INTRODUCTION

Several surgical strategies have been proposed to improve visual function in patients with keratoconus who become contact lens intolerant\(^1,2\). In mild-to-

moderate keratoconus, when the central cornea remains clear, intrastromal corneal ring segments (ICRS), and phakic intraocular lenses (PIOLs) may provide enough BSCVA, and sometimes uncorrected visual acuity (UCVA), to postpone and sometimes avoid the need for corneal transplantation. To stop the progression of the disease, these refractive procedures may be combined with collagen cross-linking (CCL) in cases of progressive keratoconus, which may grant a more sustained result\(^3-6\).

ICRS improve quality of vision and visual acuity through a dual effect. Not only do they correct myopic spherical equivalent, but they also improve topographic abnormalities by centering the corneal optical zone\(^7-13\). However, their role on ectasia stabilization remains unclear.

Long-term follow-up is especially important in the case of keratoconus because if ectasia were to progress,
the refractive correction achieved with the ICRS would be at least partially lost. In this study, we present four-year follow-up data of Intacs™ (Addition Technology Inc., Sunnyvale, CA, USA) ICRS implanted in mild-to-moderate keratoconus with signs of topographic and refractive progression, without the use of CCL.

PATIENTS AND METHODS

This study included 46 eyes of 36 patients with Keratoconus stage I-II of Krumeich’s classification14 who where contact lens intolerant and showed topographic and refractive progression during the six months previous to Intacs™ surgery. Thirty-one (67.39%) eyes of 21 (58.33%) patients were seeking refractive surgery and keratoconus was diagnosed when preoperative topography was performed. Ten of these patients had bilateral implantation, whereas 11 had unilateral implantation, as the fellow eye was stable or did not require refractive correction. Fifteen (41.66%) eyes of 15 patients with known keratoconus had previously undergone penetrating (PKP) or deep anterior lamellar keratoplasty (DALK) in the fellow eye due to severe keratoconus, and had unilateral Intacs implantation. Eleven (23.9%) eyes were implanted Intacs™ with the aim to recenter and regularize corneal topography, so as to enable further refractive correction either with contact lenses or phakic intraocular lenses (PIOLs). All patients were fully informed about the details and possible risks of the specific procedure, together with alternative refractive techniques and their respective benefits and risks. Written informed consent was obtained from all patients before surgery in accordance with the Declaration of Helsinki, and the study was approved by the ethics committee of our institution, Instituto de Microcirugia ocular, and the Universitat Autonoma de Barcelona. All the eyes were operated by the same surgeon (JLG).

Preoperative examination and follow-up

The patients underwent a complete preoperative ophthalmologic examination, including manifest refraction, Snellen’s best-spectacle corrected visual acuity (BSCVA), uncorrected visual acuity (UCVA), applanation tonometry, corneal topography (Orbscan, Bausch and Lomb, Rochester, NY, USA), ultrasound pachymetry (DGH 500 Pachymeter, DGH Technology, Inc, Exton, PA, USA), and a fundus examination.

Postoperative follow-up visits were held at 24 hours, 3 and 6 months, and at yearly intervals up to four years. The long-term study results evaluated were UCVA, BSCVA, predictability and stability of refractive correction, efficacy (ratio between the mean postoperative UCVA and the mean preoperative UCVA) and safety index (ratio between the mean postoperative BSCVA and the mean preoperative BSCVA). Complications were also recorded.

Inclusion and exclusion criteria

Inclusion criteria were: contact lens intolerant patients with mild-to-moderate Kc (Krumeich’s stage I or II)14 with topographic and/or refractive signs of progression for the previous 6 months; central pachometry >400 µm; clear central cornea; minimum follow-up of 4 years. Spherical equivalent (SE) was not a limitation.

Exclusion criteria were: eyelid abnormalities, untreated lid margin disease, or tear film abnormalities; history of herpetic eye disease; presence of central or paracentral corneal leucoma; intraocular pressure >21 mmHg or glaucoma; preexisting macular pathology or abnormal retinal condition; systemic diseases (e.g., autoimmune disorder, connective tissue disease, atopia, diabetes mellitus, or Stevens-Johnson Syndrome); central corneal thickness of less than 400 µm; scotopic pupil diameter greater than 7 mm.

Surgical Procedure

The nomogram for Intacs™ inserts selection is depicted in table 1. The thickness of the ICRS to be implanted was selected on the basis of preoperative SE. In those cases with higher degrees of myopic SE, the thickest segments (450 µm) were used. If the cone was not central, corneal pachometry at the site of incision and segment implantation was checked preoperatively.

