Hydrogel Intracorneal Inlays for the Correction of Hyperopia

Outcomes and Complications after 5 Years of Follow-up

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Purpose: To evaluate safety and efficacy of an intracorneal inlay for the correction of hyperopia.

Design: A prospective, nonrandomized, noncomparative, 2-center study.

Participants: Thirty-four hyperopic eyes were implanted with a hydrogel intracorneal inlay (Permavision, Anamed, Lake Forest, CA). Preoperative hyperopia was +3.9 diopter (D; range, +2 to +7). Uncorrected visual acuity (UCVA) was the logarithm of the minimum angle of resolution (logMAR; the decimal logarithm of decimal visual acuity with a minus sign) 0.6 ± logMAR 1, and best-corrected visual acuity (BCVA) was logMAR 0.1 ± 0.7.

Methods: Corneal flaps were created with a mechanical microkeratome (M2 [Moria, Anthony, France] or Amadeus [Advanced Medical Optics Inc, Santa Ana, CA]; 180 μm), followed by inlay implantation onto the stromal bed over the pupillary center and covered by the corneal flap. Follow-up was 5 years.

Main Outcome Measures: We measured UCVA and BCVA; patients underwent, slit-lamp examination, pachymetry, and confocal microscopy. The follow-up was up to 6 years.

Results: The UCVA improved during 3 months and was stable for up to 2 years. There was a loss of ≥2 lines of spectacle-corrected visual acuity in 35% of eyes at 2 years, and a loss of ≥2 lines in 55.5% of the eyes at 5 years. Refractive predictability was poor, with 60% of the eyes having ±3.00 D of emmetropia. A decentration of the inlay occurred in 29.4%, progressive perilenticular deposits were observed in 88.2%, haze was seen in 73.5%, and the inlay was explanted in 58.8%, with a cumulative survival rate of 58.4%.

Conclusions: An intracorneal inlay may be an option to treat hyperopia, but the tested inlay caused significant visual loss and scarring and had to be explanted in the majority of cases.

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Some of the most common corneal refractive procedures used for the correction of hyperopia are LASIK, photorefractive keratectomy, and conductive keratoplasty.[1,2] Refractive errors can be corrected by placing preformed tissue either biological (epikeratophakia) or synthetic material (synthetic keratophakia) onto or into the cornea. This modifies the optical power of the cornea by changing the shape of the anterior corneal surface or by creating a lens with a higher index of refraction of the corneal stroma. The method is additive refractive keratoplasty.

Tissue addition procedures, such as epikeratoplasty, have fallen out of favor because of the difficulty of obtaining donor tissue as well as the poor predictability of the refractive and visual results.[3–6] Synthetic inlays offer several potential advantages, such as the ability to be mass produced in a wide range of sizes and powers that can be measured and verified. Also, synthetic material may have optical properties superior to tissue lenses, which are difficult to accurately lathe. Unlike synthetic material, tissue lenticules can become distorted upon insertion and may undergo remodelling, which can prolong postoperative visual recovery and can lead to refractive instability. If necessary, the implant may be removed, and other treatment may still be available to the patient.[2,4,6,7]

Synthetic stromal inlays or intracorneal inlay implants have been investigated for nearly half a century. Barraquer[8] was the first, in 1949, followed by many researchers who used an implantable inlay to modify the refraction of the cornea.[9–15] They used flint glass and acrylics in their studies. Because of problems with reepithelialization, synthetic material generally has to be placed in the corneal stroma. The materials used in the first implants caused anterior stromal necrosis because they were impermeable to water and nutrients, followed by extrusion in the eyes implanted with this inlay.[16,17] The limitations of this impermeable membrane revealed in previous studies could be avoided by the use of more permeable materials such as hydrogel. The permeability of hydrogel material is similar to that of the corneal stroma, allowing the exchange of water and nutrients between the posterior and anterior layers of the cornea, maintaining normal physiologic characteristics.[16,17] The first hydrogel to be evaluated for refractive

