outflow pathways are *via* iris vessels, corneal endothelium, or anterior vitreous body[143].

Pharmacological treatment of glaucoma reduces IOP

Table 3 Renin-angiotensin system receptors in tears, lacrimal gland, bulbar conjunctiva, cornea, trabecular meshwork, aqueous humor and iris

RAS component	Tears lacrimal gland	Bulbar conjunctiva	Cornea	Trabecular meshwork	Aqueous humor	Iris
(P)RR		White *et al*[98]	White *et al*[98]			White *et al*[98]
AT, unknown subtype						Lin *et al*[119]
AT1R						Senanayake *et al*[110]
AT2R						Senanyake *et al*[110]
AT4R						
MasR			Vaajanen *et al*[95]	Vaajanen *et al*[95]		

Table modified and updated from the table published by Giese et Speth, 2014. AT1, 2, 4: Angiotensin Ⅱ type 1, 2, 4 receptor; MasR: Mas receptor; (P)RR: (pro)renin receptor; RAS: Renin-angiotensin system.

Table 4 Renin-angiotensin system receptors in ciliary body, non-pigmented ciliary epithelium, lens, vitreous, optic nerve head and sclera

RAS component	Ciliary body/non-pigmented ciliary epithelium		Lens	Vitreous	Optic nerve head	Sclera
(P)RR	White *et al*[98]					White *et al*[98]
AT, unknown subtype	Lograno *et al*[120] Lin *et al*[119]					
AT1R	Cullinane *et al*[123]	Senanayake *et al*[110]			Senanayake *et al*[110]	
AT2R		Senanayake *et al*[110]			Senanayake *et al*[110]	
AT4R						
MasR		Vaajanen *et al*[95]				

Table modified and updated from the table published by Giese et Speth, 2014. AT1, 2, 4: Angiotensin Ⅱ type 1, 2, 4 receptor; MasR: Mas receptor; (P)RR: (pro)renin receptor; RAS: Renin-angiotensin system.

by decreasing the rate of aqueous humor formation or by increasing the rate of aqueous humor outflow[144].

Glaucoma

It is well-known that defects in the RAS cascade are involved in several cardiovascular and renal diseases, including heart failure, hypertension, ventricular hypertrophy, cardiac remodelling, and chronic renal failure[145-147], but interestingly, imbalances in the RAS cascade are also involved in glaucoma[3], which is a neurodegenerative disorder that leads to the loss of the axons populating the optic nerve and to the death of retinal ganglion cells by non-apoptotic and apoptotic mechanisms[2,3,6]. Together with age and family history, increased IOP is one of the known major risk factors for glaucoma[2,6,7]. Diabetes, migraine/vasospasms and vascular dysfunction are also considered as risk factors for glaucoma development[5,6,129].

Ocular hypotensive medications, laser procedures and surgical means are currently the major therapeutic tools to treat glaucoma[2,6,22]. They all act by lowering IOP thus affecting the onset of the disease[5]. Interestingly, antihypertensive medications acting on RAS have been shown to lower also IOP, suggesting that compounds blocking RAS might be potential anti-glaucomatous drugs in the future[22]. ACE inhibitors can decrease Ang Ⅱ levels in aqueous humor[109]. By reducing blood flow in the ciliary body ACE inhibitors could also decrease aqueous humour production[148]. Furthermore, by preventing the breakdown of bradykinin ACE inhibitors are able to promote synthesis of endogenous prostaglandins, which, as shown with marketed prostaglandin analogues, could increase the uveoscleral outflow thus lowering IOP[149,150]. Biosynthesis of certain matrix metalloproteinases is thought to be associated with increased uveoscleral outflow which leads to relaxation of the ciliary muscle and reduction and compaction of extracellular matrix components within the ciliary muscle, the sclera, the iris and within tissues of the uveoscleral outflow route, all of which might lower IOP by facilitating aqueous humor outflow[151]. ACE-inhibitors activate also the nitric oxide pathway by preventing bradykinin breakdown which increases endothelial nitric oxide formation and causes vasodilatation. Bradykinin stimulates the synthesis of prostaglandins and nitric oxide which also antagonize the vasoconstrictive effects of endothelin-1 and inhibit the overall production of endothelin-1 by endothelial cells. Endothelin 1 is a vasoconstrictive peptide that promotes contraction in the human ophthalmic artery and in the porcine ophthalmic and ciliary arteries[152-154].

Moreover, RAS activity has been described in cultured non-pigmented human ciliary epithelial cells which participate in aqueous humor formation and many of the central components of RAS have been identified in eye structures responsible for aqueous humor formation such as ciliary body[2,119,123]. Ang Ⅱ can activate Ca^{2+} signalling system that increases potassium ion channel activity[155]. Together with cell volume loss, these effects suggest that Ang Ⅱ acts as a operated secretagogue in the non-pigmented ciliary cells[123]. In

addition, Ang Ⅱ activates Na^+/H^+ exchange which leads to an increase in cytoplasmic sodium concentration[118]. In ciliary and renal tubular epithelium sodium handling related mechanisms are common pathogenetic factors. This might explain the coexistence of glaucoma and systemic hypertension[156]. Other explanations have also been suggested for the relationship between hypertension and glaucoma development. Hypertension is shown to cause impairment in autoregulation of the posterior ciliary circulation[157] and suggested to induce microvascular damage thus worsening blood flow to the optic nerve[158]. Furthermore, antihypertensive therapy has been described to cause hypotensive episodes that can injure the optic nerve[159].

In addition to possible role of RAS in the aqueous humor formation, RAS is suggested to act in aqueous humor outflow. Ang Ⅱ is able to promote cell proliferation in bovine trabecular meshwork cells and increase synthesis of collagen *in vitro*. Moreover, intracamerally administered Ang Ⅱ reduces uveoscleral outflow[160]. Paradoxically, natural and synthetic Ang Ⅱ, when administered intravenously, lowered IOP in anaesthetized cats[161].

RAS AND OTHER EYE DISEASES

In addition to glaucoma, local intraocular RAS has been associated with other severe eye diseases that can lead to permanent vision loss, such as age-related macular degeneration (AMD), ROP and DR. Dysregulation of RAS cascade participate in the development of these severe eye diseases.

AMD

In elderly people, AMD is one of the leading causes of visual impairment. Both dry and wet forms of the disease are associated with vision loss. Dry forms of the disease accounting for 90% of the cases lead to the significant decline of photoreceptors which ultimately causes central vision loss. On the contrary, wet form of AMD is characterized with pathological growth of cloroidal blood vessels that will eventually populate retina after breaking through the underlying Bruch's membrane. In addition to old age, environmental factors, smoking, genetic susceptibility and systemic hypertension are regarded as risk factors for developing AMD. Interestingly dysregulation of the RAS cascade is suggested to play a role in the development of AMD[2,162,163].

Three key observations are held as evidence showing the possible involvement of RAS in the development of AMD. Firstly, systemic hypertension is a risk for the development of AMD. Secondly, dysregulation of RAS may have an impact on retinal pigment epithelium function and photoreceptor viability due to the observations that Ang Ⅱ can modulate retinal pigment epithelium. Thirdly, Ang Ⅱ is involved in retinal angiogenesis thus it might have a role in choroidal neovascularisation[2,162]. Animal studies have proven that administered AT1R antagonist (losartan)[164] and other AT1 receptor blockers[165] and (pro)renin receptor inhibitor[166] can reduce choroidal neovascularization thus having a positive effect on AMD.

ROP

ROP is a neovascular disease affecting premature newborns. ROP is associated with pathological retinal neovascularisation that causes complications such as tractional retinal detachment, macula dragging and vitreal haemorrhage, all of which can lead to vision loss[162]. The main risk factors for the disease are low birth weight and lower gestational age, both of which correlate with immaturity of retina at birth. In fact, in industrialized countries, approximately two-thirds of infants with birth weight less than 1.25 kg manifest some degree of retinopathy[167]. The cause of ROP is thought to be the retinal blood vessels expanding from the optic nerve which growth halts when a premature neonate is brought into a high oxygen environment. When the newborn is brought back to normal conditions, the inner vasculature in retina fails to regain normal vessel growth thus creating an avascular area and causing neovascularisation and epiretinal angiogenesis that can lead to vision loss[168].

Studies using animal models have suggested that RAS is involved in the development of ROP. Infants that are diagnosed with ROP have had elevated serum prorenin levels[169], ocular renin levels[170,171] and increased AT1R and AT2R expression[170]. Treating oxygen induced retinopathy in animal models with ACE inhibitors and AT1R antagonists during the normal air conditions reduces pathological angiogenesis on the surface of the retina[170,172-174]. On the contrary, the role of AT2R in retinal vascular pathology and the effects of the use of AT2R antagonists on retinal angiogenesis are still debatable[[171,173,175,176].

Diabetic retinopathy

The development of progressive vascular pathology within the inner retina characterizes DR which is among of the leading causes of blindness worldwide[163,177]. Alterations in the blood-retinal barrier, ischemia, dilated capillaries associated with poor retinal perfusion, retinal microaneurysms, loss of pericytes leading to changes in vascular permeability and the release of growth factors which may induce neovascularisation are all implications of DR[178]. DR can occur as non-proliferative DR (NPDR), which corresponds to the early state of the disease, or as more advanced form of the disease: proliferative DR (PDR). In NPDR the breakdown of the blood-retinal barrier and weakened retinal blood vessels lead to the formation of microanuerysms that can leak fluid into retina causing swelling of the macula. In PDR blood vessels can grow into the vitreous and on the surface of the retina[177,179]. Blocking the RAS cascade seems to reduce the incidence and progression of DR suggesting that RAS may be implicated in the pathogenesis of the disease[180-182]. However, more research is required to understand the complex interplay between RAS cascade and DR.

