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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

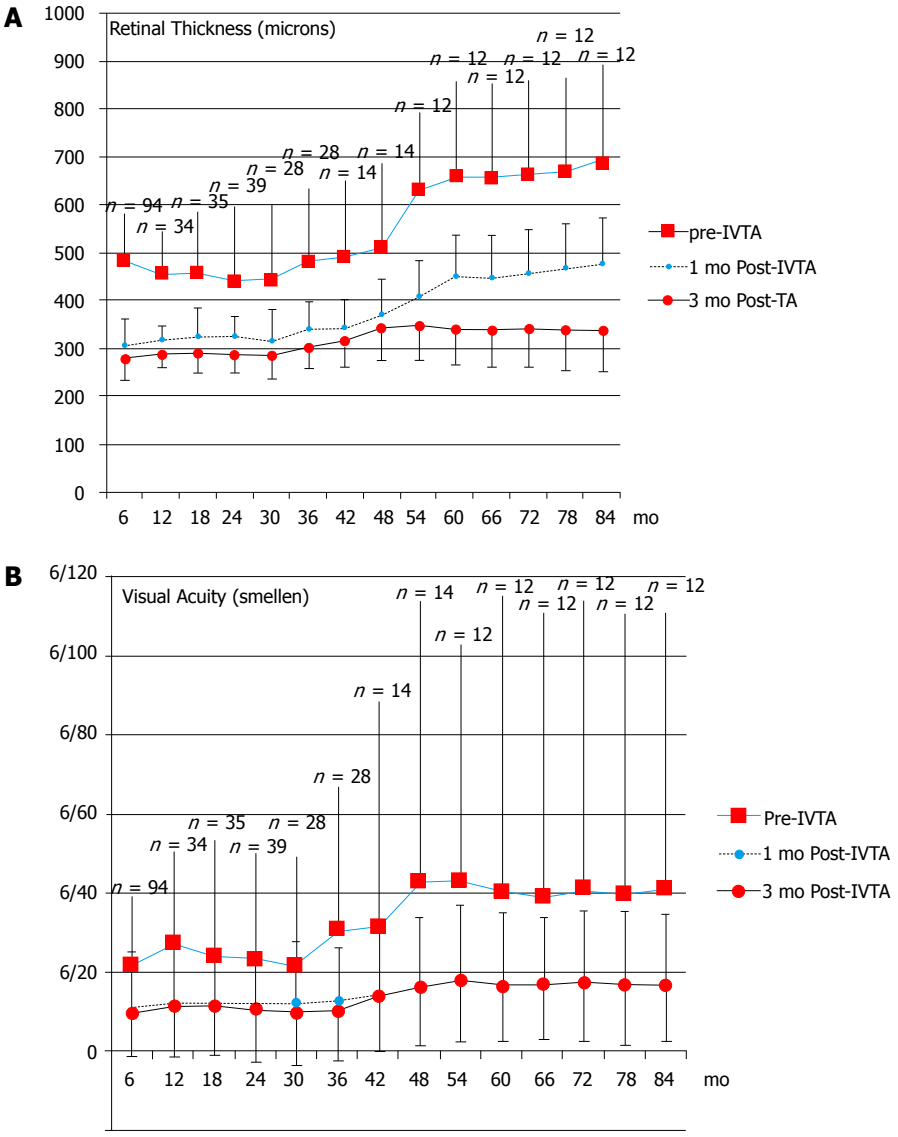

Figure 1 Mean retinal thickness (A) or visual acuity (B) following intravitreal triamcinolone injections over 7 years. Number of intravitreal triamcinolone injections from a cohort of 92 eyes receiving intravitreal triamcinolone (IVTA) in a given 6-mo period and up to 84 mo (seven years) later. Note 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,