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keratoplasty was hydroxyethyl methacrylate, by Dohlman et al[18] in 1967 and later on by other researchers in the area of refractive keratoplasty.[12,15,19] They reported excellent tolerance of hydrogel lenses in the corneas of rabbits[10,20] and humans,[9,13,21] and no signs of keratocytic activity or intrastromal fibrosis, or inflammation, ulceration, or neovascularization were found.[21,22]

We have used 1 type of synthetic hydrogel inlay for the correction of hyperopia in a consecutive series of cases. In this report, we report the outcomes at 5 years of the collaborative study in terms of refractive and visual results and complications during this period. To the best of our knowledge, this is the largest series of the intrastromal implants reported with the longest follow-up in ophthalmic literature.

Materials and Methods

This prospective, nonrandomized, noncomparative, 2-center study was performed at 2 investigational sites following the same protocol. Approval from the Ethical Board Committee was obtained at each site, and all patients read and signed an informed consent document explaining the operative procedure and possible risks in accordance with the Declaration of Helsinki.

Inclusion criteria were hyperopia of +1 to +6 diopters (D; spherical equivalent) with <1 D of cylinder, and central K-readings between 41 and 46 D. We selected patients without severe ocular diseases (corneal, retinal, or inflammatory diseases) that could compromise the results. We implanted 34 eyes of 21 patients with a mean age of 46 years (range, 24–61) and a mean hyperopia of 3.9 D (range, +2 to +7). All patients had <1 D of keratometric astigmatism. Uncorrected visual acuity (UCVA) was the logarithm of the minimum angle of resolution (logMAR; the decimal logarithm of decimal visual acuity with a minus sign) 0.6 ± logMAR 1 (range, logMAR 0.0 to 1), and the best-corrected visual acuity (BCVA) was logMAR 0.1 ± 0.7 (range, logMAR −0.2 to 0.3). Preoperative slit-lamp examinations of the anterior segment and binocular ophthalmoscopy were normal. The preoperative examinations also included corneal pachymetry using ultrasonic pachymetry (DGH-500, DGH Technology, Inc., Exton, PA), and confocal microscopy (ASL model 500; Advanced Scanning, New Orleans, LA). Inlays were implanted in 12 eyes in Alicante, Spain, and 22 eyes in Mannheim, Germany. The follow-up period was 5 years, unless complications forced us to explant the inlay earlier.

Inlay Characteristics

The PermaVision intracorneal lens (Permavision, Anamed Inc., Lake Forest, CA) is composed of hydrogel material called Nutrapore (Anamed Inc.) with a refractive index of 1.39. The water content is 78%. It is soft, flexible, autoclavable, nontoxic, and biocompatible.[13] The material is permeable to water, glucose, and oxygen to meet corneal nutrition needs when implanted. The thickness in the center is between 48 and 92 μm, diopter dependent, and the edge of the inlay 5 to 9 μm, with a base curve of 7.35 mm. The diameter ranged from 4.75 (refractive power > 6 D) to 5.25 mm for 2 to 6 D. The inlay was available from +2 to +8 D in +0.5-D increments.

Operative Technique

A corneal flap was created either with the M2 microkeratome (Moria, Antony, France),[23] or the Amadeus microkeratome (Advanced Medical Optics Inc., Santa Ana, CA), followed by inlay implantation onto the stromal bed over the pupillary center, and covered by the corneal flap. We created a 180-μm corneal flap with a diameter of 8.5 mm or an 8.5-mm inferior hinged corneal flap.[23] During the procedure, corneal pachymetry was used to measure the cornea and residual stromal bed by using an ultrasonic pachymeter (DGH-500). Immediately after the microkeratome cut was performed, the stromal bed was carefully dried using a sponge, and the inlay was placed over the pupil by means of a specific manual vacuum device as recommended by the manufacturers. The hinged corneal flap was replaced onto the bed without sutures. The gutter around the edge of the flap was dried with a sponge, and the flap was allowed to settle for 2 minutes. At the end of the procedure, we administered 0.3% ofloxacin 4 times per day for 1 week and combined tobramycin and 0.1% dexamethasone 4 times a day for 1 week. The follow-up visits were preoperative; at 1 and 15 days; at 1, 3, and 6 months; and at 1, 2, 3, and 5 years postoperative (i.e., only one preoperative visit, the rest are postoperative follow-up visits).

