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Surgery Symposium 7

Phentolamine Ophthalmic Solution Rapidly Reverses Pharmacologically Induced Mydriasis in Two Pivotal Phase 3 MIRA Trials

- David Boyer, MD
- Ronil Patel, MS
- Mitchell Brigell, PhD
- Mina Sooch, MBA
- Eliot Lazar, MD
- Jay Pepose, MD, PhD
- Kavon Rahmani
- Drey Coleman, BS
- Amar Khatri, MS, MBA

Objective:
The MIRA-2 and MIRA-3 studies assessed the efficacy of 0.75% phentolamine ophthalmic solution (POS) to reverse pharmacologically induced mydriasis (RM).

Purpose:
During eye exams and specialty visits, pupils are pharmacologically dilated, impairing vision for 6-24 hours and resulting in the inability to focus, heightened sensitivity to light, etc. Phentolamine ophthalmic solution rapidly reverses pharmacologically dsinduced mydriasis by blocking the alpha-1 receptors only found on the iris dilator muscle.

Methods:
MIRA-2 and MIRA-3 were multi-center, randomized, placebo-controlled, double-masked clinical trials in healthy subjects (approximately n=553; age ≥12 years). Stratified by iris color, subjects were randomized to mydriatic agent 3:1:1 (2.5% phenylephrine, 1% tropicamide, or Paremyd, respectively) and treatment 1:1 in MIRA-2 and 2:1 in MIRA-3 (POS or placebo [vehicle], respectively). The primary efficacy endpoint was percent of subjects returning to ≤ 0.2 mm from baseline photopic pupil diameter (PD) at 90 minutes (min). Secondary efficacy endpoints, including time to return to baseline PD, visual acuity, time-savings and change from maximum dilation, were assessed at multiple timepoints.

Results:
Across MIRA-2 and MIRA-3, 338 subjects received POS (mean age 33 years, 60% female) and 215 subjects received placebo (mean age 33 years, 62% female). Across all mydriatics agents at 90 minutes, 49% and 58% of study eyes who received 2 drops of POS returned to ≤ 0.2 mm of baseline compared to of placebo-treated subjects ($p<0.0001$) in MIRA-2 (vs. 7% placebo) and MIRA-3 (vs. 6% placebo), respectively. Similar efficacy was also seen starting at 60 minutes and lasting up to 24 hours ($p<0.0001$) with 1 or 2 drops of treatment and across light and dark irides. Mean pupil diameter was significantly lower with POS at all time points starting at 60 minutes ($p<0.0001$). POS produced a time savings of 3 to 4 hours. The only AEs observed in >5% of subjects were mild, transient conjunctival hyperemia (39 [11.5%] POS treated subjects) and mild installation site discomfort. Across both trials, there were no serious AEs and no study withdrawals due to AEs. Additionally, POS did not compromise distance visual acuity. POS showed favorable safety and tolerability in both these trials.

Conclusion:
MIRA-2 and MIRA-3 represent two well-controlled Phase 3 clinical trials demonstrating that POS rapidly returned a statistically greater number of subjects to their baseline PD regardless of the dilating agent or iris color. Based on this efficacy and its favorable safety and tolerability profile, POS will be submitted for regulatory approval for the treatment of RM.

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Dropless Vitrectomy Surgery for Epiretinal Membranes: Efficacy and Safety Compared to Standard of Care

- K. Chalam, MD, PhD, MBA, FRCS(C), FASRS
- Shailesh Gupta, MD, MBA

Objective:
Single intraoperative (trimoxi) triamcinoloneacetonide–moxifloxacin injection without postoperative drops effectively control inflammation after vitreous surgery for epiretinal membranes (ERM) and improves OCT measured retinal thickness and visual acuity compared to standard drop therapy

Purpose:
To compare the safety and effectiveness of intravitreal injection of triamcinolone

acetonide–moxifloxacin (Tri-Moxi) to a standard eye drop regimen in controlling

postoperative inflammation, visual acuity, retinal thickness and the rate of high intraocular pressure (IOP) in patients undergoing vitrectomy surgery for epiretinal membranes associated with macular edema in an academic setting

Methods:
In this retrospective longitudinal comparative study, the electronic medical

records of patients who underwent vitrectomy surgery for ERM associated with ME using single intravitreal injection of

triamcinolone acetonide–moxifloxacin injection (Imprimis) at the end of surgery were

reviewed (Group 1) and compared with patients who received a standard topical regimen of

tapering doses of steroid-antibiotic(Tobradex) eye drops (Group 2) in terms of degree of

intraocular inflammation, OCT thickness, visual acuity, and the rate of high IOP.