Surgical technique has been extensively described. In the eyes with inferior or central cone, we place the incision at 90°. The segments are placed nasally and temporally, and pushed until the inferior extremes contact with each other, as if they were embracing the cone, in an attempt to push up the cone. With this approach, the two segments act as if they were a whole inferior segment of 280°. In the eyes with oblique corneal astigmatism, two inserts of different thickness were implanted through an incision placed at the flattest meridian. The thickest segment was placed inferiorly, in the steepest axis. In those cases where the SE was lower than −0.5 D, a single inferior segment was implanted.

<table>
<thead>
<tr>
<th>Intacs thickness (mm)</th>
<th>Spherical Equivalent (D)</th>
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<tbody>
<tr>
<td>0.21</td>
<td>−0.75 to −0.975</td>
</tr>
<tr>
<td>0.25</td>
<td>−1.00 to −1.625</td>
</tr>
<tr>
<td>0.30</td>
<td>−1.75 to −2.25</td>
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<tr>
<td>0.35</td>
<td>−2.315 to −3.00</td>
</tr>
<tr>
<td>0.40</td>
<td>−3.125 to −3.75</td>
</tr>
<tr>
<td>0.45</td>
<td>−3.875 to −4.50</td>
</tr>
</tbody>
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mm: millimeters; D: Diopeters.
**Statistical analysis**

Microsoft Excel (Redmond, WA, USA) was used for compilation of data and to perform descriptive statistics. All variables were analyzed preoperatively, and postoperatively, at 3 and 6 months, and at yearly intervals up to 4 years.

Continuous variables were described with mean, standard deviation (SD) and range (maximum and minimum value). Comparison of pre and postoperative data was performed with the paired two-tailed t test. The threshold of statistical significance was defined as $p \leq 0.05$. The percent of eyes with BSCVA and UCVA $\geq 20/25$ and $\geq 20/40$ at each milestone of follow-up were also recorded. Efficacy and safety indexes were calculated for each postoperative interval.

**RESULTS**

A total of 46 eyes of 36 patients that met the inclusion criteria were implanted the Intacs™ inserts. All eyes were available for examination at the 4-year follow-up visit. Mean age was 28.45±7.7 (range 16 to 53 years of age). Two symmetrical inserts were implanted through an incision centered at 90° in 19 (41.3%) eyes (Figure 1) with the inferior extremes in contact with each other, two inserts of different thickness were implanted through an incision placed at the flattest meridian in 23 (50%) eyes, and a single inferior segment was implanted in 2 (4.34%) eyes. Intacs thicknesses were as follows: 210 microns (n=2), 250 microns (n=5), 300 microns (n=5), 350 microns (n=5), 400 microns (n=8) and 450 microns (n=21).

**Refractive outcome stability and keratometry**

Mean preoperative spherical equivalent (SE) was -3.50±2.84 (range, +1.00 to −15.00 D), and mean preoperative cylinder was −2.68±1.7 (range, 0 to −7 D). Four years postoperatively, mean SE and cylinder were −0.5±1.48 (range, −1.5 to −6) and −2.9±1.7 (range, −1.5 to −6), respectively. At 4 years, mean keratometry had decreased from 46.14±3.42 to 44.35±3.66.

Figure 2 shows spherical equivalent and cylinder at each milestone of follow-up up to 4 years for all groups, and figure 3 shows evolution of spherical equivalent for each group separately. SE was significantly reduced compared to preoperative values (paired t test; $p<0.05$), and there were no significant changes in SE throughout the follow-up period (paired t Test; $p>0.05$), which shows excellent stability of the SE refractive correction during the first 4 years of follow-up. Intacs implantation had no significant effect on refractive cylinder when compared to preoperative values, and there were no significant changes throughout the follow-up period (paired t test; $p>0.05$). Table 2 summarizes refractive and visual results for each thickness of Intacs segments.

**Visual Acuity, Efficacy and Safety**

Figure 4 shows mean UCVA and BSCVA at each milestone of follow-up. Preoperatively, 32 (69.56%) and 8 (17.39%) of the eyes presented BSCVA $\geq 20/40$ and BSCVA $\geq 20/20$, respectively. UCVA was $<20/40$ in all (100%) of the eyes. A progressive improvement of UCVA throughout the follow-up period was noticed, being most remarkable during the first 6 months. Four years postoperatively, 30 (65.21%) eyes presented...
UCVA ≥ 20/40, and none of the eyes presented UCVA ≥ 20/20. BSCVA was ≥ 20/40 in 38 (82.6%) eyes, and ≥ 20/20 in 6 (13.04%) eyes.