Statistical Analysis

The SPSS statistics Software package 1 for Windows (version 10, SPSS, Inc., Chicago, IL) was used for statistical analysis. Normality of all data samples was first checked by the Kolmogorov-Smirnov test. The Student *t*-test for paired data was used for comparison between preoperative and postoperative data when parametric analysis could be applied. In all cases, differences were considered statistically significant when $P<0.05$.

Safety

Safety was measured as the number and percentage of eyes losing ≥2 lines of BCVA.

Efficacy

We defined efficacy as the percentage of eyes with UCVA of 20/20 and 20/40.

Results

We implanted 34 eyes of 21 patients. Inlay explantation was necessary in 20 eyes (59%) up to 6.1 years postoperatively (Table 1). Of these eyes, 13 (38.2%) inlays were explanted before 2 years. Before 5 years another 6 inlays were explanted (17.6 %) and another inlay was explanted at 6.1 years (2.9%). The UCVA improved significantly during 3 months and was stable until 2 years. The UCVA at 2 years of the patients with the inlay still implanted was logMAR 0.2 ± 0.6, and the BCVA was logMAR 0.0 ± 0.5. The UCVA was logMAR 0.0 or better in 8 eyes (23.5%) and logMAR 0.3 or better in 12 eyes (35.3%). The BCVA was logMAR 0.3 or better in 17 eyes (50%) and logMAR 0.0 or better in 5 eyes (14.7%). A total of 8 eyes (23.5%) lost ≥2 lines of BCVA. At the last follow-up, 14 eyes (41.2%) with inlays remained. Mean UCVA was logMAR 0.4 ± 0.5, and BCVA was logMAR 0.10 ± 0.4. The efficacy was <50%; the UCVA was logMAR 0.0 or better in 1 eye (2.9%) and logMAR 0.3 or better in 14 eyes (41.1%), and the BCVA was logMAR 0.0 or better in 8 eyes (23.5%) and logMAR 0.3 or better in 23 eyes (67.6%). A total of 19 eyes (55.5%) lost ≥2 lines of BCVA (Table 2; available online at http://aaojornal.org).

Complications

No cases of corneal vascularization or melting were seen. Inlay explantation was necessary in 58.8% of eyes because of undercor-

Table 1. Explantations and their Reasons

Patient	Study Center	Causes of Explant	Time of Explant
1	Alicante	EPO	1 mo
2	Alicante	EPO	1 mo
3	Alicante	EPO	1 mo
4	Alicante	EPO	1 mo
5	Alicante	EPO	1 mo
6	Alicante	Moderate haze, poor vision	2 mos
7	Mannheim	Halos, glare, poor vision at night	2 mos
8	Mannheim	Halos, glare, poor vision at night	4 mos
9	Mannheim	Halos, poor vision	9 mos
10	Mannheim	Halos, poor vision	9 mos
11	Mannheim	Moderate glare, halos, poor vision	1.8 year
12	Alicante	Haze, glare, poor vision	2 yrs
13	Alicante	Moderate glare	2 yrs
14	Mannheim	Cataract unrelated to implant	2.7 yrs
15	Mannheim	Astigmatism irregular	2.8 yrs
16	Mannheim	Halos, poor vision	3.7 yrs
17	Mannheim	Halos, poor vision	3.7 yrs
18	Mannheim	Regression, poor vision	5.2 yrs
19	Mannheim	Regression, poor vision	5.2 yrs
20	Mannheim	Halos, poor vision	6.1 yrs