CONCLUSION

Systemic RAS regulates BP homeostasis, body fluid volume and electrolyte balance. An interesting new observation is intraocular, local RAS, especially existed in the eye structures which are involved in aqueous humor dynamics. Human and animal studies have both shown that antihypertensive drugs blocking RAS at any level can reduce IOP suggesting that these kind of compounds may be potential anti-glaucomatous drugs in the future. Furthermore, compounds elevating Ang(1-7) formation, activating Mas receptors and positively affecting ACE2 activity offer new intriguing opportunities for ocular pharmacology in the future. Although IOP represents the major risk factor in glaucoma, reduction of IOP does not always prevent the progression of disease like in low-tension glaucoma, indicating that factors other than elevated IOP are involved in glaucoma progression. Apoptosis of retinal ganglion cells may be the main possible unsolved reason. ACE inhibitors[183], ARBs[184] and Mas-receptor ligands[185] have showed some potential neuroprotective effects, which will stimulate research activity in the future.

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MINIREVIEWS

Intravitreal drug administration for treatment of noninfectious uveitis

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Abstract

Intravitreal treatment became popular with the discovery of the blood ocular barriers, which significantly limit drug penetration in systemic or topical administration. As the mainstay of treatment in noninfectious uveitis (NOIU) is still corticosteroids, triamcinolone acetonide (TA) was the first intravitreally used agent in this subset of patients. Although it was very effective in controlling inflammation and improving the inflammation related complications, TA was found to have a high rate of intraocular complications and a relatively short half-life necessitating frequent reinjections. Other systemically used therapeutic options such as methotrexate and anti-tumor necrosis factor-α agents were also tried intravitreally. Additionally anti-vascular endothelial growth factor agents that are widely used intravitreally in the management of diabetic retinopathy and age related macular degeneration have become an option to control the uveitis related complications like macular edema, retinal and choroidal neovascularizations. Advances in biotechnology led to the slow release biodegradable implant era. These implants have a longer duration of action, which may help in decreasing the number of reinjections. Today two forms of implants have been approved for use in NOIU, Retisert (0.59 mg flucinolone acetonide, surgical intervention) and Ozurdex (0.7 mg dexamethasone, office based intervention). Studies dealing with newer agents (cyclosporine, LFG31, sirolimus) in the management of chronic NOIU are on the way. The search for ideal effective, safe and biocompatible intravitreal agents in the management of NOIU has not ended yet.

Key words: Uveitis; Intravitreal; Steroid; Implant

Core tip: The limitations related to the systemic use of treatment options in noninfectious posterior uveitis yielded intravitreal route. The hallmark of intravitreal treatment triamcinolone acetonide has a short half-life with a high rate of intraocular complications, and this led to the development of implants as a treatment option with various agents in the market still under

investigation. In this review, we try to summarize the intravitreal therapeutic options that are being used in noninfectious uveitis.

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INTRODUCTION

Ohm first described the use of intravitreal (IV) injections for therapeutic purposes in 1911 with injection of air in the repair of retinal detachment[1]. The therapeutic use of the IV route was not developed until the early 1970s, when investigations about the blood ocular barriers were started. The results of these investigations increased the use of the IV route which enables us to bypass anatomical barriers, for the administration of therapeutic agents[1]. From the middle of the 20th century, several agents such as antibiotics, antivirals, antifungals, steroids, anti-vascular endothelial growth factors (anti-VEGFs), immunomodulatory, anti-inflammatory, and antineoplastic agents have been used intravitreally[2-6]. Nowadays, as a method for providing higher therapeutic levels especially in the posterior segment of the eye, the IV route is widely used in many blinding diseases such as age related macular degeneration, diabetic retinopathy, vascular occlusions, macular edema, endophthalmitis, viral retinitis and ocular inflammatory disorders.

Noninfectious uveitis (NOIU) with posterior segment involvement is one of the ocular diseases in which IV injection is required. The mainstay of treatment in this subset of disease and its sight-threatening complications is still systemic corticosteroids. However, to overcome the blood ocular barrier effect, higher doses are needed causing higher risk of systemic side effects like hypertension, osteoporosis, diabetes mellitus, gastritis, skin thinning, hyperlipidemia and many fluid-electrolyte imbalances[7,8]. It is also important to note that children are more prone to side effects related to corticosteroids such as growth retardation, precocious puberty, immune and hypothalamic-pituitary-adrenal axis suppression[8]. Second line treatment, used for steroid sparing, consists of immunosuppressive and immunomodulatory agents, but these too have a serious systemic side effect profile. Thus, local therapy remains an attractive treatment of choice especially in uveitis that is not associated with systemic diseases, in unilateral presentation, and in patients with compliance problems for systemic drug use. It also offers an excellent adjunctive therapeutic opportunity in cases where adequate control of inflammation cannot be provided despite systemic treatment. As the blood ocular barriers do not permit topical treatment to achieve a sufficient therapeutic level in the posterior segment, local treatment by IV route serves as a good solution in posterior segment uveitis. IV triamcinolone acetonide (IVTA) has been the most widely preferred option but has a short half-life and limited duration of action. It also has important ocular side effects like cataract and glaucoma, which mostly require surgical intervention[9,10]. The evolution of IV injections has led to the development of IV implants which aim to increase the duration of action and decrease the number of injections.

In this paper we aim to perform a literature review of recent developments in IV treatment of NOIU.

CORTICOSTEROIDS

Triamcinolone acetonide

IVTA is effective in controlling vitritis, reducing macular edema and improving visual acuity with IV doses of 2 to 4 mg when applied in NOIU with posterior segment involvement[11-13]. Its method of action is *via* different pathways including the inhibition of phospholipase A synthesis, blocking the production of inflammatory cytokines, stabilizing the blood retinal barrier and reducing VEGF levels[5,14]. Kramer *et al*[15] found that IVTA was very effective in rapid clearing of the vitreous inflammation with improvement in the visual acuity when used either alone or in combination with systemic immunosuppressive therapy. Lasave *et al*[5] used a single IVTA injection in refractory uveitic cystoid macular edema and reported that both visual acuity and macular thickness measurements had improved successfully at the 6th month visit. They also found that there was a significantly better visual improvement in macular edema cases with duration of less than a year, and therefore suggested earlier use of IVTA in refractory cases. A similar efficiency was reported by Karacorlu *et al*[16] who also found that IVTA achieved an improvement in visual acuity at the end of 6-mo follow-up in 30% of cystoid macular edema cases due to Behcet's disease. Angunawela *et al*[17] published their long-term results of IVTA injections in uveitic macular edema refractory to systemic and orbital floor steroid injections and concluded that IVTA is effective. They stated that although retreatment is required, this can be maintained with orbital floor injections. In their series, 9 of the 12 eyes had increased visual acuity at the final control (mean 40.5-mo follow-up) while 3 of them were resistant.

One of the main limitations of the IVTA is the off-label use in Europe and many other countries and the preservative used which might be toxic to the retina. The second limitation is its relatively short duration of action lasting approximately 3-7 mo that necessitates frequent re-injections[18]. It is important to note that the vitreous half-life of IVTA in vitrectomized eyes is shorter since the clearance is quicker[10,19,20]. The third and most important limitation is the occurrence of ocular side effects such as cataract and intraocular pressure elevations. Approximately 1%-2% of cases require

Table 1 Summary of some intravitreal agents

	Application	Duration of action	Visual acuity	Glaucoma surgery	Cataract surgery
IVTA 4 mg (kenalog)	Injection	3-7 mo[17]	58.3% gained ⩾ 2 Snellen lines with a median 40.5-mo follow-up[16]	1%-2%[10]	15%-30%[10]
FA 0.59 mg (retisert)	Surgical implant	30 mo[21]	23% gained ⩾ 3 lines after 3 years[21]	32%-40%[21,23,25]	Nearly 100%[21,23,25]
Dexamethasone 0.7 mg (ozurdex)	Non-surgical implant	4-6 mo[21]	38% gained ⩾ 3 lines at 6th month[29]	None[30]	1.3%[30]
MTX 400 μg	Injection	4 mo[21]	38% gained ⩾ 2 lines at 3rd month[21]	None[21]	None[21]

IVTA: Intravitreal triamcinolone acetonide; FA: Flucinolone acetonide.

glaucoma surgery, 15%-30% require cataract surgery, and the risk of the need for these procedures increases with the number of reinjections[11].

Both frequent reinjection necessity and a high risk of intraocular complications have driven researchers to investigate long-lasting implantable IV agents with different glucocorticoid agents. Nowadays, flucinolone acetonide (FA) (Retisert, surgically implanted) and dexamethasone (Ozurdex, non-surgically implanted) implants are being used in NOIU and considerable data with regards to their efficiency and side-effect profile have been collected.

FA

The beneficial effect of surgically introduced IV implant of ganciclovir for the treatment of cytomegalovirus retinitis is the hallmark in development of the posterior segment implants. This route seems to be a perfect solution for chronic NOIU with a probable improvement in the duration of action, which is the major limitation of IVTA. FA with its low water solubility is the first Food and Drug Administration (FDA) approved glucocorticoid implant (Retisert, Bausch and Lomb, Rochester, NY) to be used in NOIU[21]. The implant is surgically placed and contains 0.59 mg FA that is slowly released up to 30 mo allowing the opportunity of tapering systemic medications, avoidance of multiple IV injections and possible concurrent complications of injections. The comparison of eyes, one having implant and the other not, revealed that the FA implant reduced the recurrence rate significantly from 62% to 20% in the implanted eye whereas recurrence was 59% in non-implanted eye at the end of the 3-year follow-up[22,23]. In the Asian population, Sangwan *et al*[24] reported similar effectivity with a 0.59 mg dose to prevent recurrences with the rates declining from 43.6% to 17.1%. Studies have also found FA implant to be very successful in improving visual acuity and in reducing the need for adjunctive systemic or periocular steroid treatments[22,24,25]. Callanan *et al*[22] stated that the visual acuity increased ⩾ 3 lines in 23% of the 0.59 mg FA implanted eyes compared to 6% in non-implanted. The same rate was 31.1% *vs* 7.6% in Sangwan *et al*[24] study.