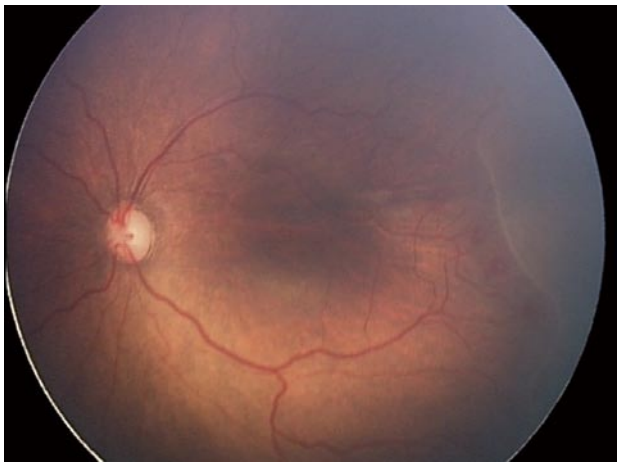

Figure 1 Previous 24 wk infant post menstral age of 32 wk presents with stage 2, zone 1 with preplus which rapidly progresses to aggressive posterior retinopathy of prematurity within 1 wk (image not shown).

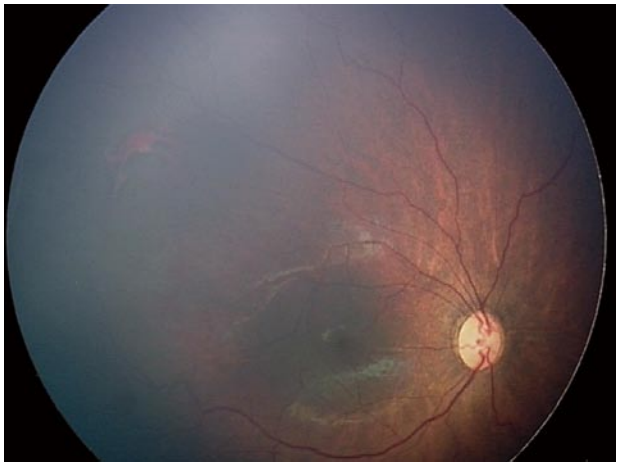

Figure 2 Previous 24 wk infant status post bevacizumab injection a for aggressive posterior retinopathy of prematurity. RetCam imaging of the right eye reveals regressed retinopathy of prematurity with vascularization into zone 2. Plus disease is no longer present. The patient is post menstral age of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

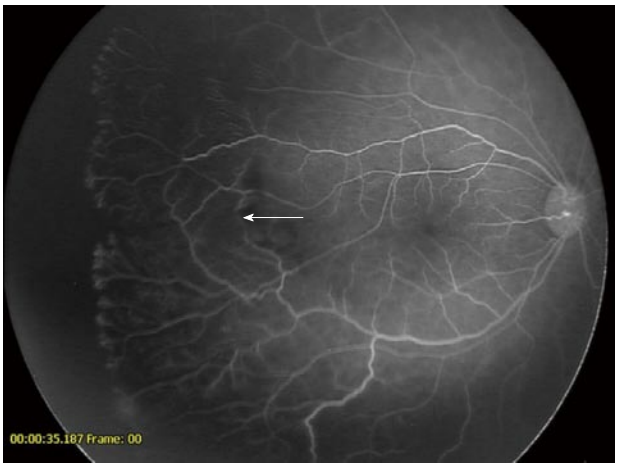

Figure 3 Fluorescein angiogram of the right eye reveals extensive areas of avascular retina. There is a well demarcated line of advancing vessels with areas of neovascularization present. The arrow depicts the original area of the stage 3 ridge in zone 1 at the time of bevacizumab injection.