EPO = epithelial perilenticular opacity.

rection, intracorneal deposits in the visual axis, irregular astigmatism, reduced vision, severe haze, implant decentration, or perilenticular opacity (Fig 1). The most common complication was the formation of intracorneal deposits or implant encapsulation. This progressive depositing of amorphous material and numerous highly reflective, irregularly shaped keratocyte nuclei was observed in 30 eyes (88%). Deposits started at the edge of the inlay and covered the implant. On slit-lamp examination, it looked like a thin capsule around the implant, with varying degrees of haze (Fig 2). We observed that the "deposits" adjacent to the inlay surface were progressive up to 3 years. These deposits seemed to reflect an encapsulation process, which caused visual loss owing to both loss in transparency and light scattering, causing glare. Moderate glare was reported in 9 eyes (26.5%) and severe glare in 15 eyes (44.1%).

Inlay decentration of >1 mm occurred in 10 eyes (29.3%). In 7 (21%), repositioning was required.

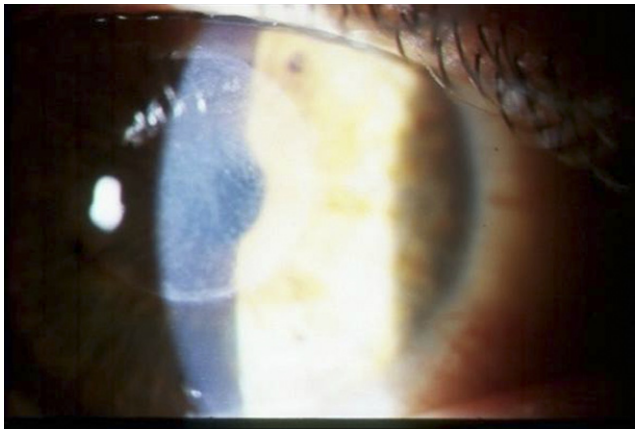

Figure 1. Epithelial perilenticular opacity (hypertensivey reaction type 4) at 1 week before explant.

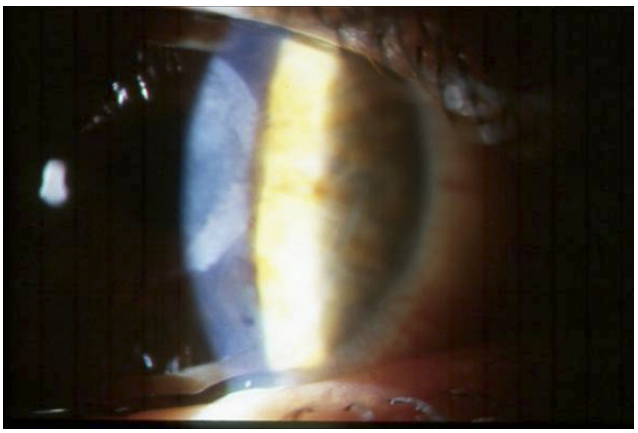

Figure 2. Deposits around the edge of inlay, at 2 years follow-up postimplant.

All 34 eyes were available for follow-up. Inlay explantation was necessary in 20 eyes (59%) up to 6.1 years postoperatively. Mean survival time was 37.46 months, with a cumulative survival of 58.4% with standard error of 2.82, and 95% confidence interval (52.9–64.0; Kaplan-Meier curve; Fig 3).