The major ocular side effects of the FA implant are cataracts and raised IOP. Nearly all of the patients required cataract surgery and 32%-40% required IOP lowering filtration surgery at the end of the 3-year follow-up[22,24,26]. Other ocular complications worthy of mention are retinal detachment (4.0%), endophthalmitis (1.0%), and hypotony which could occur at any time in 3-year follow-up (34.0%)[21]. Although 0.59 mg FA implant requires surgical implantation and further surgical interventions to treat ocular side effects like cataract and glaucoma, a recent review that compared systemic corticosteroid *vs* 0.59 mg FA implantation in terms of cost-effectivity has found the implant to be reasonably cost-effective in unilateral noninfectious intermediate, posterior and panuveitis cases[27].

Iluvien (Alimera Sciences Inc., Alpharetta, GA) is another FA implant approved to be used in diabetic macular edema. Its difference from Retisert is that Iluvien can be applied in the office setting without the need for surgical intervention. It also releases lower doses of medication and preliminary data suggest that the risk of a rise in IOP is lower compared to Retisert[28]. However, there are no data up to date for its use in uveitis.

Dexamethasone

Dexamethasone is approximately 3-5 times more potent compared to triamcinolone acetonide (TA) and 7.5-12.5 times more potent compared to FA. Its implant form is Ozurdex (Allergan Inc, Irvine Calif, United States) which is a bioerodible device composed of a mix of polylactic acid and polyglycolic acid polymers that releases 0.7 mg of dexamethasone for up to 6 mo. One of the major advantages over the former approved glucocorticoid implant Retisert is the office based application without any need for surgery[29]. The FDA approved its use in retinal vein occlusion, uveitis and diabetic macular edema[30]. The first data about the use of Ozurdex in uveitis were gathered from the results of HURON (Chronic uveitis evaluation of IV dexamethasone implant) trial[31]. The HURON study revealed that a single injection resulted in efficient control of inflammation and good visual outcomes for up to 6 mo in noninfectious intermediate or posterior uveitis. A recent multicenter study which evaluated Ozurdex implants in NOIU confirmed the success of the implant in controlling vitreous haze, cystoid macular edema and visual acuity[30]. Authors noted that the improvement in uveitis presentation can be observed as early as 2 to

4 wk after the injection. The percentage of eyes that gained ⩾ 3 lines in visual acuity were 38% at the end of the 6th month. The median time to reinjection was 10 mo and the time to uveitis relapse considering the changes in macular thickness, vitreous haze and visual acuity was 6 mo, which is comparable to the previously performed studies[32,33]. The main problems with the former glucocorticoid implant Retisert (high rate of a raised IOP and cataracts) were found to be significantly less with Ozurdex. The HURON study reported that only 23% of eyes required IOP lowering medications without any surgical intervention and 1.3% needed cataract extraction[31] (See Table 1).

Zero point seven mg dexamethasone implant Ozurdex has many advantages, *i.e.*, 22G office based application and lower risk of IOP rise and cataract formation. However, considering the disease is mostly chronic and recurrent, reinjections are mostly needed.

Methotrexate

Methotrexate is an antimetabolite immunosuppressive that has been used in NOIU for many years as a steroid sparing agent[34,35]. It is also used in the treatment of intraocular lymphoma cases as IV injections at 400 μg doses[36,37]. In a retrospective study, Hardwig *et al*[38] reported that IV methotrexate preserved or improved visual acuity in seven of eight uveitis patients. Similarly, in a prospectively designed study Taylor *et al*[39] have announced that in 30 of 38 eyes, intraocular inflammation was successfully controlled with improved vision and without any ocular side effects. From 30 eyes that responded well, only 8 have relapsed and 7 of them responded to the reinjection. They also emphasized that 57% of the patients were able to reduce systemic treatments. IV methotrexate might serve as a preferable option in noninfectious posterior uveitis with high efficacy, nearly no side effect and an extended duration of action (Table 1).

Anti-tumor necrosis factor-α

Anti-tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that is involved in regulation of immune cells, tumor suppression and inhibition of viral replication[40,41]. It is also mentioned in the pathophysiology of ocular inflammatory conditions related to autoimmune diseases and ocular diseases that have an inflammatory component such as diabetic macular edema and neovascular age related macular degeneration[42-45]. There is a significant amount of data on systemic use of anti-TNF-α agents in uveitis especially in Behcet's disease, juvenile idiopathic arthritis and ankylosing spondylitis. However, the systemic side effects like fatal blood disorders, secondary infections, reactivation of latent infections, and demyelinating nerve system disorders limit its use[46]. As in the case of glucocorticoids, IV route was tried to avoid systemic side effects. For all TNF-α agents, the optimal IV dose was decided after the animal studies were completed. The results of the studies that will be discussed in this paper are mostly case series and the literature lacks standardized well-designed prospective works.

Etanercept was studied in a pilot study involving seven patients with resistant diabetic macular edema. At the end of 3 mo, no significant improvement or side effects were seen with a safe dose of 2.5 mg IV injection that was repeated at 2 weekly intervals[47]. It was then abandoned and no further studies were conducted afterwards. Thus, there are no available data on its use in uveitis.

Infliximab, a murine-based monoclonal antibody, was investigated in animal studies and IV doses below 2 mg were reported to be well-tolerated[48]. The Pan-American Collaborative Retina Study Group, the largest series that was conducted about the IV use of infliximab in diabetic macular edema and exudative age related macular disease, has concluded that IV infliximab did not result in any anatomic or functional benefit whereas 37.5%-42% of the injected eyes developed severe uveitis[49,50]. Its use in noninfectious posterior uveitis and Behcet's disease was found to improve vision initially but failed to stabilize the vision in the long-term[51,52]. In short, studies demonstrated that IV infliximab might be useful in uveitis but not in diabetic macular edema or exudative macular disease.

Adalimumab is also one of the preferred anti-TNF-α options that is successfully used in the treatment of NOIU[53]. Hamam *et al*[54] recently published the only study of IV adalimumab use in human. They performed an IV adalimumab injection of 0.03 mL (1.5 mg) at 0, 2 and then every 4 wk for a total 26-wk duration in 7 patients (13 eyes). Only 1 patient had worsened ocular inflammation and was removed from the study and switched to systemic and local corticosteroid treatment. Visual acuity improved in 7 of 12 eyes with ⩾ 2 ETDRS lines, whereas the other 5 eyes remained stable or improved 1 line. In 8 eyes with macular edema, 5 achieved complete resolution. No ocular or systemic side effects were reported. Authors had noticed that 4 patients had Behcet's disease, which might affect the results since anti-TNF-α has favorable results in this particular disease. More numerous studies are required to reach a conclusion about the IV use of adalimumab.

Anti-VEGF agents

IV anti-VEGF agents are widely used for age related macular degeneration related choroidal neovascularizations, and macular edema related to diabetic retinopathy and retinal vascular occlusions[55,56]. Their use in uveitis is mostly related to the management of secondary complications of uveitis such as macular edema and choroidal neovascularizations[57,58]. In a study comparing IV anti-VEGF agents and IVTA, Lasave *et al*[5] reported that a single injection of IVTA is superior to IV bevacizumab in chronic resistant uveitic macular edema cases with regards to improvement in visual acuity and macular thickness. A prospective non-comparative

therapeutic trial has been published recently evaluating the effect of ranibizumab on macular edema in clinically well-controlled 5 eyes of 5 uveitis patients. They performed 4.6 injections on average in the first 6 mo and 1.8 injections in the second 6-mo period according to the criteria they put forth at the beginning of their study. The 12th month follow-up visit for the same study revealed that there was a statistically significant 12.2 letter increase in visual acuity and 45.4% decrease in macular thickness. Another interesting study about the effect of anti-VEGF agents in uveitis was the retrospective study performed by Al-Dhibi *et al*[59] that evaluated the effect of bevacizumab in infectious uveitis and NOIU. Similarly, they reported improvement in visual acuity and macular thickness. The latest finding is that bevacizumab is effective and safe without any immunosuppressive effect against infectious agents.

In summary, they are not superior to IVTA and have short half-life necessitating reinjections. Therefore, they do not seem to be ideal agents for uveitis, which is mostly chronic and recurrent. The major advantage of these agents might be the relatively low incidence of ocular complications like cataract and IOP rise when compared to glucocorticoids. This might be very helpful especially in steroid responder cases. Additionally, they might be of use in uveitis induced choroidal or retinal neovascularizations.

Future intraocular devices and agents for the treatment of NOIU

I-vation is a screw shaped implant, which is twisted through the pars plana from a 0.5 mm sclerotomy. It contains 0.925 mcg TA that is reported to have 1-year duration of release. The 1-year results demonstrated that it was effective in diabetic macular edema with decrement in macular thickness and increment in visual acuity[60]. The phase 2 results have not been published yet. There are no data for uveitis patients as of yet.