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

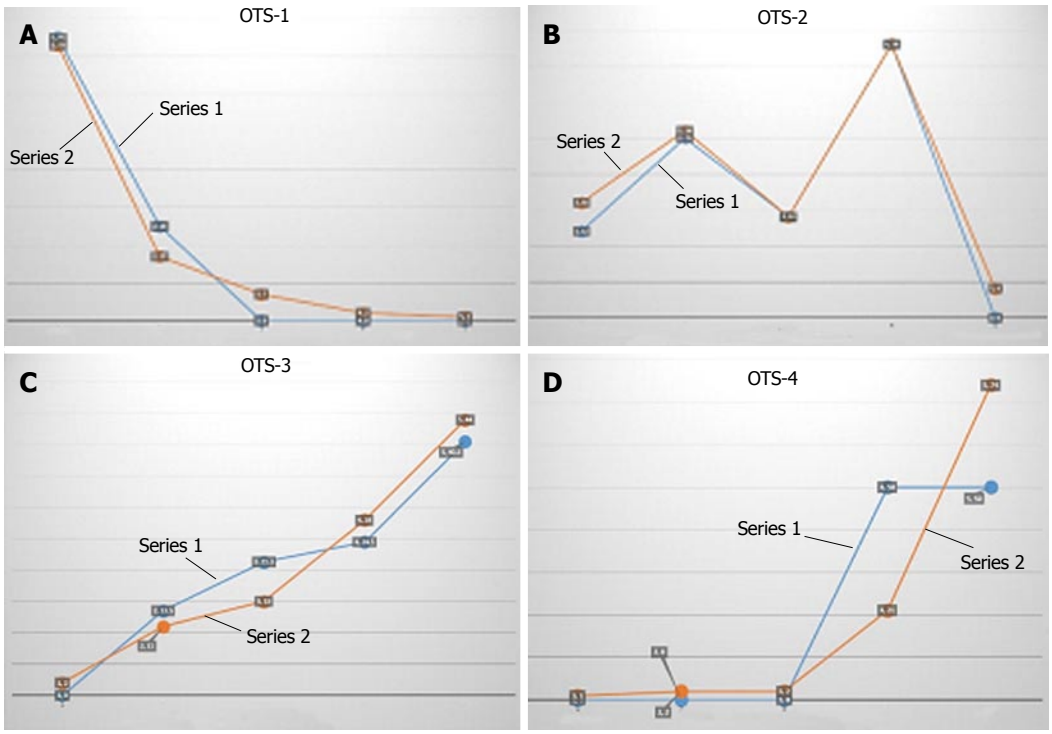

Figure 1 Comparison between ocular trauma score and achieved results. A: Comparison between OTS and achieved results in OTS-1 score category; B: OTS-2 score category; C: OTS-3 score category; D: OTS-4 score category. OTS: Ocular trauma score.