We explanted 7 inlays (20.5%) within the first 3 months. Reasons for explantation were epithelial perilenticular opacities which occurred in 5 eyes (14.4%). The opacity was evident after 1 week. The appearance was very similar to diffuse lamellar keratitis, leading to the initial diagnosis, but the corneal opacity was limited to the edges of the inlay. Otherwise the cornea was not affected by opacity (Fig 1). The symptoms were night glare, moderate photophobia, starburst, and blurry vision. All eyes were treated with antibiotics and steroids. Explantation of the inlay was performed after 1 month of follow-up. After explantation, topical steroids and antibiotics were continued. Corneal transparency improved in all the eyes, although some eyes still showed mild stromal peripheral opacity around the central cornea. The reasons for the other 2 explantations at 2 months were visual symptoms

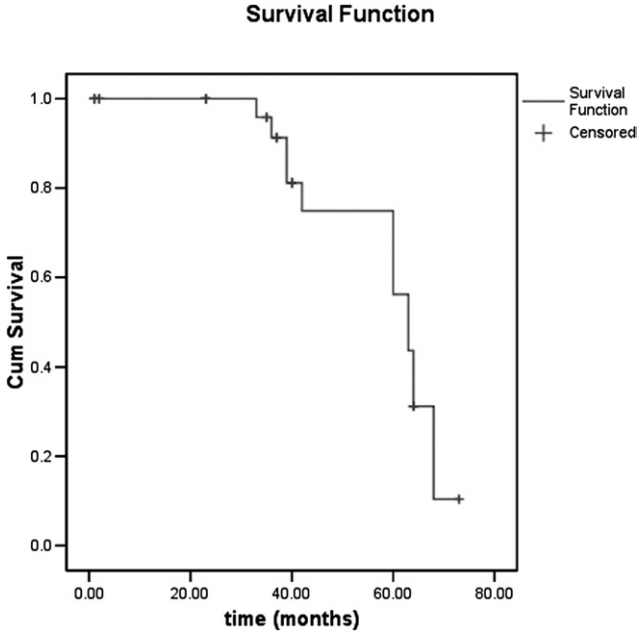

Figure 3. Kaplan-Meier survival curve.

such as halos and poor vision. Of the inlays with perilenticular opacity, 3 had inlay exchanges and another 2 cases of inlay exchange were not related to perilenticular opacity.

Within the first 12 months, another 4 inlays (11.7%) were explanted owing to visual symptoms such as halos, glare, and poor night vision. Finally, another 9 inlays (26.5%) were explanted between 18 months and 6.1 years postoperatively. The reasons for these late explantations were progressive opacity encapsulating the inlay with poor vision and glare caused by light scattering, and in 1 case cataract unrelated to the implant.

In the group in which the inlay was explanted, the UCVA pre-explant was logMAR 0.4 ± 0.8 and BCVA was logMAR 0.3± 0.6. After implant removal, the patients achieved a BCVA postexplant to logMAR 0.2 ± 0.7 (UCVA postexplant was logMAR 0.7 ± 0.8). The loss of BCVA was 2 lines of vision in 4 eyes (11.8%), 3 lines of vision in 6 eyes (17.6%), and ≥4 lines of vision in 9 eyes (26.5%). The majority of explanted eyes were corrected with hyperopic LASIK technique or hyperopic iris claw intraocular lens implantation. The confocal microscopy through focusing technique has been developed for measurement of corneal sublayer thickness and estimation of the intensity of postoperative haze with special attention to the reaction at the corneal flap interface.

The intended flap thickness in all eyes was 180 μm. However, confocal microscopy revealed that the flap interface was located 165±25 (range, 150–210 μm). Most of the eyes presented with microfolding of the Bowman layer. Interspersed particles of variable size and reflectivity were observed in the interface of all eyes. It was impossible to define the nature of the particles, except in the case of metallic particles. It cannot be excluded that they were salt crystals. A progressive depositing of amorphous material and numerous highly reflective, irregularly shaped keratocyte nuclei were observed. Deposits started at the edge of the inlay and covered the implant. This occurred in almost every patient. In some patients, it produced an encapsulation of the implant. We observed that the deposits adjacent to or in the lens surface were progressive up to 3 years. Deposits were usually seen along the anterior or posterior interface of the implant and the stroma. There was an increase of keratocyte density, and collagen fibrils were somewhat disrupted in the compressed area between stroma and inlay by the rapid change in curvature. The inlays that developed epithelial perilenticular opacity showed that the corneal epithelium and the stroma behind the basal membrane were normal. The keratocytes of the anterior stroma were activated and a zone of apoptotic keratocytes was found on the anterior inlay surface. Many epithelial and epithelioid cells were observed in the posterior inlay and around the edge. The posterior stroma and the endothelium were normal.

