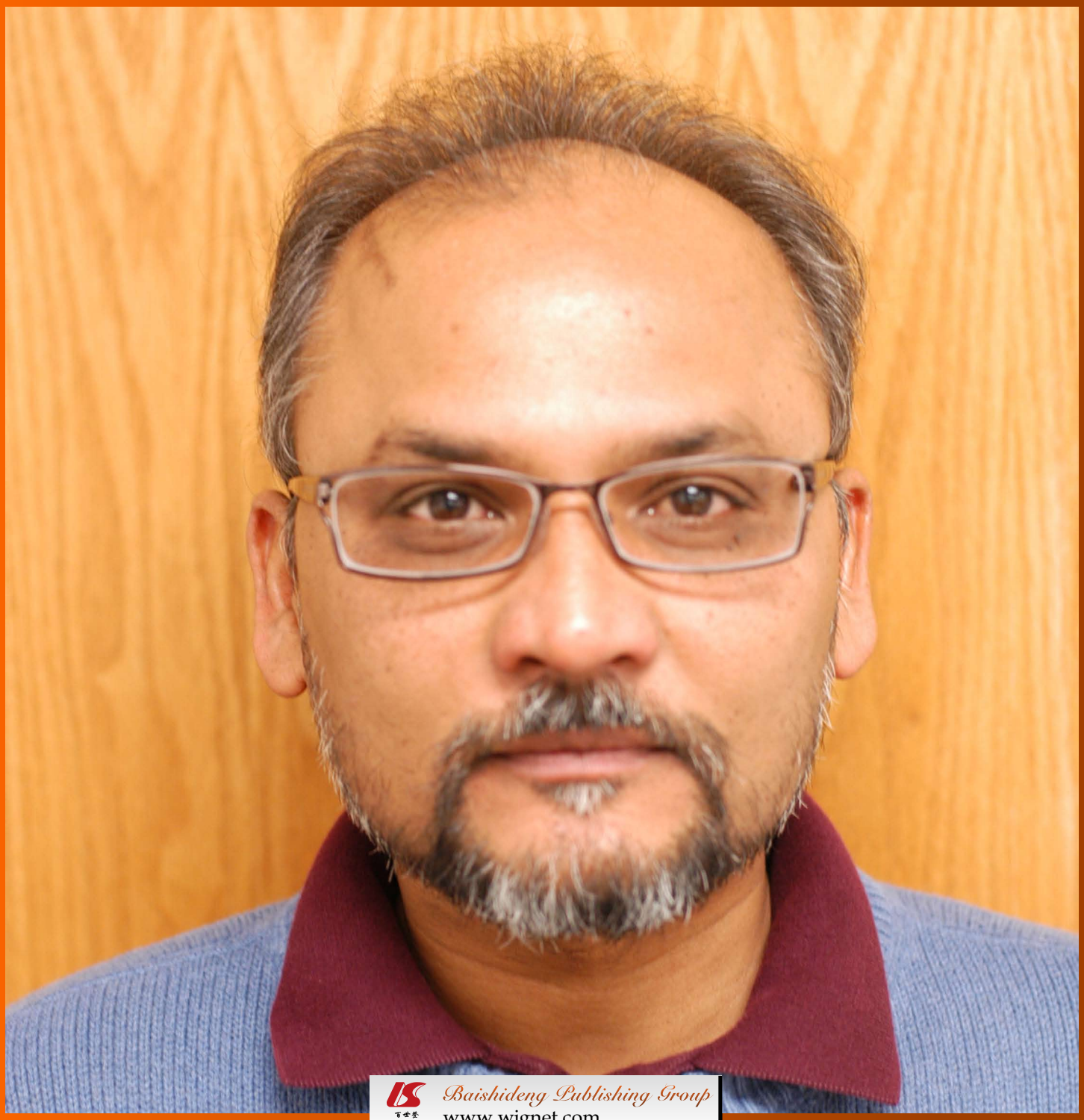
ISSN 2218-6239 (online)

World Journal of *Ophthalmology*

World J Ophthalmol 2013 August 12; 3(3): 20-31



Baishideng Publishing Group
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WJO World Journal of Ophthalmology

A peer-reviewed, online, open-access journal of ophthalmology

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WJO World Journal of Ophthalmology

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Quarterly Volume 3 Number 3 August 12, 2013

World Journal of Ophthalmology
Volume 3 Number 3 August 12, 2013

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NAME OF JOURNAL
World Journal of Ophthalmology

ISSN
ISSN 2218-6239 (online)

LAUNCH DATE
December 30, 2011

FREQUENCY
Quarterly

World Journal of Ophthalmology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
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http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China
Fax: +852-6555-7188
Telephone: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
August 12, 2013

World Journal of Ophthalmology

Online Submissions: http://www.wjgnet.com/esps/
wjophthalmol@wjgnet.com
doi:10.5318/wjo.v3.i3.20

World J Ophthalmol 2013 August 12; 3(3): 20-31
ISSN 2218-6239 (online)

Keratoconus therapeutics advances

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Author contributions: All the authors fulfill the Vancouver definition of authorship; Jaimes M and Navas A contributed to conception and design, drafting the article and final approved of the version to be published; Ramirez-Miranda A and Graue-Hernández EO contributed to acquisition of data, revising the article for important intellectual content and final approved of the version to be published.

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Received: June 29, 2013 Revised: August 10, 2013
Accepted: August 11, 2013
Published online: August 12, 2013

Abstract

Keratoconus is a progressive, usually bilateral disease of the cornea that significantly diminishes visual acuity, secondary to a progressive corneal deformity which is characterized by corneal thinning, variable degrees of irregular astigmatism and specific abnormal topographic patterns. Normally it initiates during puberty and is progressive until the third or fourth decade of life, when normally the progression rate is diminished or waned. There are multiple scales to clinically classify keratoconus. One of the most commonly used is Amsler-Krumeich and recently with the development of morphometric and aberrometric techniques, additional scales have been created that allow keratoconus to be classified according to its severity. Despite certain etiology of keratoconus remains unknown, current treatment options are available in patients with ectatic corneas and they vary depending on the severity of the disease and they include spectacles, contact lenses, intrastromal rings, keratoplasty both penetrant or lamellar, cross-linking, refractive lens exchange with intraocular lens implant, phakic intraocular lenses and the combination of these alternatives. Some authors have been using excimer laser in patients with keratoconus but the safety of the procedure is controversial. Currently, the techniques for the management of keratoconus can be classified in 3 types: corneal strengthening techniques, optical optimization techniques and combined techniques.