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

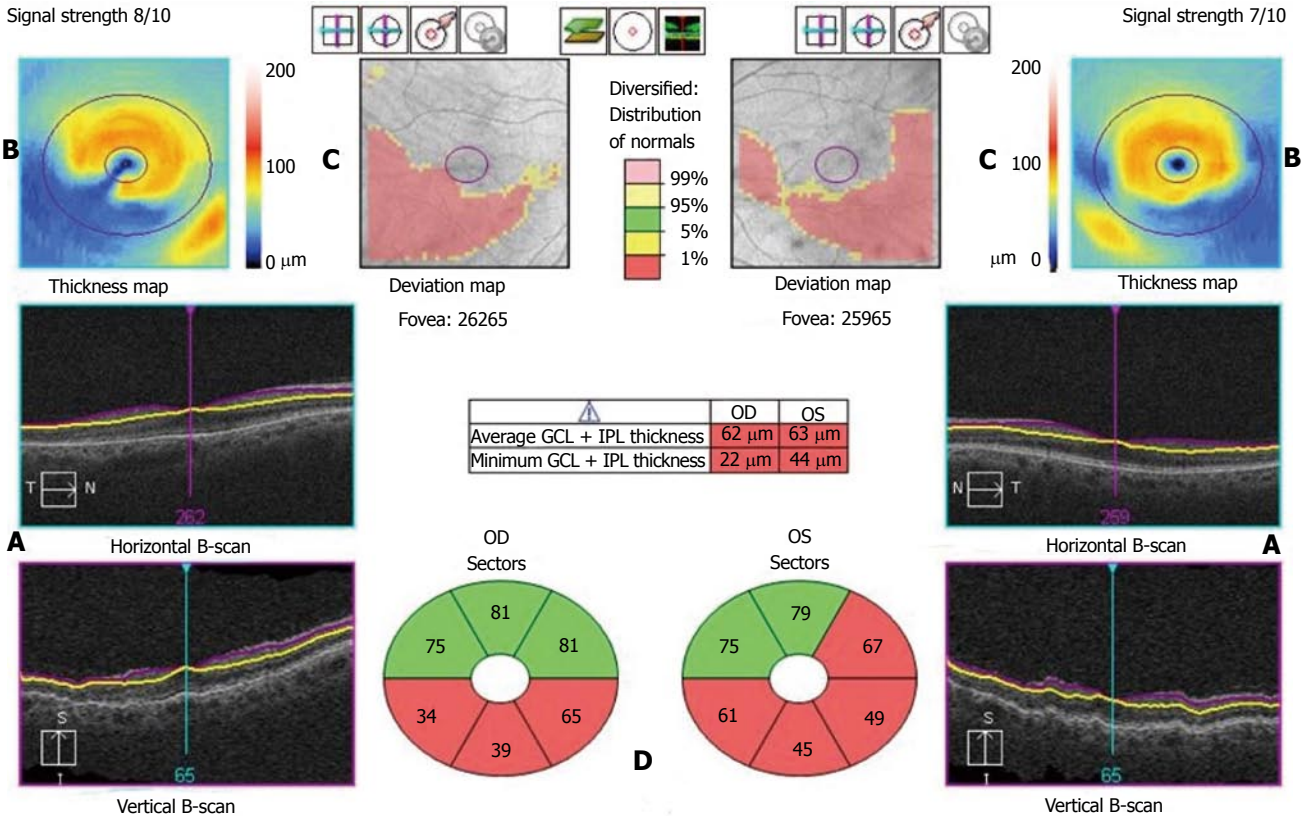

Figure 1 Cirrus HD-optical coherence tomography. A: Segmentation. Horizontal and vertical B-scans. The purple line represents the inner boundary of the ganglion cell layer and the yellow line represents the outer boundary of the inner plexiform layer; B: Thickness map. Calculation of the ganglion cell 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

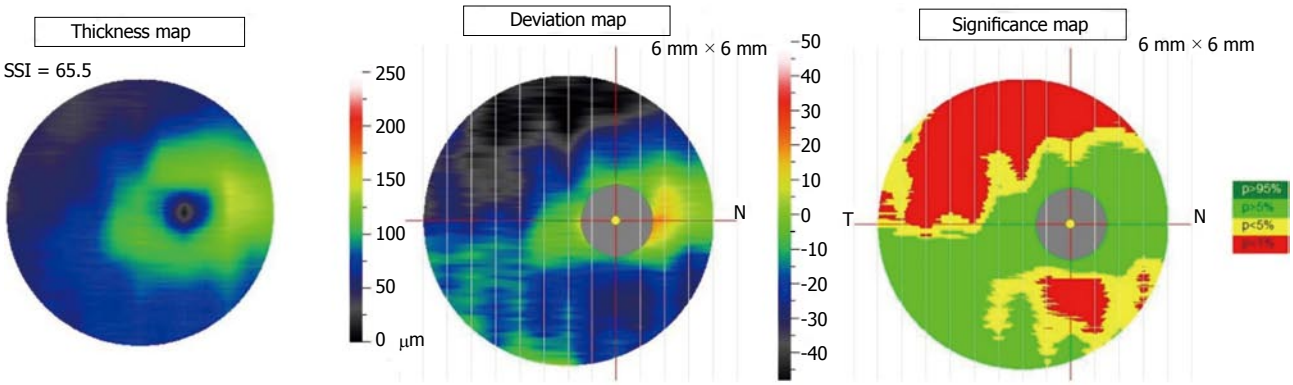

Figure 2 RTVue. A: Thickness map. The thickness map is color coded where thicker regions of the ganglion cell complex are displayed in hot colors (yellow and orange), and thinner areas are displayed in cooler colors (blue and green); B: Deviation map. Calculated based on comparing the thickness map to 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).