Discussion

The long-term tolerance of hydrogel intracorneal inlays has been reported previously in monkeys,[12,24–26] rabbits,[20,27] and humans.[9,13,21,23,28] The clinical experience has demonstrated the feasibility of using hydrogel intracorneal lenses to achieve good refractive predictability, stability, and biocompatibility in adult patients. There are different types of materials,[8,15,18,29,30] but hydrogels have been the most popular until now because they are more permeable to water and nutrients, with different pore sizes.[31] Despite the porosity of the material, we believe that the inlay used is too thick to allow a good passage of different nutrients,[31,32] or that passage is sufficient initially but decreases with time as those pores become obstructed by accumulating deposits.[23] This hypothesis is supported by the fact that the inlay tested is a convex lens with very thin external edges, but much thicker and with less permeability in the inlay center.[26,31] Previous experimental studies have demonstrated that hydrogel lenses need to be placed at a depth between 36% and 60% of the corneal thickness for success.[24,33] However, limitations to this procedure have also been demonstrated. Postoperative lens migrations, interface deposits, irregular astigmatism, and induction of corneal aberrations in significant levels[34] necessitated lens removal, repositioning, or replacement of the inlay.[35]

The method by which intracorneal inlays are implanted within the cornea consists of creating a corneal flap with an automated microkeratome[21,23,28] and, more recently, by femtosecond laser,[36,37] which allows a deeper placement. The irregular stromal bed affects the optical quality producing visual aberrations, and the percentage varies from 4.6%,[28] and 11.7% to 25.7% (percentage of cases of irregular astigmatism or irregular stromal bed).[13]

The UCVA improved significantly during the first 3 months and was generally stable from 3 months to 2 years. We observed a poor predictability, with 67.6% within ± 1.0 D of emmetropia only and a significant number of eyes losing ≥2 lines of BCVA (32% at 2 years and an increase to ≥3 lines of visual acuity loss in 52.9% at 5 years follow-up) owing to an increase of the deposits on the inlay surface. Others authors reported a higher predictability and unchanged BCVA at 12 months.[21] However, these good results were observed in a small group of patients only, and other authors reported a predictability similar to our results.[28]

Some complications were associated with technical difficulties or the development of inflammation in the early postoperative period.[37–41] Many eyes with early postoperative edema eventually formed deposits in the ensuing months. Excessive microkeratome suction during the surgery seemed to be a major contributor to early edema. Cholesterol crystals can be deposited because of degenerative changes occurring after corneal edema.[41,42] These crystals can accumulate as degenerating cells fail to metabolize

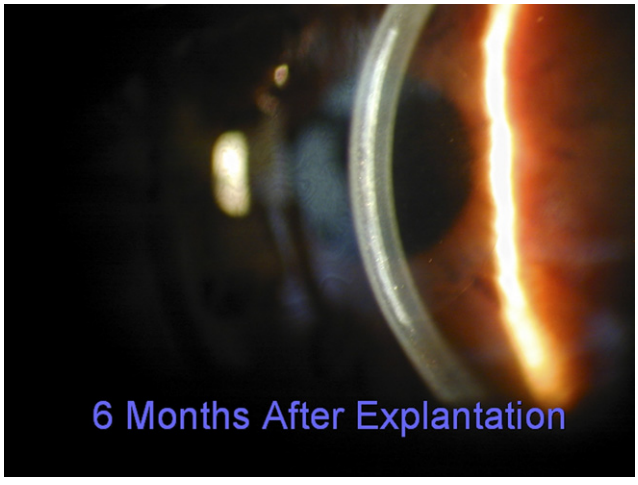

Figure 4. Deposits remaining 6 months after inlay explantation.