Key words: Keratoconus; Treatment; Management; Corneal ectasia; Therapeutics

Core tip: There are several treatment options for the current management of keratoconus patients. These alternatives are increasing and better outcomes could be obtained. The purpose of this review is to summarize the therapeutics advances in keratoconus.

Jaimes M, Ramirez-Miranda A, Graue-Hernández EO, Navas A. Keratoconus therapeutics advances. *World J Ophthalmol* 2013; 3(3): 20-31 Available from: URL: http://www.wjgnet.com/2218-6239/full/v3/i3/20.htm DOI: http://dx.doi.org/10.5318/wjo.v3.i3.20

INTRODUCTION

Keratoconus is a corneal ectasia that significantly diminishes visual acuity, secondary to a progressive corneal deformity which is characterized by corneal thinning, variable degrees of irregular astigmatism and specific abnormal patterns (Figure 1) of corneal elevation[1].

It has an approximate incidence, which varies between 50 to 230 cases in 100000 inhabitants in general population (1:2000). The estimated prevalence is of 54.5:100000 inhabitants. Normally it initiates during puberty and is progressive until the third or fourth decade of life, when normally the progression rate is diminished or waned[2].

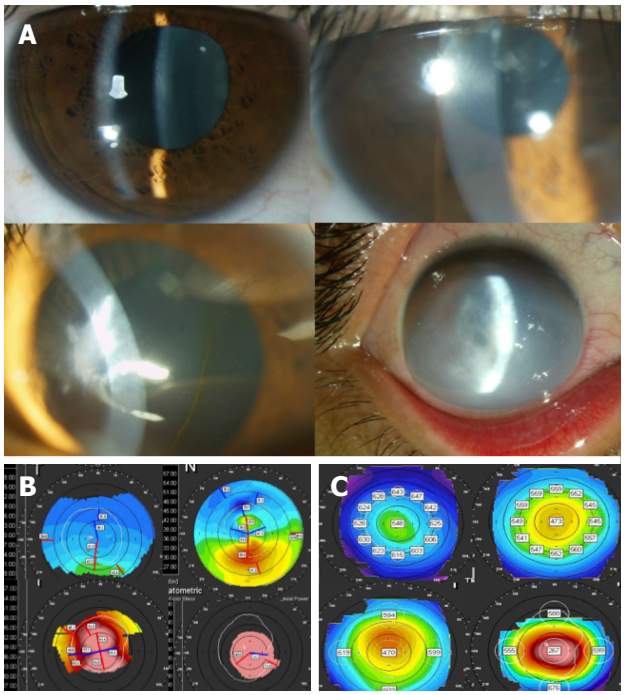

Figure 1 Keratoconus clinical and topographic variation examples. A: Several clinical presentations and severity of keratoconus cases; B: Different keratometric stages of keratoconus; C: Pachymetric maps showing different grades of KC cases.

There are multiple scales to clinically classify keratoconus. One of the most commonly used is Amsler-Krumeich[3] (Table 1) and recently with the development of morphometric and aberrometric techniques, additional scales have been created that allow keratoconus to be classified according to its severity[4] (Table 2).

Currently, the techniques for the management of keratoconus can be classified in 3 types: corneal strengthening techniques, optical optimization techniques and combined techniques[5].

Among the strengthening techniques are: corneal collagen cross-linking and placement of intrastromal rings segments (which also have a refractive effect). The optical optimization techniques include the use of spectacles, rigid, soft or optimized contact lenses; excimer laser, lamellar or penetrating keratoplasty (which also have a strengthening effect), phakic lenses and pseudophakic lenses.

The combined procedures are those that are utilized in a sequential manner to obtain optical and refractive results and they include a wide array of possible combinations of the procedures previously described to obtain these objectives (Figure 2).

One of the main criteria to consider the more suitable technique or treatment for our patient is refraction, age, the thinning degree and the irregular astigmatism. If it is possible to obtain a correct subjective and objective refraction and the patient shows an improvement in their visual acuity with optical correction, then the options of treatment will have as an objective to correct the refractive error more so than to stabilize the keratoconus. According to this, we present an algorithm suggested for decision making in respect to surgical criteria in patients with keratoconus (Figure 3). Evidently, every patient needs to be individualized.

Table 1 Clinical classification of keratoconus[3]

Stage	Characteristics
Stage I	Eccentric bulging
	Induced myopia and/or astigmatism of 5 D
	Average central keratometry of 48 D
Stage II	Induced myopia and/or astigmatism of 5 to 8 D
	Average central keratometry > 48 D but < 53 D
	Absent scarring
	Minimum corneal thickness of 400 microns
Stage III	Induced myopia and/or astigmatism of 8 to 10 D
	Average central keratometry > 53 D
	Absent scarring
	Central corneal thickness of 300 to 400 microns
Stage IV	Invaluable refraction
	Average central keratometry > 55 D
	Central corneal scar
	Corneal thickness < 200 microns

SPECTACLES

These represent the best option for treatment of fruste keratoconus and keratoconus with small irregular astigmatism that are refractable and have a visual capacity > 20/40 or do not wish surgery to treat the ectasia or the slight ametropia. The recommendation in these cases is to have topographic follow ups every 6 mo to evaluate progression.

CONTACT LENSES

Contact lenses are treatment of choice for 90% of the patients with keratoconus. The degree of keratoconus influences the selection of the type of contact lens and also many of the patients that have been treated with penetrating keratoplasty use contact lenses[6].

The most commonly used contact lens design in patients with keratoconus is the unique base curve in rigid gas permeable material. Lenses with multiple base curves can also be used. In patients with highly advanced keratoconus, hybrid or scleral lenses have been used[6].