Sirolimus, a macrolide antibiotic (rapamycin), was originally developed as an antifungal agent. After the immunosuppressive and antineoplastic effects were discovered, it is now being investigated for the treatment of different ocular diseases including uveitis. It suppresses T and B cell proliferation and inhibits interleukins-2, -4 and -5[61]. Sirolimus as Therapeutic Approach to Uveitis study has announced its 6-mo results, which reported equal success in improving vitreous haze with subconjunctival or IV administration[62]. The ongoing phases 2 and 3 studies will help clinicians to reach a better conclusion about the effectiveness and safety profile of local sirolimus treatment in NOIU.

LFG316 is a monoclonal antibody that inhibits activation of complement protein 5 and a phase 1 single ascending dose study of IV injections was performed in advanced AMD patients[63]. The IV use in multifocal choroiditis and panuveitis is currently under investigation.

Cyclosporine is a well-known second-line immunosuppressive agent, which is used especially in chronic NOIU patients. The IV implant form of cyclosporine was tested in 2 experimental uveitis models in rabbits and found to be effective and safe[64,65].

CONCLUSION

Uveitis is still one of the most challenging issues of ophthalmology from diagnosis to treatment. For a long time, corticosteroids served as the only treatment option in NOIU and are still the mainstay of treatment although many new agents have emerged. The IV route is a great option for clinicians to reach therapeutic levels in the posterior segment of the eye, since the blood ocular barriers significantly limit the efficacy of topical and systemic administrations. It also allows for a reduction in systemic treatment doses of therapeutic agents and thus a decrease in side effects related to higher doses. IV treatment is an excellent treatment of choice especially in cases with unilateral involvement, in uveitis not associated with systemic disease and in patients who have problems with systemic drug use. It is also a good adjunctive treatment in patients with active ocular inflammation despite optimal systemic therapy. The high rate of cataract, IOP rise and relatively short half-life, which requires frequent reinjections with conventional IVTA, has evoked the innovations of implant technology. Today, Retisert and Ozurdex are the most commonly preferred glucocorticoid options in uveitis management with some advantages and disadvantages. The systemic agents that are being successfully used in NOIU management (methotrexate, anti-TNF-α agents) are also being tested for IV administration. IV anti-VEGF agents might be an option for uveitic macular edema especially in steroid responder cases. However, studies performed for evaluation of IV drug administration in uveitis are mostly non-standardized (length of follow-up, doses, patient selection, criteria for effectiveness) and retrospective case series with small samples, which limit the clinicians' ability to reach a conclusion. It seems that the search for safe, cost-effective and long acting agents in uveitis management has not reached to an end yet.

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MINIREVIEWS

Diabetic macular edema: Efficacy and safety of anti-vascular endothelial growth factor therapy

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Abstract

Diabetic retinopathy is one of the prominent causes of vision impairment in the working-age population in industrialized countries and is related to 1%-5% of cases of blindness in the world. Among patients with diabetic retinopathy, diabetic macular edema (DME) is the major reason of vision impairment and represents a significant public health problem. Previous studies demonstrated the role of vascular endothelial growth factor (VEGF) in diabetic retinopathy and DME pathogenesis, and also revealed the efficacy of anti-VEGF agents for the management of these disorders. This review summarizes the outcomes of clinical studies that evaluated the anti-VEGF therapy including pegaptanib, ranibizumab, bevacizumab, and aflibercept for the management of DME. A significant number of clinical trials indicated favorable functional and anatomical results of anti-VEGF therapy for DME. Therefore, these agents should be considered an option in the treatment of DME in routine clinical practice.

Key words: Anti-vascular endothelial growth factor; Aflibercept; Bevacizumab; Diabetic macular edema; Pegabtanib; Ranibizumab

Core tip: Diabetic retinopathy is one of the prominent reasons of vision loss in the industrial countries. Among these patients, diabetic macular edema (DME) is the main reason of vision impairment. Previous studies have shown that vascular endothelial growth factor (VEGF) has a major role in the pathogenesis of diabetic retinopathy and DME, as well as demonstrated favorable results for DME treatment. This review summarizes the outcomes of clinical trials that evaluated anti-VEGF agents including pegaptanib, ranibizumab, bevacizumab, and aflibercept in DME treatment.

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INTRODUCTION

Diabetic retinopathy is the main reason of visual impairment in the industrial countries and is related to 1%-5% of cases of blindness worldwide[1]. The main reason of vision decrement in diabetic retinopathy is diabetic macular edema (DME) which could be detected during non-proliferative or proliferative stage[2,3]. According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the prevalence of DME was 20.1% for type Ⅰ diabetes mellitus and 25.4% for type 2 diabetes mellitus receiving insulin treatment[4].

DME is generally classified into two subtypes. First is the focal edema which consists of localized areas of retinal thickening originating from the leaking micro-aneurysms and is generally associated with hard exudates. Second is the diffuse macular edema which consists of generalized leakage of dilated capillaries and disrupted retinal pigment epithelial barrier[5,6].

DME is associated with hypertension, poor blood glucose regulation, cardiovascular disease, impaired renal function, increased number of microaneurysms and vitreomacular traction[7,8]. Regulation of blood glucose level, systemic hypertension and hyperlipidemia along with following the at-risk patients are the most efficient ways to prevent the vision loss from diabetic retinopathy[2,9].

The gold standard treatment for DME has been macular photocoagulation (MPC) in recent decades[10]. The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that approximately 40% of the patients had achieved ⩾ 6 letters in best corrected visual acuity (BCVA) with focal laser treatment in 3 years[10,11]. Recently, the Diabetic Retinopathy Clinical Research Network (DRCR.net) has demonstrated BCVA improvement of more than 5 letters of vision in 51%, 47% and 62% of eyes treated with MPC after 1, 2 and 3 years of follow-up, respectively[12].

In recent years, alternative or adjunct treatments for DME have been studied, and various pharmacological compounds are under investigation, such as therapies using inhibitors of VEGF[13,14]. The purpose of this assessment is to review the evidence for current anti-VEGF pharmacotherapies in the treatment of DME.

ANTI-VEGF AGENTS FOR DME

The expression of VEGF which stimulates angiogenesis, inflammation and vascular permeability increases due to hypoxia[15]. VEGF molecule breaks down the blood-retinal barrier by its distracting impact on the endothelial zona occludens and induction of fenestrations on the endothelial cells[16,17]. In addition, VEGF causes degeneration in endothelial basement membranes which deteriorate the structure of the retinal microvessels with leakage of blood plasma proteins into the extracellular space[18,19]. The proinflammatory effect of VEGF is related to over-expression of intercellular adhesion molecule-1 which leads leucocyte adhesion to the vascular endothelium, capillary occlusion and endothelial cell apoptosis[20]. VEGF 165 is the leading isoform which is most associated with the increased angiogenesis and vascular permeability[21]. Therefore, VEGF inhibition may be an effective option for management of DME. Several studies have been conducted that have addressed the efficacy and safety of anti-VEGF agents, including ranibizumab (Lucentis, Genentech, Inc., United States), pegaptanib (Macugen, OSI/Eyetech, United States), aflibercept (EYLEA; Regeneron, United States) and bevacizumab (Avastin, Genentech, Inc., United States), in the treatment of DME (Table 1).

CLINICAL TRIALS FOR DME

Pegaptanib sodium (macugen)

Pegaptanib is the first intravitreal VEGF antagonist drug that was approved by the Food and Drug Administration (FDA) for the management of exudative age related macular degeneration (AMD). This molecule is 28-nucleotide chemically synthesized single-stranded nucleic acid (aptamer) that only targets the VEGF 165 isoform[22].

Macugen Diabetic Retinopathy Study Group (a double-masked multicenter controlled phase 2 randomized clinical trial) evaluated the efficacy of pegaptanib in DME[23]. Totally 172 patients with DME who were randomly divided into four arms were enrolled: 0.3 mg, 1 mg, 3 mg intravitreal pegaptanib or sham. Intravitreal pegabtanib injections were administered at weeks 0, 6 and 12. After week 12, additional injections could be performed according to the discrimination of the investigators. In addition focal laser treatment could be chosen as a beginning at week 13. At week 36, better results were achieved in BCVA, central foveal thickness (CFT) and need for additional MPC, in the pegaptanib groups compared to the sham group, in particular the 0.3 mg group. In addition, the better improvements in the pegabtanib groups were determined despite the fact that focal or grid laser was applied 23% more to the sham group between weeks 12 and 36. The proportion of improvements in BCVA was 73% in the 0.3 mg pegabtanib group whereas 51% in the sham group. In detail, the mean increase in BCVA was 4.7 letters and 18% gained 3 or more Snellen lines for the 0.3 mg pegabtanib group. A phase 2/3 randomized, controlled, multicenter trial compared the affectivity and safety of 0.3 mg pegaptanib (administrated for every 6 wk for two years) and sham injections in patients with DME[24]. The total number of subjects included in the first and second year analyses were 260 (133 pegaptanib, 127 sham) and 207 (107 pegaptanib, 100 sham), respectively. The number of patients who gained ⩾ 10 letters in BCVA were 49 (36.8%) and 25 (19.7%) for the pegaptanib and sham groups, respectively, at week 54. At year 1, the BCVA was significantly ($P < 0.05$) improved in the pegaptanib group (gained 5.2 letters) compared to sham (gained 1.2 letters). At year 2, these were 6.1 letters in the pegaptanib group and 1.3 letters in the sham arm ($P < 0.01$).