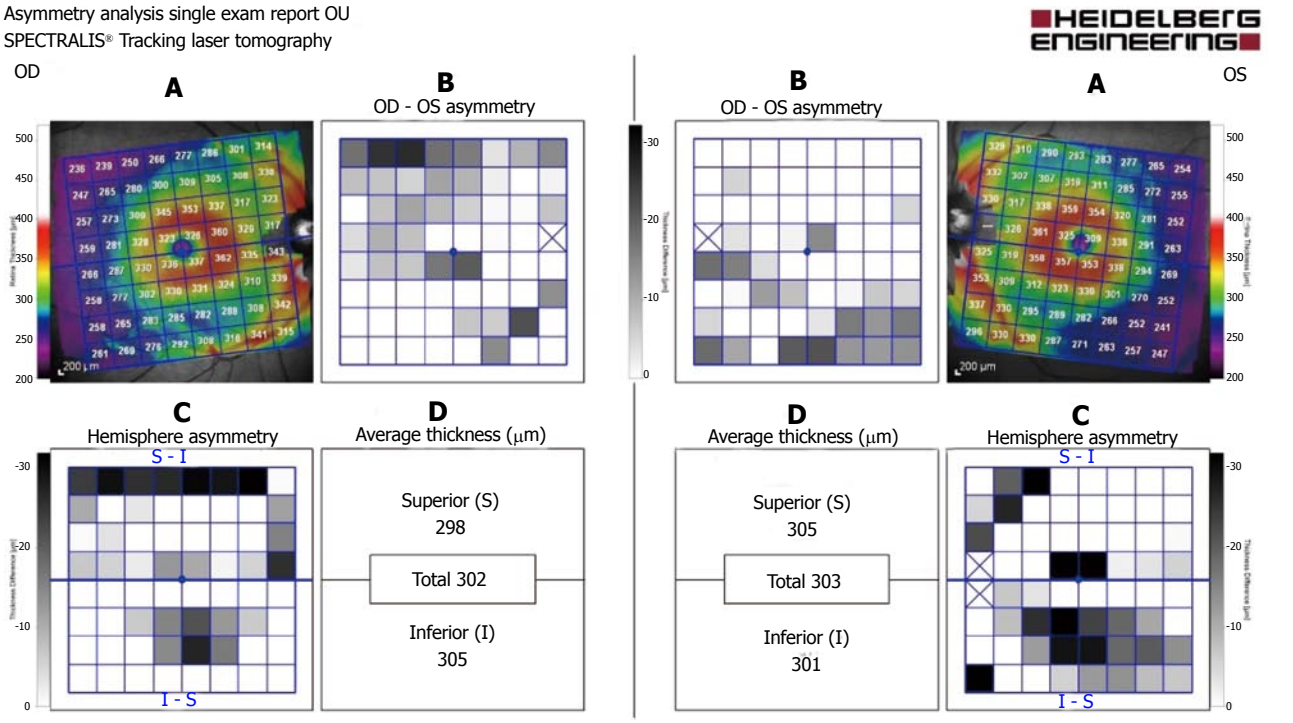

Figure 3 Spectralis. A: Thickness map - the entire retinal thickness in the posterior pole displayed as a color coded thickness map for an 8 × 8 grid centered on the foveal pit positioned symmetrically to the fovea-disc axis; B: Asymmetry map - examination by grid of the asymmetry between the thicknesses 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