In recent studies, it's been identified that 79% of patients with keratoconus use contact lenses; of which, 21.3% have already had at least one penetrating keratoplasty. Sixty-seven point seven percent of the patients use the hybrid gas permeable lens, 13% soft contact lens, 4.2% scleral gas permeable lens and 15.1% use other types of contact lenses[7].

Presently, new personalized lens models have been designed for the treatment of keratoconus for those with intolerance of the conventional contact lens. Examples of these include the PROSE lens (Prosthetic replacement

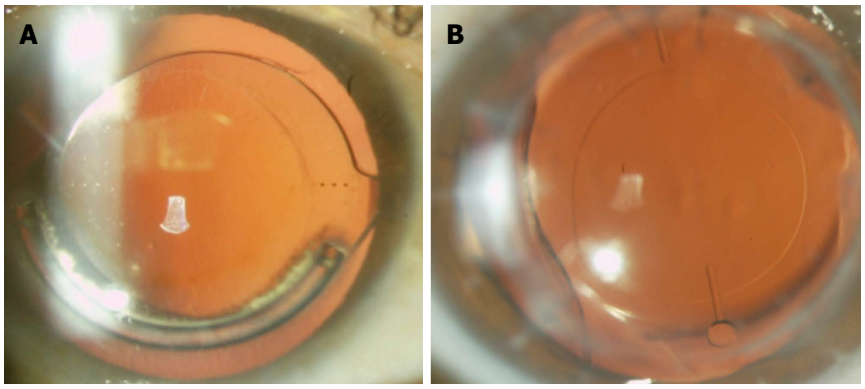

Figure 2 Combined procedures. A: Combination of intrastromal ring segments and pseudophakic toric intraocular lens; B: Pseudophakic plate toric intraocular lens following penetrating keratoplasty.

Table 2 Paraclinic criteria for diagnosis of keratoconus[4]

Criteria	Values in keratoconus
Curvature	> 46 to 47 D
Asymetry I-S	> 1.4 D
Irregularity	> 20 or 30 degrees with respect to the vertical meridian
Keratometric difference between the 2 eyes	> 1 D
Anterior elevation	< 15 m in Placido rings images and < 12 m in Scheimpflug images
Posterior elevation	< 35 m in Placido rings images and < 18 m in Scheimpflug images
Pachymetry	Thinnest, decentered point, difference of 100 m between center and periphery
Aphericity (Q)	Between -0.5 and < -1
Eccentricity	Approaching 1
Form factor	Approaching 0
Corneal irregularity	> 1.1-5
Medium toric keratometry	47.3-60 D
Surface irregularity index	> 1.55
Predicted corneal acuity (Holladay Report)	> 0
Keratoconus index (Maeda)	> 0
Keratoconus % index	> 100
Keratoconus prediction index	> 0.38
Surface variation index	> 41
Vertical asymmetry index	0.32
Keratoconus index	> 1.07
Central keratoconus index	> 1.03
Smallest curvature radius	> 6.71
Largest asymmetry index	> 21
Height decentration index	> 0.016
Aberration coefficient	> 1
Aberration	Vertical Coma and Coma-like RMS (> 1.5 m)
Corneal volume analysis	> 57.98 ± 2.65 mm^3
Corneal hysterisis	> 9.64 mmHg
Corneal resistance factor	> 9.6 mmHg

of the ocular surface ecosystem; BFS, Needham, MA); a device manufactured from a gas permeable polymer of fluorosilicone-acrylate with a Dk index of 85 × 10-12 mL O^2/s mL mmHg, which currently has reported 88% use success with 93% of the patients with AV > 20/40[8].

The SynergEyes lens (SynergEyes, Inc, Carsbd, CA) is a third generation hybrid lens with a rigid gas permeable center and a "skirt" of hydrophilic material; it has the highest coefficient of oxygen diffusion of previous generations. The use of these lenses is associated with a corrected distance visual acuity (CDVA) improvement of 85.2% of the keratoconus cases treated and a usage success rate of 86.9% of the keratoconus cases in which it was fitted[9].

Another lens design is the personalized rigid gas permeable lens (Rose K Lens, Con-Cise Contact Lens Company, San Leandro, CA), with a 76% success rate in lens fitting[10] and aberrometry guided scleral lens fitting, which recently have been tested for the treatment of high order aberrations in keratoconus. These lenses have proven to be effective in the correction of corneal aberrations such as vertical coma and secondary astigmatism, achieving an CDVA of 20/30 in average and corneal aberrations compatible with a corneal pattern of healthy population and low reduction of contrast sensitivity compared to conventional rigid gas permeable contact lenses[11].

PHAKIC INTRAOCULAR LENSES

From 2003 to date, there have been increasing reports published of the use of phakic lenses as a sole or sequential procedure for the treatment of stable keratoconus. One of the firsts reports in literature was made by Leccisotti *et al*[12], when he reports for the first time the use of an anterior chamber phakic lens with angular support for the treatment of keratoconus. Following this, multiple studies with different types of phakic lenses (anterior and posterior chamber, toric and spherical) have been employed for the treatment of keratoconus and even for the management of residual ametropia following penetrating keratoplasty[13].

The safety, efficacy and predictability indexes of all of the studies have demonstrated to be very suitable in cases in which the patient has been selected appropriately, in particular, adequately identifying progression and refractability; and given the case where the keratoconus is not stable, it is useful to utilize strengthening techniques such as cross-linking and placement of intrastromal rings in a simultaneous or sequential manner (Table 3).