Table 1 Major trials of anti-vascular endothelial growth factor drugs for diabetic macular edema

Ref.	Drug	Design	*n*	Treatment regimen	Follow-up	Results
Sultan *et al*[24]	Pegaptanib	Phase 2/3, randomized, sham-controlled, multicenter	260 patients	(1) 0.3 mg IVP; or (2) sham injections at baseline and every 6 wk in yr 1 and focal/grid laser beginning at wk 18. In year 2, (1) 0.3 mg IVP; or (2) sham up to every 6 wk PRN	2 yr	Improvement of ≥ 10 letters at 54 wk: (1) 36.8%; and (2) 19.7% (P = 0.0047). BCVA letters gained at week 102: (1) 6.1 letters; and (2) 1.3 letters (P < 0.01). No significant difference in CFT decreases at 54 and 102 wk between (1) and (2)
Macugen Diabetic Retinopathy Study Group[23]	Pegaptanib	Phase 2, randomized, double-masked, dose-ranging, controlled	172 patients	(1) 0.3 mg PEG; or (2) sham at baseline, wk 6 and wk 12; additional injections of focal LPC as needed for an additional 18 wk	36 wk	Mean VA at week 36: (1) 20/50; and (2) 20/63 (P = 0.04). Ten letters gained: (1) 34%; and (2) 10% (P = 0.003). CRT at week 36: (1) -68 μm; and (2) +4 μm (P = 0.02). PEG doses of 0.3 mg, 1 mg, and 3 mg all well tolerated
Elman *et al*[28] (DRCR)	Ranibizumab	Randomized, prospective, multicenter	854 eyes of 691 patients	(1) 0.5 mg IVR plus prompt laser; (2) 0.5 mg IVR plus deferred laser (> 24 wk); and (3) 4 mg IVT plus prompt laser; (D) sham injection plus prompt laser	1 yr	Mean VA letter improvement at 1 yr: (1) +9 ± 1, P < 0.001; (2) +9 ± 12, P < 0.001; (3) +4 ± 13, P = 0.31; and (4) +3 ± 13
Mitchell *et al*[33] (RESTORE)	Ranibizumab	Randomized, prospective, multicenter	345 patients	(1) 0.5 mg IVR monthly × 3 then PRN + sham laser; (2) 0.5 mg IVR monthly × 3 then PRN + laser; and (3) sham injections + laser	12 mo	VA better for (1) and (2) from months 1 to 12 compared with (3); 12-mo VA: (1) +6.1 letters; (2) +5.9 letters; and (3) +0.8 letters (P < 0.0001 for both); BCVA 20/40 or better: (1) 53%; (2) 44.9%; and (3) 23.6%. No significant differences between (1) and (2) at 12 mo
RISE Trial[31]	Ranibizumab	Phase 3, randomized, sham-controlled, multicenter	377 patients	(1) 0.3 mg IVR; (2) 0.5 mg IVR; and (3) sham injection. All given monthly injections × 24 mo and with rescue laser available at 3 mo	2 yr	Improvement of ≥ 15 letters at 2 yr: (1) 44.8% (56/125); (2) 39.2% (49/125); and (3) 18.1% (23/127). Statistically significant for both (1) and (2) compared with (3) at P < 0.001 and P < 0.002, respectively
RIDE Trial[31]	Ranibizumab	Phase 3, randomized, sham-controlled, multicenter	382 patients	(1) 0.3 mg IVR; (2) 0.5 mg IVR; and (3) sham injection. All given monthly injections × 24 mo and with rescue laser available at 3 mo	2 yr	Improvement of ≥ 15 letters at 2 yr: (1) 33.6% (42/125); (2) 45.7% (58/127); and (3) 12.3% (16/130). Statistically significant for both (1) and (2) compared with (3) at P < 0.001
Massin *et al*[27] (RESOLVE)	Ranibizumab	Phase 2, randomized, sham controlled, multicenter	151 patients	(1) 0.3 mg or 0.5 mg IVR monthly × 3 mo then as needed (dose doubling allowed after 1 mo); or (2) sham injection monthly × 3 mo then as needed (as-needed rescue LPC in)	1 yr	Month 12 mean ± SD BCVA change: (1) 10.3 ± 9.1 letters; and (2) -1.4 ± 14.2 letters; P < 0.001. Gain ≥ 10 letters: (1) 60.8%; and (2) 18.4% (P < 0.001). Mean change in CFT: (1) -194.2 μm; and (2) -48.4 μm (P < 0.001)
DRCR[41]	Bevacizumab	Randomized, prospective	121 patients	(1) Focal LPC; (2) IVB 1.25 mg at baseline and 6 wk; (3) 2.5 mg IVB at baseline and 6 wk; (4) 1.25 IVB at baseline and sham at 6 wk; or (5) 1.25 IVB at baseline and 6 wk with focal LPC	24 wk	Baseline CFT: 411 μm; at 3 wk, CFT reduction greater in (2) and (3) than in (1); CFT reduced > 11% at 3 wk in 43% of IVB-treated eyes and 28% of LPC treated eyes, and at 6 wk in 37% of IVB treated eyes and 50% of LPC-treated eyes. Mean 12-wk VA improvement in (2) and (3) of 1 line better than (1). No significant short-term benefit combining IVB and laser
Michaelides *et al*[42], 2012 (BOLT)	Bevacizumab	Randomized, prospective	80 patients	(1) Focal/grid laser; or (2) IVB 1.25 mg at baseline, 6 and 12 wk, then as needed	24 mo	Mean gains in BCVA at 24 mo: (1) +2.5 letters; and (2) +9 letters (P = 0.005). Mean change in CFT at 24 mo; (1) -118 μm; and (2) -146 μm
Do DV *et al*[38], 2012 (DA VINCI)	Aflibercept	Phase 2, randomized, multicenter	221 patients	VEGF Trap-Eye (1) 0.5 mg every 4 wk (0.5q4); (2) 2 mg every 4 wk (2q4); (3) 2 mg every 8 wk after 3 initial monthly doses (2q8); (4) 2 mg dosing as needed after 3 initial monthly doses (2PRN); or (5) macular laser photocoagulation.	2 yr	Mean improvements in BCVA in the VEGF Trap-Eye groups at week 52 were 11.0, 13.1, 9.7, and 12.0 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, *vs* -1.3 letters for the laser group (P ≤ 0.001 *vs* laser)

BCVA: Best-corrected visual acuity; CFT: Central foveal thickness; DRCR: Diabetic Retinopathy Clinical Research Network; IVB: Intravitreal bevacizumab; PRN: Pro re nata; IVP: Intravitreal pegaptanib; IVR: Intravitreal ranibizumab; IVT: Intravitreal triamcinolone; LPC: Laser photocoagulation; VEGF: Vascular endothelial growth factor.

Ranibizumab (lucentis)

Ranibizumab is a humanized antibody fragment which shows affinity to all VEGF-A isoforms. In 2006, Nguyen *et al*[22] showed the crucial effect of VEGF in DME pathogenesis for the first time and suggested that application of VEGF antagonists such as ranibizumab may reduce retinal edema. Major clinical trials compared the affectivity and safety of ranibizumab with sham or with laser photocoagulation and intravitreal triamcinolone acetonide (IVTA).

The READ-2 study demonstrated that intravitreal ranibizumab achieved better visual results compared to

photocoagulation[25]. Subjects were randomly divided into three groups: 0.5 mg ranibizumab (group 1), focal or grid laser photocoagulation (group 2), or laser plus ranibizumab (group 3). The mean improvement in BCVA was 7.24, 0.43, and 3.8 letters after the primary end point at month 6. At month 24 these were 7.7, 5.1, and 6.8 letters, respectively. The CFT values at month 24 were 340 μm, 286 μm, and 258 μm, respectively. In the ranibizumab group, the mean BCVA (ΔBCVA letters = 3.1, P = 0.009) and CFT (ΔCFT = 70 μm, P = 0.006) were significantly improved at month 36 compared to month 24. However, these were not statistically significant in the laser (-1.6 letters and -36 μm, respectively) and the ranibizumab + laser groups (+2.0 letters and -24 μm). This study showed that long-term results of ranibizumab therapy for DME are favorable, however, injections should be performed frequently in many patients to control edema and maintain the vision[26].

The safety and efficacy of ranibizumab in diabetic macular edema with center involvement study was a multi-center, randomized trial including 151 patients who were administrated either sham, ranibizumab 0.3 mg, or ranibizumab 0.5 mg injections monthly for 3 mo and followed by PRN (Pro Re Nata) treatment[27]. Ranibizumab was increased to 0.6 mg and 1 mg, respectively, if the CFT persisted > 300 μm at the first month or if the CFT was > 225 μm with a decrease in CFT < 50 μm compared to the preceding measurement at any visit following the baseline injection. The injections were interrupted at any monthly visit following the third injection if the CFT was < 225 μm and the BCVA was > 79 letters. The injections were restarted if the CFT increased by > 50 μm or the BCVA worsened ⩾ 5 letters and was < 74 letters. At 12 mo, the improvement in BCVA was 10.2 letters in the ranibizumab group whereas decreased 1 letter in the sham group. Regarding the change in CFT, it was decreased 200 μm in the ranibizumab group and 40 μm in the sham group. The crucial point of this study is to evaluate the outcome of ranibizumab retreatment strategy that could be applicable in clinical practice.