fats.[32,43] Small deposits along the intracorneal lens–stromal interface developed in 29%,[26] 37%,[13] and 88.2%, respectively, in our study. Deposits were usually seen along the anterior or posterior interface of the implant and stroma. Contrary to other investigators[21] who reported that the deposits were nonprogressive after 6 months, we observed that the deposits adjacent to or in the lens surface were progressive up to 4 years postoperatively. A thin fibrous layer encircled the inlay. This may have been collagen material deposited along the inlay–stromal interface. There was an increase of keratocyte density, and collagen fibrils were disrupted. This produced progressive visual acuity loss. Many corneal changes seemed to be reversible with inlay removal.

However, the deposits remained in the corneal interface >6 months after inlay explantation (Fig 4). In some eyes that had developed corneal deposits, 10 months after the inlay was removed, the deposits were barely detectable under the slit lamp.[26]

Another type of opacification was the epithelial perilenticular opacity, a hypersensitivity reaction type 4.[23,44] These cases had previously required flap lifting and inlay repositioning because of inlay decentration shortly after the first implantation. In no case was there evidence of epithelial ingrowth from the edge of the flap. A study of the corneal stroma using confocal microscopy showed that the corneal epithelium and the stroma behind the basal membrane were normal. The keratocytes of the anterior stroma were activated and a zone of apoptotic keratocytes was found on the anterior inlay surface.[36,45–47] We observed many epithelial and epithelioid cells in the posterior inlay and around the edge (Fig 5). The posterior stroma and endothelium were normal. Immunologic rejection depends on whether the host recognizes the implanted material as foreign and produces specific persistent antibodies, as in the case of intracorneal inlay. According to pathologic and confocal microscopy analyses, the implantation of epithelial cells and their further ingrowth on the inlay surface was the cause of the perilenticular opacity. The implantation of epithelial cells in the interface may occur during the microkeratome cut, through backflow during irrigation, carrying floating epithelial cells, and through migration under the flap.[48]

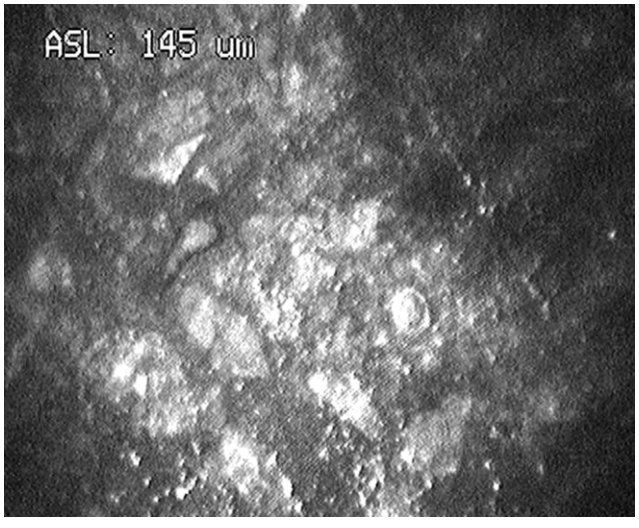

Figure 5. Epithelioid cells and activated keratocytes: confocal image.

One of the theoretical advantages of the inlay is that the refractive results are potentially reversible and adjustable by removing the lens or replacing it with another of different power.[14,37,42] However, if it was removed, the corneal changes such as deposits and haze were not reversible in many cases, remaining 6 months after inlay explantation (Fig 4).[26] In other cases, the results of hyperopic LASIK 6 months after inlay explantation confirm the hypothesis of reversibility.[7] Inlay survival decreased up to 20 months, with inlay explantation in 20 cases, the majority of cases because of poor vision (44.1%), and 14.7% because of epithelial perilenticular opacity.