The current criteria for the placement of a phakic lens in keratoconus takes into account a stable keratoconus, correctable refractive error due to the types of phakic lenses available, endothelial count greater than 2500 cel/mm^2, anterior chamber depth > 2.8 mm in cases of

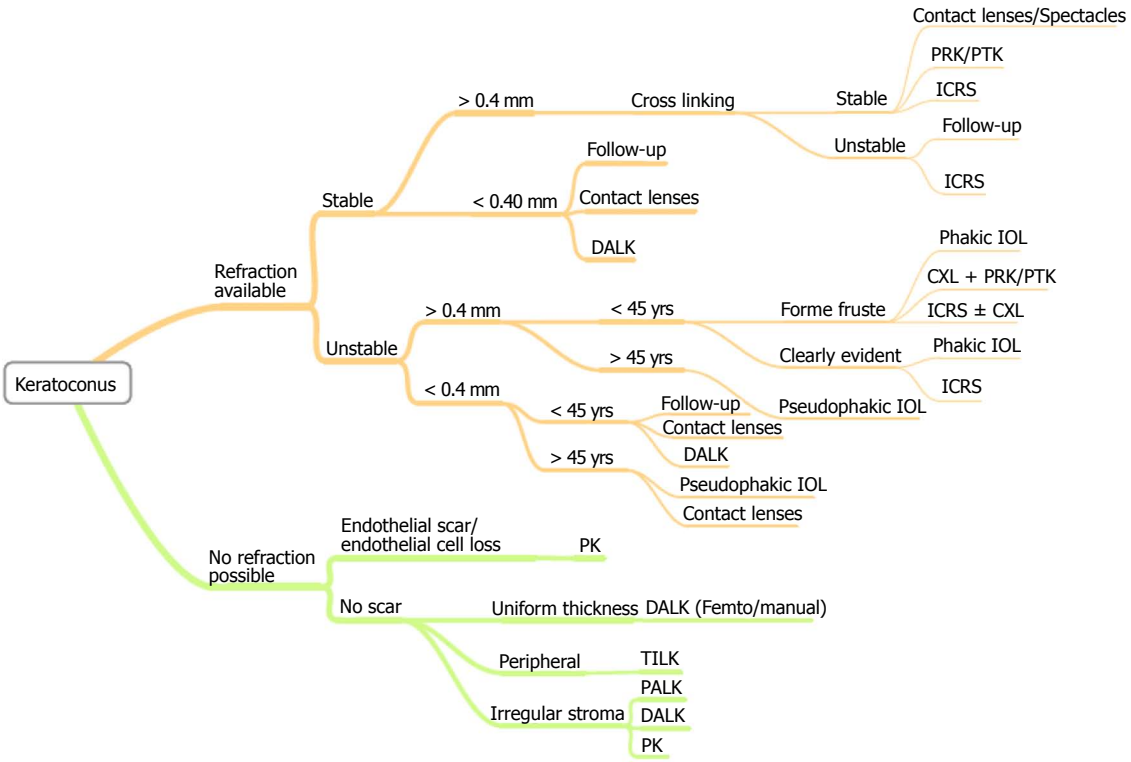

Figure 3 Proposed algorithm for keratoconus treatment. PRK: Photorefractive keratectomy; PTK: Phototherapeutic keratectomy; ICRS: Intrastromal corneal ring segments; DALK: Deep anterior lamellar keratoplasty; CXL: Corneal collagen cross-linking; IOL: Intraocular lenses; PK: Penetrating keratoplasty; TILK: "Tuck-In" lamellar keratoplasty; PALK: DALK assited by pachymetry.

posterior chamber lenses (Figure 4), absence of uveal pathology or glaucoma.

PSEUDOPHAKIC INTRAOCULAR LENSES

The current trend for management of large ametropias in patients over 45 years old with keratoconus is the use of replacement of the crystalline lens with pseudophakic[26] intraocular lenses (Figure 5). These options are considered specifically in this age group given the tendency for arrested progression of the keratoconus starting the forth decade of life[27].

Previous reports have been published by our group in 2011[28] about this treatment option. Our experience consists of the treatment of 19 eyes of patients with keratoconus which underwent refractive lens exchange for the correction of ametropia of the compound myopic astigmatism type in stable keratoconus. The preoperative and postoperative sphere was of -5.25 ± 6.4 D and 0.22 ± 1.01 D respectively. The preoperative and postoperative cylinder was of -3.95 ± 1.3 and 1.36 ± 1.17, with preoperative spherical equivalent of -7.10 ± 6.41 D and postoperatively of -0.46 ± 1.12 D. The preoperative UDVA was 1.35 ± 0.36 (logMAR) and postoperative of 0.29 ± 0.23 (logMAR). The procedure was safe, predictable, effective and subjectively gratifying for all of the patients[28].

Recently, Nanavaty *et al*[29] reported a series of 12 cases of keratoconus patients treated with a plate toric pseudophakic lens implant for the management of ametropia. Their results report a UDVA of 20/40 or better in 75% of the patients and CDVA of 20/40 or better in 83.3% of the treated cases. The preoperative sphere of -4.8 ± 5.6 D was reduced to 0.3 ± 0.5 D and the cylinder decreased from 3 ± 1 D to 0.7 ± 0.8 D. None of the cases reported in both series had keratoconus progression[29].

There are also a few reports of combined intraocular lens treatment (piggyback) for the management of residual ametropia in keratoconus patients who underwent cataract surgery either at the same time or considering sequential implant[30].

The great advantage of this technique over the others is that it allows for the appropriate ametropia correction, caused by the keratoconus, to be made in just one procedure without the need of additional treatments and, with current techniques such as biometry through interferometry and corneal topography/tomography, the lens calculation tends to be more accurate every time[28].

CORNEAL COLLAGEN CROSS-LINKING

The collagen crosslinking technique was first described in the 70's; however, it wasn't until 2003 that ultraviolet light A (370 nm) combined with riboflavin for the strengthening of the corneal collagen fibers in human eyes was used to stop keratoconus progression[31].