UCVA significantly improved in 43 (93.4%) of eyes, and worsened in 3 (6.6%) of eyes. BSCVA improved in 7 (15.21%) eyes, remained unchanged in 31 (67.31%) eyes, and worsened in 8 (17.39%) eyes (Figure 5). BSCVA did not significantly change throughout the follow-up period (t test; p > 0.05). At 4 years, overall efficacy and safety indexes were 0.8 and 1.1, respectively.

Adjustability of the refractive result

Intacs™ inserts of 400 microns were exchanged for thicker segments of 450 microns in one (2.1%) eye due to unexpected undercorrection. Exchange surgery was uneventful. In 11 (23.9%) cases, Intacs™ implantation was performed even though preoperative SE was greater than −4.5 D, with the aim to recenter the corneal optical zone and regularize corneal topography. One patient was successfully readapted to soft contact lens use, one eye of another patient underwent PRK over Intacs, and both eyes of another patient underwent toric phakic iris-claw Artisan (Ophtec B.V., Groningen, The Netherlands) intraocular lens (IOL) implantation to correct the remaining refractive error.

Complications

No intraoperative complications occurred. Two eyes (4.3%) required repositioning of a segment that had been implanted too deeply in the corneal stroma. Four months after Intacs implantation, one patient had lost 6 lines of BSCVA, even though no clinical complication was observed. Intacs were explanted and penetrating keratoplasty was performed uneventfully. A hyperopic shift occurred in the patient that underwent PRK over Intacs due to severe epithelial hyperplasia in the mid-periphery of the cornea, that acted as a negative lens. Finally, one eye presented with aseptic infiltration.
of the intrastromal channel one month after surgery that required the extraction of one of the inserts. This infiltration was probably related to underlying rosacea that was diagnosed postoperatively (Figure 7).

DISCUSSION

It is well known that BSCVA with spectacles is often unsatisfactory in patients with KC, specially when anisometropia and high astigmatism is present. Although RGPCL may provide better BSCVA even if significant irregular astigmatism is present, 27% of chronic CL users become intolerant. In such circumstances, surgical intervention is required to achieve optimal visual rehabilitation.

The indications for Intacs inserts in keratoconic eyes are contact lens intolerant patients, with clear cornea and central pachymetry greater than 400 microns. In the case of peripheral conus or pellucid marginal degeneration, where the greatest thinning occurs in the periphery of the cornea, pachymetry in the site of Intacs implantation should be checked preoperatively to avoid perforation into the anterior chamber or immediate or late extrusion of the segments. At least 100 microns of posterior stroma under the ring should be left.

Data on long-term follow-up of Intacs implantation in keratoconus is scarce. There is only one report that included 17 keratoconic eyes that were followed for 5 years after Intacs implantation. Being keratoconus a primary ectasia that may progress, long-term follow-up data is essential to establish if Intacs' effect remains stable over time. Unfortunately, not only there is a wide variety of evolutive patterns, but also a large number of eyes do not show any signs of evolution even though no surgical procedure is performed. These factors limit the evaluation of the effect of Intacs implantation itself.

This case series included 46 eyes with mild-to-moderate keratoconus that had shown topographic and/or refractive signs of progression before Intacs implantation. If the ectasia had progressed, refraction, keratometry and visual acuity would have changed over time. In our group of patients, both refraction and keratometry have remained stable over the 4 years of follow-up. The question remains if their refraction would have remained stable without surgery anyway.

The lack of a control group is a clear limitation of this study. Therefore, the role of ICRS in stopping the progression of keratoconus remains controversial.

Some authors have proposed UV-A irradiation-induced corneal collagen cross-linking (CCL) as a first step to stop the progression of keratoconus, and then correct the remaining refractive errors with a different approach, excimer laser corneal surgery or phakic IOL implantation. CCL performed after Intacs implantation in keratoconic eyes has provided better results and has a more logical rationale than Intacs insertion alone as evidenced by greater reductions in manifest cylinder and keratometry readings. A simple additive effect of both procedures in flattening the central cornea and a greater local rigidity across the Intacs segment may account for this synergistic effect. Kamburoglu et al. performed CCL one day and 1 month after Intacs implantation in both eyes of a patient that exhibited secondary ectasia after LASIK. However, taking into account that the refractive effect after ICRS implantation may take several weeks or months, leaving some time before CCL is performed after Intacs implantation may be a better strategy than performing CCL immediately after Intacs surgery. From our point of view, CCL is ideally indicated as soon as any sign of progression is detected or when the corneal shape improvement stops.

Coskunseven et al. compared the effect of CCL followed by ICRS implantation and ICRS implantation followed by CCL and found that implantation of ICRS followed by CCL resulted in greater improvement in CDVA, SE, and mean K in a group of patients with keratoconus. Mean interval between procedures was 7 months in both groups.