The DRCR.net is a multicenter, randomized clinical trial evaluating whether ranibizumab combined with prompt (within 10 d) or deferred (no sooner than 6 mo) laser, and IVTA combined with prompt laser, might improve BCVA compared to focal/grid photocoagulation alone in central involved DME. At the first year, the mean BCVA significantly improved both in the ranibizumab + prompt laser (+9 ± 11 letters, P < 0.001) and the ranibizumab + deferred laser (+9 ± 12 letters, P < 0.001) groups, however, it was not in the triamcinolone + prompt laser group (+4 ± 13 letters, P = 0.31) compared to the sham + prompt laser group (+3 ± 13 letters). The mean decrease in the CFT was similar between the triamcinolone + prompt laser group and both ranibizumab groups. In addition, these were greater compared to the sham + prompt laser group. Regarding the 3-year results, ranibizumab + prompt laser therapy did not show better BCVA outcomes, and possibly worse, compared to the ranibizumab + deferred laser. They suggested that these BCVA differences may be associated with fewer cumulative ranibizumab injections in the prompt laser treatment group during the follow-up period[28,29]. The 5-year results have recently been reported[30]. The mean BCVA improvement was 7.2 letters in ranibizumab + prompt laser group and 9.8 letters in the ranibizumab + deferred laser group (mean difference was -2.6 letters, P = 0.09). No additional laser treatment was performed in 56% of patients from the deferred laser group during the 5-year follow-up period. The median number of injections in the prompt and deferral groups was 13 and 17, respectively. The percentage of patients receiving no injections in the prompt and deferral groups were 54% and 45% during 4 years of follow-up, respectively, and 62% and 52% during 5 years of follow-up, respectively. The 5-year results demonstrated that BCVA was not significantly different between the ranibizumab + prompt laser and ranibizumab + deferred laser treatment groups. Despite the fact that half of the eyes from the deferred laser treatment group did not receive additional laser treatment during 5 years, more injections were administrated in such eyes to achieve these results. Finally the BCVA improvement was sustained in most eyes from year 1 to 5 with a small number injection after the year 3 in both ranibizumab groups.

The RISE and RIDE are parallel, phase 3, multicenter, sham controlled, randomized studies comparing sham injections with 0.3 or 0.5 mg ranibizumab injections on a monthly basis for 24 mo[31]. Macular laser was available per-protocol–specified criteria. The RISE study showed that the percentage of patients gaining ⩾ 15 letters was 18.1% in sham, 44.8% in 0.3 mg (P < 0.001) and 39.2% in 0.5 mg ranibizumab (P < 0.001) groups. In RIDE, 12.3% of sham patients, 33.6% of 0.3 mg patients (P < 0.001) and 45.7% of 0.5 mg ranibizumab patients (P < 0.0001) gained ⩾ 15 letters. RISE and RIDE studies demonstrated that monthly ranibizumab achieved better improvements in visual acuity than PRN. The FDA approved ranibizumab for the DME treatment based on the satisfactory outcomes of RISE and RIDE. At 36 mo, the percentage of patients gaining ⩾ 15 letters was 22.0% in sham, 51.2% in 0.3 mg (P < 0.001) and 41.6% in 0.5 mg ranibizumab (P < 0.001) groups in RISE, and 19.2%, 36.8% (P < 0.001) and 40.2% (P < 0.001), respectively, in RIDE. These data revealed that the BCVA improvement at month 24 was sustained through month 36[32].

The RESTORE study compared the mean BCVA change in the ranibizumab 0.5 mg monotherapy or combined laser therapy with the laser alone therapy over 12 mo in 345 DME patients[33]. Both ranibizumab groups received three monthly injections followed by PNR injections through the primary end point (month 12). The mean BCVA improvement was 6.1 letters in the ranibizumab monotherapy group, 5.9 letters in the combination group and 0.8 letters in the laser monotherapy group. The percentage of patients who

gained ⩾ 15 letters at month 12 was 26, 27, and 9 for all groups, respectively. At 2 years, the mean BCVA gain observed at month 12 was maintained in the ranibizumab and combined laser groups (7.9 and 6.7 letters, respectively). In the laser alone group, the mean BCVA was improved from month 12 to 24 (5.4 letters) with an average of 4.1 ranibizumab injections[34]. The 3-year results have also been published[35]. The mean BCVA improvement was 8.0 letters in the ranibizumab monotherapy group, 6.7 letters in the combination group with the mean injection numbers of 6.8 and 6.0, respectively. In the laser only group, the mean BCVA improvement was 6.0 letters with a mean of 6.5 ranibizumab injections from month 12 to 36. They suggested that ranibizumab achieves improving and maintaining BCVA with a progressively decreasing number of injections over 3 years

Aflibercept (EYLEA)

Different from ranibizumab and bevacizumab, aflibercept combines the domains of VEGF receptor (VEGFR-1 and VEGFR-2 receptors) to the FC segment of human immunoglobulin G1. It has the highest affinity to all VEGF-A isoforms among anti-VEGF agents. In addition it binds the other VEGF molecules such as placental growth factors 1 and 2 which have been reported to cause an increased vascular permeability[36]. Its efficacy and safety have been evaluated in patients with DME, AMD and retinal vein occlusions. The European Union has recently approved aflibercept for treatments of exudative AMD and retinal vein occlusion and FDA approved for DME treatment.

The DA VINCI is a multicenter, randomized clinical trial comparing the efficacy of aflibercept with laser photocoagulation in DME patients[37,38]. In this study, patients were randomly divided into five aflibercept application groups: 0.5 mg monthly, 2 mg monthly, 2 mg every 8 wk, 2 mg if necessary following 3 initial monthly injections or macular laser treatment. At 24 wk, the increase in BCVA was from 8.5 to 11.4 letters in aflibercept groups and 2.5 letters in the laser group. The BCVA improvement at 52 wk ranged from 9.7 to 12 letters and 1.3 letters, respectively. Regarding the decrease in CFT, it ranged from -165.4 to 227.4 μm in the aflibercept groups and 227.4 to 58.4 μm in the laser groups.

VISTA (DME) and VIVID (DME) were two double-masked, randomized, phase 3 trials comparing the efficacy of 2 mg aflibercept every 4 wk, 2 mg every 8 wk following the 5 incipient monthly doses, with macular laser photocoagulation[39]. At the first year of VISTA, the mean BCVA improvement was 12.5, 10.7 and 0.2 letters, respectively (P < 0.001). These were 10.5, 10.7 and 1.2 letters, respectively (P < 0.001) in the first year of VIVID. The percentages of patients gaining ⩾ 15 letters were 41.6%, 31.1% and 7.8%, respectively (P < 0.001), in VISTA, and 32.4%, 33.3% and 9.1%, respectively (P < 0.001), in VIVID. Regarding the mean CFT decrease, these were 185.9, 183.1 and 73.3 μm, respectively (P < 0.001), in VISTA, and 195.0, 192.4 and 66.2 μm, respectively (P < 0.001), in VIVID. In conclusion, aflibercept groups achieved better functional and anatomic outcomes at the first year compared to the laser group. However, these were similar between the 4 wk and 8 wk injection groups. After two years of VIVID, the mean BCVA improvement for 2 mg aflibercept every 4 wk and 2 mg every 8 wk was 11.4 and 9.4 letters (P < 0.001), respectively, however, it was 0.7 letters for the laser photocoagulation group. Additionally, the percentage of patients gaining ⩾ 15 letters was 38.2% and 31.1% in the 2 mg aflibercept every 4 wk and 2 mg every 8 wk groups, respectively (P < 0.001) compared to the laser photocoagulation group with a percentage of 12.1. These results demonstrated that the improvement in BCVA resumes after two years.

Protocol T, phase 3 study sponsored by the DRCR will compare the safety and efficacy of intravitreal aflibercept (2.0 mg), bevacizumab (1.25 mg) and ranibizumab (0.5 mg) for DME in 660 patients recruited from different clinical centers in the United States. According to the protocol-specified algorithm, the drugs were injected every 4 wk. The primary outcome in this study is to evaluate the changes in BCVA at month 12. At last visit, the mean BCVA improvement score (range, 0 to 100, and a score of 85 is approximately 20/20) was 13.3 with aflibercept, 9.7 with bevacizumab, and 11.2 with ranibizumab. The BCVA improvement was better in aflibercept group (P < 0.001 for bevacizumab and 0.03 for ranibizumab); however, these were not clinically significant because these differences were due to the eyes with worse baseline BCVA (P < 0.001 for interaction). There were no differences in BCVA among the study groups if the baseline visual loss is mild, however, better improvement was achieved by aflibercept at worse initial BCVA[40].

Bevacizumab (avastin)

Bevacizumab is a full-size, humanized, recombinant monoclonal immunoglobulin G which combines all VEGF A isoforms. It is approved by the FDA for colorectal cancer treatment; however, its usage for ocular diseases is off-label. It is widely used for DME treatment due to its favorable cost and availability[6].

DRCR.net is the first study to suggest that bevacizumab warrants phase 3 evaluation for DME treatment[41]. This randomized study evaluated 121 eyes with DME over 12-wk follow-up (safety data are reported for 24 wk). Five treatment groups were studied: (1) focal photocoagulation; (2) 1.25 mg of bevacizumab administrated at 0 and 6 wk; (3) 2.5 mg of bevacizumab administrated at 0 and 6 wk; (4) 1.25 mg of bevacizumab at baseline plus sham injection at 6 wk; and (5) 1.25 mg of bevacizumab at 0 and 6 wk plus focal photocoagulation at 3 wk. Sixty-nine percent of the study eyes had previous DME treatment. BCVA

was significantly improved in the groups receiving two bevacizumab injections compared to the laser group, and this was continued through the 12-wk follow-up period. The increase in BCVA was 7 letters in the 1.25 mg group and 8 letters in the 2.5 mg group at week 9 (following the second injection). Similar to BCVA, these injection groups showed a greater improvement in CFT compared to others with a similar trend in CFT during follow-up. The CFT results did not show any significant difference between the 1.25 and 2.5 mg groups. The results did not show any difference between the single injection group and the photocoagulation group. The laser and bevacizumab combination group showed similar results with the laser-only group. The BCVA results suggested a worsening trend in these two groups different from the two bevacizumab injections groups. In summary, DRCR.net trial revealed that bevacizumab is a favorable agent for treatment of DME in primary cases and also in previously treated DME eyes. This trial identified two trends: (1) Greater improvement is achieved in the primarily treated eyes (P = 0.04) than the refractory eyes; and (2) The initial subretinal fluid may be associated with a greater improvement in BCVA (P = 0.06).