Since then, numerous studies have been published

Table 3 Phakic intraocular lenses for keratoconus studies

Ref.	Criteria	Lens	Preoperative	Postoperative	*P*-value
Leccisotti *et al*[12]	12 eyes. KC Ⅰ y Ⅱ	Angular supported, spherical	Sphere -10.23 ± 2.85 D Cyl -2.79 ± 1.11 D CDVA 0.13 ± 0.17	Sph 0.46 ± 0.45 D Cyl -2.35 ± 1 D UCVA 0.44 ± 0.8 CDVA 0.03 ± 0.05	0.002
Alfonso *et al*[14]	25 eyes	Posterior chamber, spherical	Sph -8.54 ± 4.15 D Cyl -1.24 ± 1.19 D CDVA 0.13 ± 0.15	Sph 0.0 ± 0.25 D Cyl -0.45 ± 0.73 D SE -0.32 ± 0.55 D UCVA 0.17 ± 0.19 CDVA 0.12±0.12	< 0.05
Venter *et al*[15]	18 eyes	Iris supported, toric/ spherical	Sph -4.64 ± 2.74 D Cyl -3.07 ± 2.04 D CDVA ≥0.5	SE -0.46 ± 0.6 D UDVA ≥ 0.2 en 94%	< 0.05
Alfonso *et al*[16]	30 eyes	Posterior chamber, toric	SE -5.38 ± 3.26 D Cyl -3.48 ± 1.24 D UDVA 0.8 logMar CDVA 0.10	SE -0.08 ± 0.37 D Cyl 0.41 ± 0.61 D UDVA 0.10 logMar CDVA 0.10	
Kamiya *et al*[17]	27 eyes, mild KC	Posterior chamber, toric	SE -10.11 ± 2.46 D Cyl -3.03 ± 1.58 D UCVA 1.51 ± 0.2 CDVA -0.11 ± 0.08	SE 0.00 ± 0.35 D UCVA -0.09 ± 0.16 CDVA -0.15 ± 0.09	
Sedaghat *et al*[18]	16 eyes,	Anterior chamber, iris supported	Sph -12.5 ± 4.61 D Cyl 2.95 ± 4.06 D SE -13.9 ± 4.61 D UDVA CF CDVA 0.21 ± 0.14	Sph -0.03±1.81 D Cyl 2.08 ± 1.04 D UDVA 0.15 ± 0.13 CDVA 0.11 ± 0.1	< 0.0001
Kato *et al*[19]	36 eyes	Iris supported, toric, spherical	SE -8.38 ± 3.42 D Cyl 2.44 ± 2.25 D UDVA 1.39 ± 0.42	SE -0.42 ± 0.89 D Cyl 0.62 ± 0.69 D UDVA 0.02 ± 0.21	
Hashemian *et al*[20]	22 eyes	ICL toric	SE -4.98 ± 2.63 D Cyl -2.77 ± 0.99 D UDVA 0.63 ± 0.2 dec.	SE -0.33 ± 0.51 D Cyl -1.23 ± 0.65 D UDVA 0. 85 ± 0.21 dec.	
Combined procedures					
Moshirfar *et al*[21]	19 eyes	Intacs/verisyse, sequential *vs* simultaneous	SE -12.38 ± 4.2 D Cyl 3.3 ± 1.8 D UCVA 2.025 ± 0.32 CDVA 0.34 ± 0.22	SE -1.2 ± 1.15 D Cyl 2.06 ± 1.1 D UCVA 0.465 ± 0.18 CDVA 0.15 ± 0.09	No difference regarding sequential *vs* simultaneous
Izquierdo *et al*[22]	11 eyes Progressive KC Ⅰ and Ⅱ	Crosslinking/verisyse	Sph -5.7 D Cyl -1.45 D SE -6.42 D UDVA 1.4 ± 0.4 CDVA 0.14 ± 0.06	Sph -0.27 D Cyl -0.9 D SE -0.72 D UDVA 0.16 ± 0.06 CDVA 0.04 ± 0.05	< 0.05
Alfonso *et al*[23]	40 eyes	Keraring/ICL	SE -9.65 ± 6.9 D UDVA 1.0 CDVA 0.3	SE -1.2 ± 1.3 D UDVA 0.3 CDVA 0.18	
Güell *et al*[24]	17 eyes Progressive KC Ⅰ and Ⅱ	Crosslinking and toric artiflex/artisan	SE -6.99 ± 3.2 D Cyl -3.54 ± 1.38 D UDVA < 1 CDVA 0.1 ± 0.09	SE -0.22 ± 0.33 D Cyl -0.62 ± 0.39 D 0.17 ± 013 CDVA 0.10 ± 0.09	
Navas *et al*[25]	11 eyes KC Ⅰ-Ⅳ	ICRS and toric and spherical ICL	Sph -9.04 ± 6.03 D Cyl -2.95 ± 1.35 D SE -10.52 ± 5.88 D UDVA 1.31 ± 0.37 CDVA 0.289 ± 0.14	Sph -0.06 ± 0.46 D Cyl -1.22 ± 0.65 D SE -0.68 ± 0.45 D UDVA 0.14 ± 0.04 CDVA 0.16 ± 0.08	< 0.01

CDVA: Corrected distance visual acuity; UDVA: Uncorrected distance visual acuity; ICRS: Intrastromal corneal ring segments.

about the effect of UVA light on keratoconus. It is known that the more meaningful effects are the progression halt of the keratoconus and in some reports there's also mention of its regression on an average of 2 D (from 1 to 4)[32,33].

At this moment, the long term effects of the implementation of this procedure are still unknown, with minimal or inexistent adverse effects being described in many of the cases with longer follow ups[32,33]. Some publications report a central haze, which tends to resolve itself with time, as the main complication and that it is more evident when performing a corneal[34] densitometry,

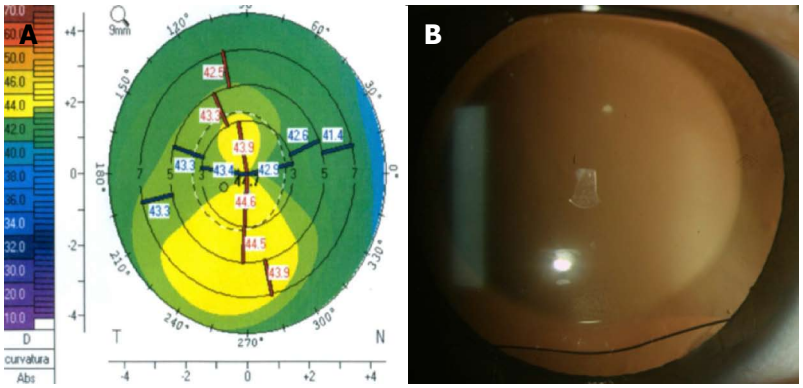

Figure 4 Phakic toric intraocular lens implantation in (A) forme fruste keratoconus case, (B) notice the rhomboidal marks of the lens toricity axis.