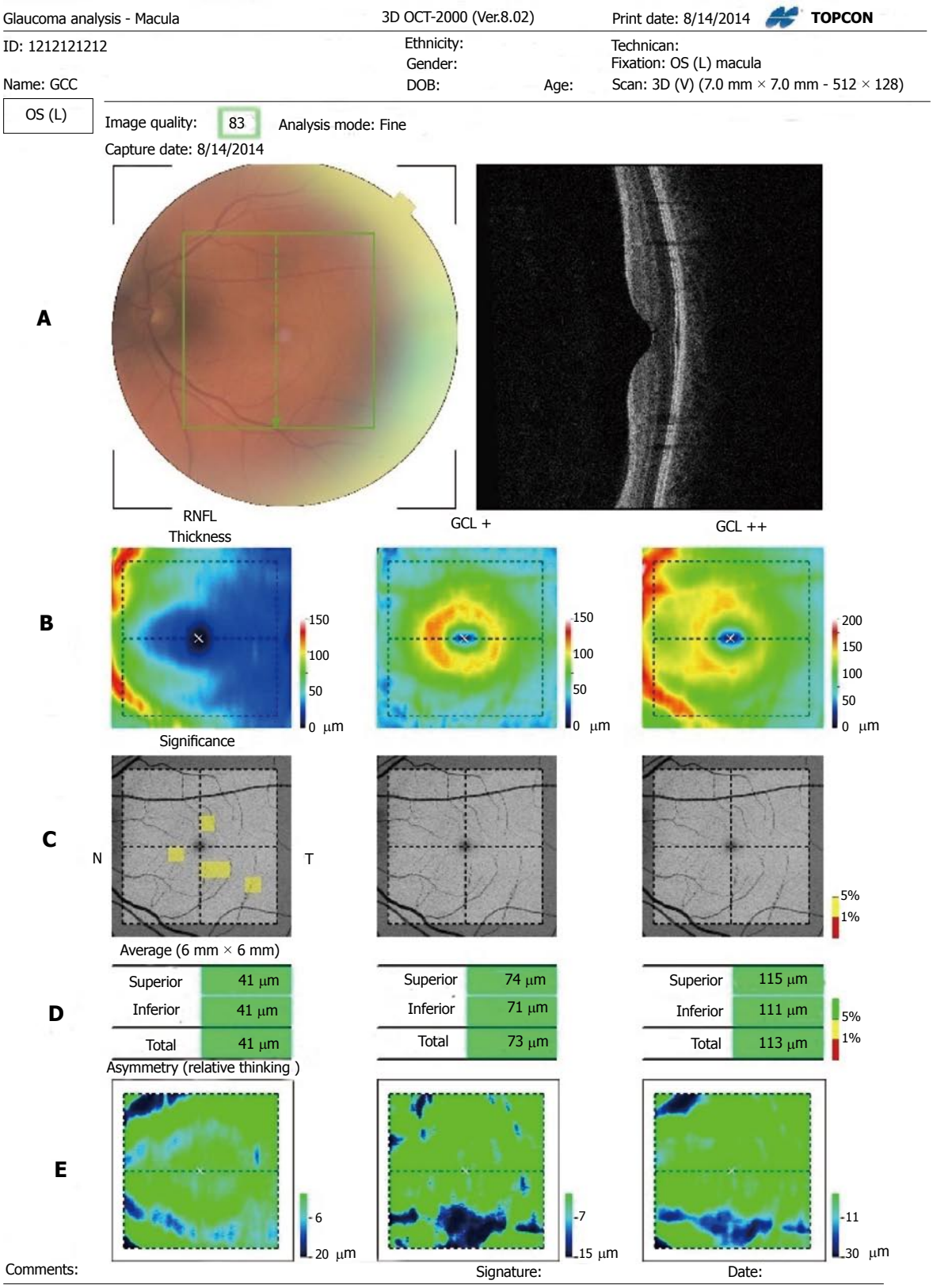

Figure 4 Three dimensions optical coherence tomography 2000. A: Segmentation: 7 mm^2 area centered on the fovea with a scan density of 512 vertical × 128 horizontal scans; B: Thickness map. Average regional thickness is calculated for RNFL, GCL+ (GCL + IPL), GCL++ (RNFL + GCL + IPL). Each cell is calculated 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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