BOLT study is a prospective study comparing bevacizumab treatment with laser in eyes with persistent DME[42]. In this study 80 eyes were randomly assigned into two groups: (1) bevacizumab group (injections applied every 6 wk, with a minimum of 3 and a maximum of 9 injections); and (2) photocoagulation group (performed at 4 mo and a minimum of 1 and a maximum of 4 sessions). After 1 year, the BCVA and CFT results showed greater improvements in the bevacizumab group than in the laser group. After 2 years, the mean BCVA improvement was 9 letters in the bevacizumab and 2.5 letters in laser groups, and 45% of bevacizumab-treated patients had gained 10 or more letters, which was achieved in 7% of the laser group. In addition CFT was significantly decreased in both groups at 2-year follow-up. This study identified two trends: (1) The patients with better baseline BCVA needed fewer injections; and (2) The eyes with subretinal fluid required more injections compared to eyes with diffuse and cystoid edema.

Ahmadieh *et al*[43] performed a randomized study including 115 eyes with DME. Patients were assigned into three groups: bevacizumab-only group (three 1.25 mg bevacizumab injections every 6 wk), IVTA/bevacizumab combination group (additional injection of 2 mg of triamcinolone at the baseline visit only), and placebo group. The first two groups achieved higher improvement in BCVA compared to placebo only with the exception of the bevacizumab monotherapy group at the first 6 wk. Regarding the difference between the first two groups, no significant difference was found for BCVA and CFT. Following the final injection, the effect of bevacizumab continued for 12 wk without any obvious trend of thorough worsening in BCVA and CFT over that period.

Faghihi *et al*[44] compared bevacizumab monotherapy with combined bevacizumab/IVTA and laser in a pure group of patients with no treatment history for DME. Patients received intravitreal injections of 1.25 mg bevacizumab and 2 mg triamcinolone at the initial visit only. CFT was significantly decreased in all groups at both 6 and 16 wk. The bevacizumab monotherapy group had better improvement in BCVA and CFT compared to the laser group at 6 wk but not at 16 wk. However, the combination group achieved better BCVA and CFT at both 6 and 16 wk than the laser group.

Soheilian *et al*[45] compared the efficacy of bevacizumab alone and in combination with IVTA and laser therapy in treatment of DME in a randomized study with 2-year follow-up. Totally 150 eyes were assigned into three groups: 1.25 mg bevacizumab, bevacizumab/IVTA, and bevacizumab/IVTA/laser. The bevacizumab group yielded a significant increase in BCVA at month 6, which was decreased after month 24. In addition the mean BCVA increase was greater in the bevacizumab alone group compared to other study groups. The combined IVTA/bevacizumab group also achieved higher BCVA results than the laser group. Regarding the reduction in CFT, no significant differences were found between groups; however, this may probably be related to study protocol such as the 3-mo retreatment intervals, when indicated, or the missing data in 24.6% of the cases at the final follow-up.

Pan-American Collaborative Retina Study Group performed a retrospective study including DME patients treated with 1.25 mg or 2.5 mg bevacizumab injections[46,47]. At 2-year follow-up, the rate of patients who gained 2 or more ETDR lines was 51.8% whereas 44.6% eyes remained stable, and 3.6% eyes decreased 2 or more ETDRS lines of BCVA. At the last visit, the OCT findings demonstrated that CFT decreased from 446.4 ± 154.4 μm to 279.7 ± 80 μm. The comparison between 1.25 mg and 2.5 mg bevacizumab groups did not reveal any significance in BCVA and CFT.

Different from the other published studies, Haritoglou *et al*[48] included bevacizumab treated DME patients unresponsive to previous treatment, and with diffuse chronic edema. The intravitreal 1.25 mg bevacizumab injections were administrated at baseline, and were repeated based on the BCVA or CFT responses. The mean CFT significantly improved from 463 to 374 μm at 6 mo (P < 0.001).

SAFETY

Pegaptanib has been approved by FDA for the management of exudative AMD. Two clinical studies were performed to study the efficacy and safety of pegaptanib in patients with DME. Cunningham *et al*[23] reported a case of endophthalmitis that occurred in 1 of 652 injections [0.15%/injection; *i.e.*, 1/130 (0.8%) pegaptanib subjects]. In addition, pegaptanib did not show any association with severe BCVA impairment. In the phase 2/3 study[24], the pegaptanib and sham groups were comparable regarding the frequency of

drug interruptions, drug adverse events, treatment-related adverse events and serious adverse events. No case of endophthalmitis or retinal detachment was reported in either treatment group. For serious events cerebrovascular accidents (CVA) were rare, occurring in 2 (1.4%) and in 1 (0.7%) subjects in the pegaptanib and sham arms, respectively. Coronary artery disease and angina pectoris each occurred in 2 (1.4%) pegaptanib treated and 1 (0.7%) sham treated subjects, hypertension was noted for 1 subject in each group (0.07% for both), and unstable angina was experienced by 2 pegaptanib treated and no sham-treated subjects.

Recently ranibizumab has been approved by FDA for treatment of DME. Each of the above mentioned trials for ranibizumab also reported safety data. In these trials, the most common ocular adverse effect is endophthalmitis. In the RISE and RIDE studies there were four total cases of endophthalmitis out of 500 patients in the two-year follow-up of the study (0.8%; 1 in RISE with 0.3 mg ranibizumab, 3 in RIDE, 1 from 0.3 mg group and 2 from 0.5 mg group)[31]. The three-year follow-up of the DRCR study reported a total of 3 cases of endophthalmitis out of 375 (also 0.8%) patients receiving ranibizumab injections, in either the prompt or deferred laser group[29]. The RESTORE study had no cases of endophthalmitis[33]. RESOLVE had 2 cases of endophthalmitis out of 102 injection patients (2%) over the year of the study[27].

The major systemic safety concern with anti-VEGF treatment is thromboembolic events. In the one-year RESTORE study there were 6 arterial thromboembolic events (5.2%) in the ranibizumab (0.5 mg) group, whereas only one such event occurred in the laser group and the laser plus ranibizumab group[33]. The group sizes were similar, and the analysis did not support a statistical difference between ranibizumab treated groups and the laser only group. The one-year RESOLVE study also reported a low incidence of arterial thromboembolic events with no significant difference among treatment groups (3 of 102 in ranibizumab groups, 2 of 49 in sham group)[27]. The three-year follow-up of the DRCR study also reported no significant difference in thromboembolic events in ranibizumab or sham treated groups[29]. In the RISE and RIDE studies, thromboembolic events and deaths were similar between sham and treatment groups[31]. These studies did report that the number of deaths and CVAs were numerically higher in the ranibizumab groups compared to sham groups, with the highest incidences of CVA and death being in the ranibizumab 0.5 mg group. The number of CVAs in the RISE and RIDE studies combined were 4 out of 250 (1.6%), 3 out of 250 (1.2%), and 8 out of 250 (3.2%), in the sham, 0.3 mg, and 0.5 mg groups, respectively. The number of deaths in the combined studies was 3 out of 250 (1.2%), 7 out of 250 (2.8%), and 11 out of 250 (4.4%) in the sham, 0.3 mg, and 0.5 mg groups, respectively.

The largest study evaluating the safety of bevacizumab reported the data from 1173 patients administrated intravitreal bevacizumab and followed for 12 mo[49]. In this retrospective study these following adverse effects were detected: elevated blood pressure in 7 patients, 6 strokes, 5 myocardial infarctions, 5 deaths, bacterial endophthalmitis in 7 patients, tractional retinal detachment in 7 patients, and uveitis in 4 patients. These reported adverse effects were similar to those detected for the other anti-VEGF substances.

The DA VINCI study reported the safety data for aflibercept therapy for DME at one-year follow-up[38]. Similar systemic side effect profile was reported including hypertension (9.7%), cerebral vascular accidents (1.1%), and myocardial infarction (1.1%). The most of ocular side effects were related to intravitreal injection rather than the drug. Serious adverse effects included endophthalmitis (1.1%), uveitis (0.6%), corneal abrasion (0.6%) and retinal tear (0.6%).

Briefly the majority of safety data for anti-VEGF agents come from studies including patients with neovascular AMD; however, the patients with DME tend to be younger, with a high incidence of heart and kidney diseases in addition to the different ocular status. Because the increased rates of neovascularization and fibrous tissue that may lead to contraction and cause additional ocular complications, further safety studies for DME patients are to be necessary.

COST EFFECTIVENESS

To our knowledge, only two cost-effectiveness analyses have evaluated anti-VEGF treatments for DME. Dewan *et al*[50] compared the cost-effectiveness of ranibizumab with that of intravitreal corticosteroids using the data from the DRCRnet study trial and found that ranibizumab met acceptable cost-effectiveness standards relative to intravitreal corticosteroids for phakic patients (those without previous cataract surgery), and intravitreal corticosteroids were the most cost-effective treatment option for pseudophakic patients (those who had undergone cataract surgery). Bevacizumab was not considered in any of their analyses.

Recently Stein *et al*[51] compared the cost-effectiveness of bevacizumab and ranibizumab. They found that intravitreal bevacizumab confers a better value than ranibizumab. They suggest that insurers and health policymakers should consider endorsing the use of intravitreal bevacizumab over other treatment options as first-line therapy for DME, as this may curtail some of the rapidly rising costs of managing patients with this condition.