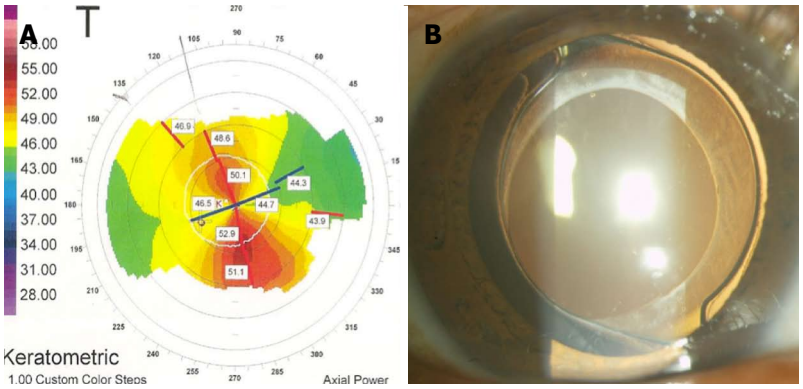

Figure 5 Pseudophakic toric intraocular lens in (A) frank keratoconus, (B) notice the three dot marks for toric intraocular lenses alignment.

remaining in up to 8.6%[35]. Up to now, in the majority of the studies done, no significant endothelial cell loss has been reported[36], but recently it has been identified that the pre-operatory corneal thickness > 400 microns is an important factor which determines the absence of CXL effects on the endothelium[37]. Through confocal microscopy it has been identified that during early phases of the scarring process some changes occurs such as a hyperreflective phenomenon in the collagen fibers of the medial to posterior stroma[36], as well as epithelial thinning, stromal edema and keratocytes apoptosis in the first 4 to 6 wk. Subsequently, an epithelial thickness and collagen compaction occurs[38].

Today, the more widely accepted criteria to perform a corneal crosslinking include patients with topographic evidence of keratoconus progression, corneal thickness > 400 microns and keratoconus without deep stromal scarring or history of corneal hydrops. Numerous modifications have been developed to the technique, amongst which we have the transepithelial crosslinking and accelerated cross-linking (Figure 6) for the optimized effect on experimental models[39-41].

EXCIMER LASER

Until a few years ago, the keratoconus or its fruste form was considered a total contraindication to keratorefractive surgery with excimer laser. Recently, these techniques have been utilized in the treatment of patients with fruste keratoconus or its mild forms with satisfactory visual results. Currently, there have been results of photorefractive keratectomy with and without being combined with crosslinking as an adjunctive treatment in the management of ametropia secondary to keratoconus.

The advantage of this technique is that it does not need the creation of an epitelial/stromal flap; this way, performing the ablation immediate to the ocular surface, the structural loss associated to LASIK is prevented, which has proven to be a factor related to ectasia progression in keratoconus. This technique is ideal for the treatment of small ametropias, such that it is not recommended for large ablations (ideally, less than 50 microns) given the possibility of postoperative haze. It is important to be cautious considering that there are reports of ectasia even when employing this technique[42]. In regards to this technique, Bilgihan *et al*[43] and Bahar *et al*[44] have reported an improvement UDVA in fruste keratoconus patients treated with PRK. During the follow up period they don't report keratoconus progression. Based on these results, the authors conclude that photorefractive keratectomy seems to be a safe strategy on eyes suspected of having frank keratoconus. Recently, Guedj *et al*[45] have reported follow up of keratoconus suspects treated with PRK, where they demonstrate lack of ectasia progression in any of their 62 eyes at 5 year follow up, considering an average refractive sphere error of -3.48 ± 3.14 D and cylinder -0.97 ± 0.92 D.

The combination of PRK with crosslinking has been a most utilized strategy and, in these cases, the criteria for its application has to do with the residual stromal bed posterior to ablation, which ideally should be greater than 400 microns. The techniques that combine these proce-