Inlays offer an alternative to invasive surgery; nevertheless, we must consider the poor predictability and the long list of complications. With the materials currently available, and considering the results reported herein, we cannot recommend this procedure at this time.

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Table 2. Changes in Visual Acuity (Logarithm of the Minimum Angle of Resolution [logMAR])

	Preimplant		2 Years		Pre-explant		Time of	Postexplant		Last Follow-up	
Patient	*UCVA*	*BCVA*	*UCVA*	*BCVA*	*UCVA*	*BCVA*	Explant	*UCVA*	*BCVA*	*UCVA*	*BCVA*
1	0.7	0.8	0.0	0.8						0.5	0.2
2	0.5	−0.1	0.1	0.0						0.2	0.1
3	0.9	0.0	0.4	−0.1						0.5	0.0
4	0.6	−0.2	0.4	0.0						0.3	0.2
5	0.7	0.1	0.0	0.0						0.2	0.2
6	0.0	−0.1	0.3	0.1	0.8	0.7	3.7	0.5	0.5	0.5	
7	0.0	−0.1	0.3	0.1	0.5	0.4	3.7	0.3	0.1	0.3	0.1
8	0.9	−0.2	0.1	−0.1						0.7	0.1
9	0.9	−0.1	0.2	−0.1						0.7	0.1
10	0.3	0.0	0.0	0.0	0.3	0.4	5.2	1.0	0.2	1.0	0.2
11	0.1	0.0	0.0	0.0	0.2	0.2	5.2	0.7	0.3	0.7	0.3
12	1.0	0.0	0.1	0.0						0.1	0.0
13	0.3	−0.2	0.1	−0.1	0.4	0.2	2.8	0.2	0.2	0.1	−01
14	0.0	−0.2	−0.2	−0.2	0.5	0.2	2.7	0.2	0.2	0.7	0.2
15	0.0	−0.1	0.1	0.0						0.6	0.2
16	1.0	−0.1	−0.1	−0.2	0.2	0.1	1.8	0.2	0.2	−0.1	−0.2
17	0.8	−0.1	0.2	0.1	0.2	0.1	6.1	1.0	0.2	0.1	0.0
18	0.7	−0.2	0.1	0.0	0.3	0.0	0.4	1.0	0.0	0.0	0.0
19	0.0	−0.2			0.4	0.1	0.2	1.0	0.0	0.1	0.0
20	0.0	0.0			0.2	0.2	0.9	0.8	0.1	0.1	0.0
21	0.6	0.0			0.2	0.2	0.9	0.7	0.2	0.1	
22	0.8	0.0								0.5	0.1
23	1.0	0.0	0.1	0.0						0.2	0.1
24	1.0	0.0	0.1	0.0						0.2	0.1
25	1.0	0.0	0.5	0.4	0.5	0.4	2	1.0	0.0		
26	1.0	0.0	0.3	0.3	0.3	0.3	2	1.0	0.0		
27	1.0	0.7			FC	0.1	0.1	1.0	0.4		
28	0.5	0.2	05	0.1						1.0	0.7
29	1.0	0.1			0.4	0.4	0.1	0.8	0.0		
30	1.0	0.0			0.2	0.2	0.1	0.3	0.0		
31	1.0	0.1			0.7	0.3	0.2	0.3	0.2		
32	0.7	0.2	0.3	0.1						0.7	0.5
33	1.0	0.0			1.0	0.7	0.1	1.0	0.2		
34	1.0	0.0			1.0	1.0	0.1	1.0	0.2		

BCVA = best-corrected visual acuity; logMAR = the decimal logarithm of decimal visual acuity with a minus sign; UCVA = uncorrected visual acuity.