CONCLUSION

Review of the literature available to date suggests that intravitreal anti-VEGF pharmacotherapy is reasonably safe and effective for the treatment of DME. However, it may be associated with serious complications in spite of the satisfactory improvement in BCVA and macular edema reduction.

Future studies should focus on longer-term safety

and efficacy of anti-VEGF treatment for DME and should evaluate the comparative efficacy of different pharmacologic agents. Future research should also investigate new molecular targets to prevent or delay the progression of DME and novel strategies for sustained intraocular delivery of anti-VEGF agents to reduce the burden, cost, and risks of injections.

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EDITORIAL

Curing diabetic retinopathy: Is a strategy emerging?

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Abstract

Diabetic macular edema (DME) is the leading cause of blindness among working aged individuals of industrialized countries. The Early Treatment of Diabetic Retinopathy Studies (ETDRS) demonstrated that timely laser photocoagulation significantly decreases vision loss from DME, thereby establishing laser as standard- of-care for over 2 decades. Unfortunately, only a minority of patients treated in the ETDRS experienced significant improvements in visual acuity (VA), leaving researchers to look for more effective interventions. The recently introduced drugs (ranibizumab, aflibercept) that prevent the binding of vascular endothelial growth factor (VEGF) to its trans-membrane receptors produce superior improvements in VA over laser, either when administered as monotherapy or when combined with as-needed supplemental macular laser photocoagulation. The pivotal phase Ⅲ trials featured monthly (ranibizumab, aflibercept) or bimonthly (aflibercept) injections of each drug for 2 years during which a significant number of patients experienced improved diabetic retinopathy (DR) severity scores. The need for anti-VEGF injections dropped significantly after 1-3 years in both the RISE/RIDE and DRCR.net Protocol Ⅰ trials indicating that VEGF production had diminished. These data led to the FDA approval of both ranibizumab and aflibercept for the treatment of DR complicated by DME. Physicians may now treat vision-threatening DME with ranibizumab or aflibercept while simultaneously improving DR and possibly achieving long-term regression.

Key words: Diabetic macular edema; Ranibizumab; Aflibercept; Diabetic retinopathy; Vascular endothelial growth factor

Core tip: Drugs that prevent the binding of vascular endothelial growth factor (VEGF) produce greater gains in best corrected visual than can be achieved with laser photocoagulation. The recently completed pivotal phase Ⅲ trials showed that regular injections of ranibizumab and aflibercept over 2 years also improved the severity of diabetic retinopathy (DR). Both drugs have now been approved for the treatment of DR in patients with diabetic macular edema (DME) thereby allowing physicians to consider VEGF inhibition to improve DR in patients with vision threatening DME.

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INTRODUCTION

The widespread use of drugs that bind vascular endothelial growth factor (VEGF) has reduced the incidence of blindness from neovascular age-related macular degeneration by up to 50%[1], thereby leaving diabetic retinopathy (DR), which had long been the leading cause of blindness in working-age individuals of industrialized nations, in the leading overall position. DR is the result of a complex set of biochemical abnormalities and histopathological changes, and though the exact cause of DR is not completely understood, evidence from the large Diabetes Control and Complications Treatment Trial and the United Kingdom Prospective Diabetes Study implicates poor blood glucose control in patients with both type 1 and type 2 diabetes[2,3]. Elevated blood glucose interferes with hexosamine flux, the polyol pathway, protein kinase C, and advanced glycation endproducts, each of which halts electron transport through the mitochondria, limits oxygen utilization, and causes tissue ischemia[4]. Ischemia stabilizes the cell's natural oxygen sensor, hypoxia-inducible factor-1α, and upregulates VEGF synthesis. VEGF induces swelling, growth and migration of vascular endothelial cells, abnormalities that are potentiated by other conditions such as systemic arterial hypertension and elevated blood lipids.

Neuroretinal dysfunction is the earliest manifestation of DR but retinal vascular changes are much easier to detect. Capillary endothelial damage disrupts the blood-retinal barrier with loss of pericytes, thickening of the capillary basement membrane, and upregulation of intercellular adhesion molecule (ICAM-1). The induced margination of leukocytes closes capillaries, exacerbates ischemia, and further amplifies VEGF production, thereby leading to vascular and stromal proliferation.

Fibrovascular proliferation characterizes the most advanced form of DR and though fibrosis does not regress, pre-fibrotic vascular changes are reversible. Timely, effective pan-retinal photocoagulation involutes neovascular vessels, reverses vascular dilation, and resolves retinal hemorrhages, but unfortunately it causes permanent loss of the peripheral visual field. Though substituting one pathologic condition for another may constitute a therapeutic success (a post-laser scarred retina is much preferred over a traction retinal detachment) true reversal of retinopathy with complete restoration of visual function never occurs.

VEGF may improve oxygen delivery to ischemic tissues by dilating retinal vessels, so retinal specialists have long recommended that anti-VEGF therapy be administered with caution to eyes with capillary non-perfusion for fear of worsening ischemia. But as a pluripotential cytokine, VEGF causes other retinal vascular changes that worsen blood flow. VEGF narrows capillary lumens by causing vascular endothelial cells to swell and blocks lumens by upregulating ICAM-1, which marginates leukocytes. Therefore, VEGF's net effect is to decrease overall capillary perfusion and worsen the severity of the retinopathy.

The incorporation of anti-VEGF drugs into diabetic treatment algorithms has been slow, but encouraging results from the recent ranibizumab (Genentech®, S. San Francisco, CA/Roche, Basel, Switzerland) and aflibercept (Eylea®, Regeneron, Tarrytown, NY) registration trials[5,6], as well as phase Ⅲ trials with the dexamethasone delivery system (Ozurdex®, Allergan, Irvine, CA) and the fluocinolone acetonide insert (Iluvien®, Almera, Alpharetta, GA)[7,8], promise to further increase the use of intravitreal pharmacotherapy in patients with diabetic macular edema (DME). These phase Ⅲ registration trials met their primary endpoints – proportion of eyes improving by at least +15 letters – as well as several secondary functional and morphologic endpoints. Visual acuity (VA) improvements following macular laser photocoagulation average +2 to +3 ETDRS letters over 2 years, but improvements of +10 to +12 letters are achieved with monthly injections of ranibizumab and aflibercept. Macular edema significantly improves after the first injection, followed by slower additional gains with continued monthly therapy[5,6]. VA and macular thinning does not further improve after one year, but extension studies show that these gains stabilize through 5 years despite a decreasing frequency of injections[9].

Important secondary findings included improvements in average Early Treatment of DR severity scores[5,6]. More eyes treated with ranibizumab than sham/laser experienced 2-level (37.8% to 40.9% *vs* 23.4% to 24.3%) and 3-level improvements (11.3% to 15.4% *vs* 2.6% to 4.0%) in ETDRS severity and fewer experienced 2-level (0.9% to 4.3% *vs* 8.9% to 9.6%) and 3-level (0.8% to 1.7% *vs* 3.2% to 4.3%) worsening[10]. At the 2-year point in VIVID and VISTA more aflibercept-treated patients compared to sham/laser experienced 2-level (33.8% and 29.1% *vs* 14.3%) improvements in ETDRS severity scores[6]. Though only a subset of the RISE/RIDE cohort was followed from years 3 through 5 with as-needed injections, decreased treatment frequency did not worsen DR scores. These results suggest that VEGF blockade not only improves the retinopathy through 2 years but it reverses the underlying pathophysiologic processes responsible for DR development.

How VEGF blockade improves DR severity despite a decreasing treatment frequency after 3 years is not known. Anti-VEGF drugs bind only soluble VEGF and prevent it from activating the trans-membrane receptor VEGFR2 but do not directly inhibit VEGF synthesis. However, these drugs dampen VEGF amplification by inhibiting ICAM-1 synthesis and the resultant margination and activation of leukocytes. Since activated

leukocytes synthesize VEGF and initiate a self-sustaining, positive feedback loop, binding diffusible VEGF actually decreases overall VEGF production. Downregulated VEGF together with other as yet unidentified factors may permanently shut down VEGF synthesis and reverse retinopathy in some patients.

Drug developers are now working to expand the indications for anti-VEGF therapy by focusing on eyes at risk of DME-mediated vision loss. Ranibizumab was recently approved for the treatment of fovea-threatening DME due to DR[11] and Regeneron will launch a phase Ⅲ aflibercept trial for eyes at risk of vision loss due to DR - those with moderate non-proliferative DR or early posterior segment neovascularization. The hope is that intravitreal aflibercept every 8 or 16 wk will prevent adverse outcomes - DME and high-risk proliferative DR - by stabilizing or improving the severity of DR. If this trial produces successful results with an acceptable safety profile, it is easy to imagine subsequent trials that target lower risk retinopathy.

Despite these encouraging results physicians need to be careful when using anti-VEGF therapy in eyes with DME and widespread retinal non-perfusion. Regular anti-VEGF injections may successfully resolve macular edema while simultaneously preventing the development of retinal neovascularization or neovascular glaucoma. Stopping injections, however, might precipitate rapid growth of neovascularization and blinding complications. Anti-VEGF therapy may open the door for curing retinopathy but predictable, dramatic, and permanent improvements will probably require combination therapy with inhibitors of angiopoietin 2 or integrins, or platelet derived growth factor added to a regimen of regular anti-VEGF injections.

The anti-VEGF era began by treating vision loss due to DME but this encouraging journey now has us thinking that we can not only prevent vision loss but perhaps even reverse and cure DR.

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