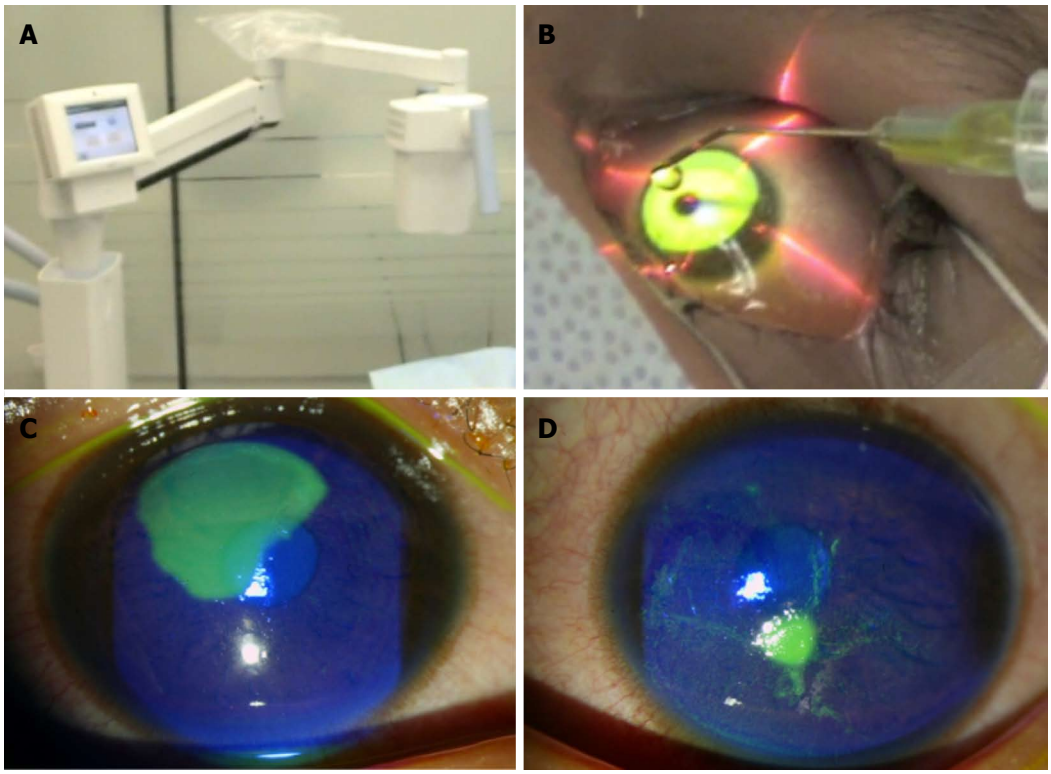

Figure 6 Collagen cross-linking. A, B: Accelerated corneal collagen cross-linking (A) equipment (B) and riboflavin instillation, collagen cross-linking (CXL) treatment could be decreased to 3 min with Ultraviolet-light intensity of 30 mW/cm^2 achieving the same energy on cornea of conventional CXL of 5 J/cm^2; C: Right eye three days after accelerated cross-linking showing corneal epithelium recovery; D: Left eye also after three days following accelerated CXL.

dures can be sequential or be applied in the same surgical time and, in the majority of the reports, the combination of these techniques are associated with a significant improvement in respect to UDVA, improvement in keratometries and ceasement of keratoconus progression[46-48].

However, laser treatment experiences in keratoconus must be taken with caution because of the few reports and short term follow-up reported until now in the literature. Our knowledge about the progression in this kind of cases is still poor and the risk-benefit ratio in low ametropia treatment must be taken in consideration.

INTRASTROMAL RING SEGMENTS

Intrastromal segments are manufactured of polymethyl methacrylate (PMMA) and were initially utilized for the treatment of myopia and astigmatism[5] (Figure 7). Recent studies have reported the effective use in the treatment of keratoconus and currently its stabilizing effect on ectasia is still controversial[49-51]. There are 5 models available, each with variations in their curvature radius, thickness and arc longitude, according to the effect to be achieved: (1) Ferrara rings (Mediphacos Inc, Belo Horizonte, Brazil); (2) Bisantis segments (Opticon 2000 SpA and Soleko SpA, Rome, Italy); (3) Intrastromal rings, Intacs (Addition Technology, Fremont, California, United States); (4) Myoring (Dioptex, GmbH, Austria); and (5) Cornealring (Visiontech Medical Optics, Belo Horizonte, Brazil). This technology is ideal for use in patients with central corneal thickness over 400 microns and clear central cornea[49]. For their placement it is important to consider the algorithm designed for each one of the manufacturing companies to obtain the optimum effect given that such effect tends to be somewhat unpredictable[52]. In 1991, the first intrastromal segment implant on human eyes was done[53] and, through time, numerous studies have been published about the refractive results of this technology[49-56]. The majority of the authors concur that the refractive result that is obtained with the rings is better in patients with keratoconus of Ⅰ and Ⅱ Amsler Krumeich degree and refraction with a low spherical equivalent in which myopia in less than the astigmatism; additionally, the refractive effect tends to remain in time but not the case of the corneal curvature effect, which tends to present regression[50].

Alió *et al*[56] has described that in keratometries > 53 D an optimal visual effect was not observed. In the treatment of fruste keratoconus, with spherical equivalent of -4.5 D, Güell *et al*[57] report at 4 year follow up, UDVA and CDVA improvement with 82.05% of eyes within a ± 1 D refraction in range of emmetropia without showing progression of keratoconus during the follow up period.

The channels for the insertion of the segments can be created mechanically or with a femtosecond laser. The most common complications associated with the mechanical dissection are: epithelial defects on the insertion site, anterior and posterior perforations, inadequate depth placement of the ring, extrusion, infectious keratitis, stro-

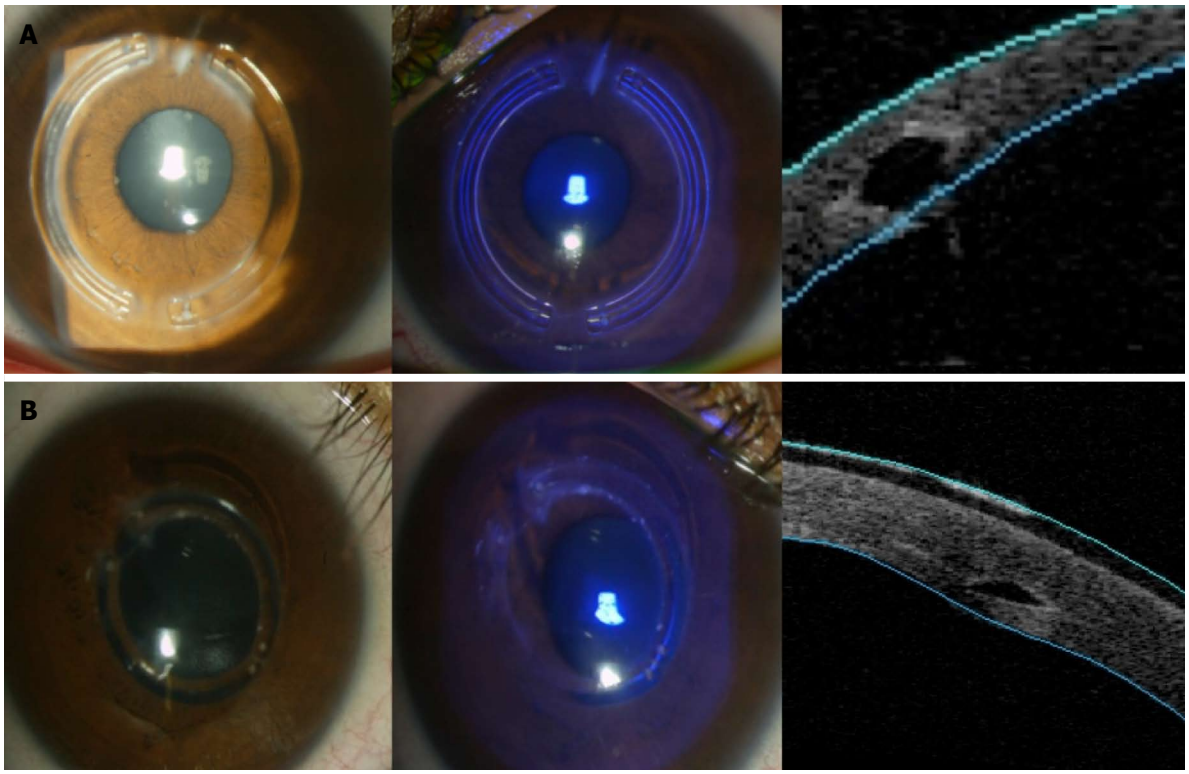

Figure 7 Different intrastromal ring segments models (A) clinical and optical coherence tomography showing hexagonal shape and (B) another design with triangular shape.