Similar to previous studies in both myopia correction and keratoconus, both spherical equivalent and UCVA improve progressively during the first 6 months and then have a steady evolution, as long as the corneal ectasia remains stable. On the other hand, Intacs implantation in keratoconic eyes may provide unexpected refractive cylinder and visual results. In some cases, the topography recentering with improvement of the I-S ratio and irregular astigmatism is not accompanied with an improvement in UCVA and/or BSCVA. In others, UCVA and BSCVA significantly improve even though the refractive cylinder error...
remains almost unchanged due to the regularization of the topography. The reason of these unexpected results remains unknown. Ultrastructural variability of the corneal stroma of different patients with keratoconus or different genetic basis may be some reasons for this phenotypic variability after Intacs implantation, even though the topography or refraction may be similar.

Generally, a trend towards undercorrection is recommended, as the same Intacs thickness has a greater effect in thinner corneas. Nevertheless, being an adjustable and reversible technique, Intacs may be removed or exchanged for a thicker or thinner one in case the refractive result obtained is not the desired. Moreover, in case penetrating or deep anterior lamellar keratoplasty is needed, trephination of the recipient cornea may be performed uneventfully and the mid-peripheral cut in presence of the segments may be more homogeneous and perpendicular to the corneal surface.

In our study, we observed that thicker segments showed better refractive and visual results than the thinner ones. Although the small number of patients in each group did not allow reliable comparisons, thicker segments may induce a higher change in the distribution of the corneal tissue than thinner segments, which may account for this better result.

Intacs inserts only correct a limited range of myopia, and high refractive errors commonly seen in patients with keratoconus may remain. Intacs implantation is first performed to recenter the topography and decrease irregular astigmatism and, then, residual refractive errors may be corrected with spectacles or soft contact lenses. Also, TPIOLs have been implanted after ICRS, as we did in one of the patients of this series, and some other later on.

Several nomograms have been proposed for Intacs implantation in keratoconic eyes: same-thickness inferior and superior segments, a single inferior segment, thicker inferior and a thinner superior segments, etc. However, there is lack of scientific evidence in terms of prospective, comparative, randomized studies that demonstrate the superiority of one approach over the other. Sharma et al. compared the effect of implanting a single inferior segment vs two segments in peripheral cones, obtaining better visual and keratometric results when a single inferior segment was inserted. According to this author, single segments induced localized flattening inferiorly and steepening in the upper cornea, which leads to a greater decrease in I-S ratio. Our preferred approach has been to place the segments through an incision in the flattest meridian, pushing them until the inferior extremes contact with each other, as if they were embracing the cone. With this approach, the inserts act as an only inferior segment of 280°, and the inferior cone is «elevated», with similar effects in decreasing I-S ratio and recentering the topography.

Ocular infection is a serious complication of refractive surgery and may lead to a significant reduction in visual acuity. The incidence of infectious keratitis after Intacs implantation is low (0.2% and 0.63%). Apart from those microorganisms frequently found in ocular infections such as gram positive aerobic bacteria (e.g. Staphylococcus epidermidis), anaerobic bacteria have also been reported as a cause of infectious keratitis after Intacs implantation. The anaerobic conditions in the intrastromal channel may predispose to the development of the anaerobic infection. Although infections usually appear within 3 weeks after surgery, late bacterial keratitis has also been reported. In some cases topical antibiotics alone are ineffective and channel irrigation with antibiotics and Intacs extraction are required.

Aseptic inflammatory reaction inside the intrastromal channel has also been described after Intacs implantation, especially in patients with atopia or keratoconus. One of our patients presented with aseptic infiltration of the nasal intrastromal channel on the right eye one month after surgery that required the extraction of one of the inserts. This infiltration was probably related to underlying rosacea that was diagnosed postoperatively. Differential diagnosis with an infectious ethiology is not always straightforward. In fact, we first suspected infectious keratitis, and irrigation of the channel with balanced salt solution for the collection of microbiological samples followed by irrigation with cefazidime was performed at the onset of symptoms. Microbiological workup did not show any microorganism and the patient only improved after the nasal segment was taken out and topical steroids were started. Rau et al reported a prevalence of corneal infiltrates of 13.3%. Immediate treatment of such infiltrates is mandatory to prevent irreversible adverse effects on visual acuity.

In conclusion, this study shows that Intacs implantation in mild to moderate keratoconus provides stable refractive and topographic results, and improves UCVA and BSCVA in the majority of patients. However, our knowledge on how and when Intacs segments will be effective in keratoconic eyes is still limited. A longer follow-up and prospective, comparative, randomized clinical trials are still needed to establish their role in the stabilization of the ectasia.

REFERENCES