mal thinning, stromal edema, intraepithelial growth in the tunnel, corneal melting and tunnel vascularization[58-61]. The use of the femtosecond laser reduces the risk of complications in the creation of the tunnels, however it has been reported that the main complication with this technique is the incomplete formation of the tunnel (up to 2.7% of the cases), among those cited previously for the manual technique[62]. Recently, the combined technique of intrastromal segments and crosslinking has been used sequentially with the purpose of attaining stability in cases of progressive keratoconus, nevertheless, no long term favorable results have been reported for this trend[63,64].

KERATOPLASTY

The first keratoplasty reports in history were in 1840 by Franz Mühlbauer, who described a technique of triangular grafts to perform the first anterior lamellar keratoplasty. However, these early efforts to perform corneal grafts were not successful. The penetrating transplant was considered the treatment of choice for keratoconus for many decades; nevertheless, one of the principal disadvantages has to do with the risk of immunological rejection which can occur in up to 20% of the patients with good prognosis, such as the case of keratoconus[65]. This technique continues to be the treatment of choice when there are endothelial scars (secondary scars to hydrops) or low receptor endothelial cell count.

The current tendency in keratoplasty is to preserve the receptor's endothelium with the objective of avoiding the risk of endothelial rejection, which is normally a conditional for graft failure[66]. The advantages of the lamellar techniques over the penetrating keratoplasty are that these techniques have lower recuperative time periods, earlier management of astigmatism and sutures and lower incidence of post-operative glaucoma and graft rejection[67].

In recent years, multiple more advanced and reproducible surgical techniques have been developed to achieve this objective. Currently there are techniques based on manual and automated dissection of the donor and receptor graft (microkeratome, femtosecond laser and excimer laser) to obtain lamellar transplants at different depths depending on the treatment expected outcome[68-70].

The most frequently used techniques are the techniques of manual dissection, due to the little additional material required in terms of that used in a penetrating keratoplasty[66]; within this category we have Melles'[71] water and air dissection technique, the big-bubble dissection technique[72], divide and conquer technique and Anwar's[73] visco-dissection technique. Unfortunately, the great majority of these techniques require specially advanced surgical skills, given that the conversion rate to penetrating keratoplasty can be up to 40% in inexperienced hands and 2% to 6% in experienced surgeons[74].

Perhaps the most important limitations of the lamellar techniques continue to be the irregular borders of the corneal surface dissection that are obtained through manual technique, also the endothelial folds that are con-

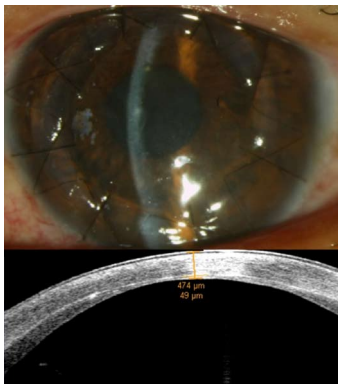

Figure 8 Femtosecond anterior lamellar keratoplasty, upper image showing the clinical photograph and lower image optical coherence tomography showing the residual stromal and endothelial tissue of around 50 microns.

ditioned by structural alterations of the receptor cornea in its posterior or more internal section (determined by the anterior and posterior curvature of the treated patient). Another of the limitations is the CDVA that patients reach that, although it's true that have lower post-surgical astigmatism than the PKP patients, CDVA, high order aberrations and contrast sensibility are similar to the penetrating technique[75].

One of the new trends is to use the femtosecond laser (Figure 8) to perform a tissular disruption at predetermined depths by the surgeon and this way can be more precise in the graft dissection to be placed as well as the receptor with the aim of achieving better visual results. However, the reported short term results have not been able to overcome the penetrating technique[76].

The deep anterior lamellar transplant assisted by pachymetry (PALK) was described by Carriazo *et al*[77] in 2007. The purpose of this technique is to perform a photoablation with an excimer laser guided by topography and pachymetry of 95% of the stromal surface in a way that more regular cuts can be made at specific diameters without observing adverse perforation effects of the Descemet membrane. The initial visual results are similar to the reported by other techniques of lamellar keratoplasty and not superior in visual quantity or quality to the penetrating keratoplasty; nevertheless, showing improvement in terms of recuperation periods, post-surgical astigmatism and the use of pharmaceuticals and the suture management in the post-operatory period. This same technique has recently been reported by Spadea *et al*[78], obtaining 20/40 CDVA at 2 years in 89% of the patients in that series.

CONCLUSION

Keratoconus continues to be one of the most frequent corneal pathologies worldwide, being one of the primary causes of corneal blindness. Its early detection is essential and each day there are more complex and improved resources/equipment for its detection. The historic evolution, in terms of treatments, has currently supplied us with many resources for its management, which can provide gratifying visual results for the patient and are ideal in terms of surgical techniques and lower complication rates. In order to be able to choose one of the treatments previously set out, it's important to consider the main outcome objectives for the desired treatment and the patient expectations regarding their visual rehabilitation. In the future, surely new treatment techniques will have scientific foundations in molecular mechanisms which can halt the initial onset of ectasia.

ACKNOWLEDGMENTS

The authors would like to thank Yvonne Machain for her skillful help with the translation and edition of this manuscript.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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