Postoperative observations were made at days 1, 42 (6 weeks) and 90 (three months).

Anterior chamber cell reaction and corneal edema were graded on a scale of 0 -4.

Results:
A total of 278 consecutive eyes (Group 1 [139 eyes], Group 2 [139 eyes]) of 270

patients were included in the study. The anterior chamber cell reaction severity decreased

by 14.0%, and 26.0% at 6 weeks and 90 days, respectively, after surgery following

triamcinolone acetonide–moxifloxacin injection (Group 1) compared with standard eye drop

therapy ($P < .001$ and $P < .02$, respectively). The best corrected visual acuity improved

about 3 lines on average in both groups, 90 days after surgery compared with the

pre-operative values ($P < .001$).

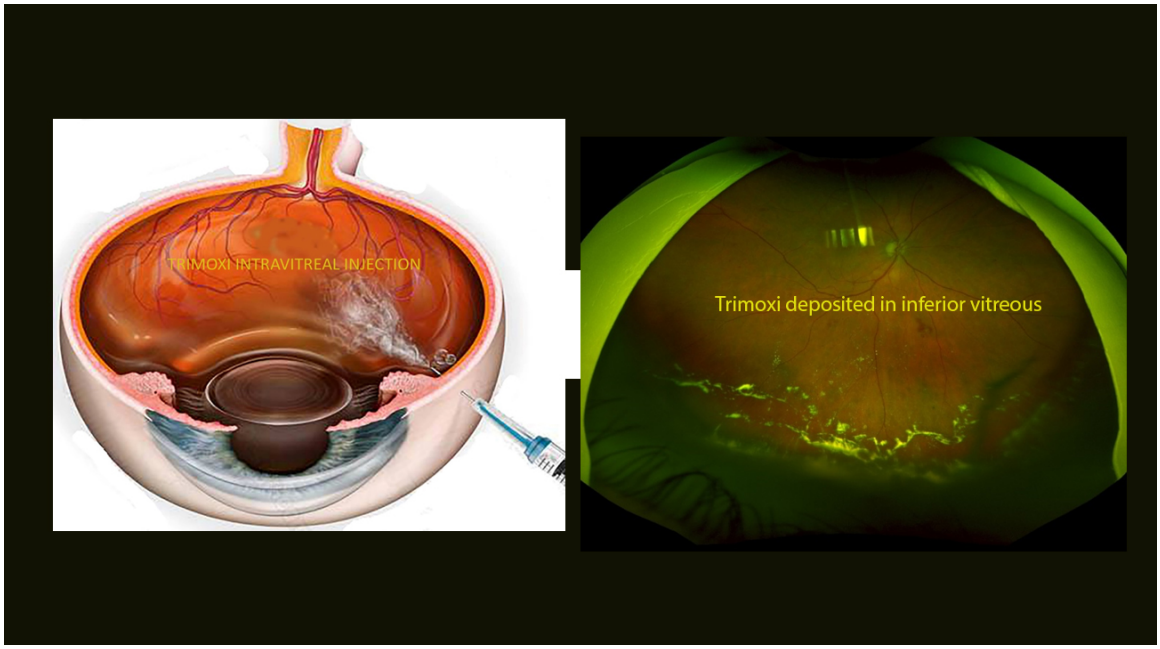
Group 1 was associated with improvement in reduction of central subfield thickness (CST) on OCT at 6 weeks and 90 days. Mean reduction in macular thickness was statistically significant (142µ ± 38 vs 78µ± 26; $P < 0.001$) at 90 days postoperatively. There was no statistically significant difference in the rate of high IOP

between the two groups at different time points postoperatively.

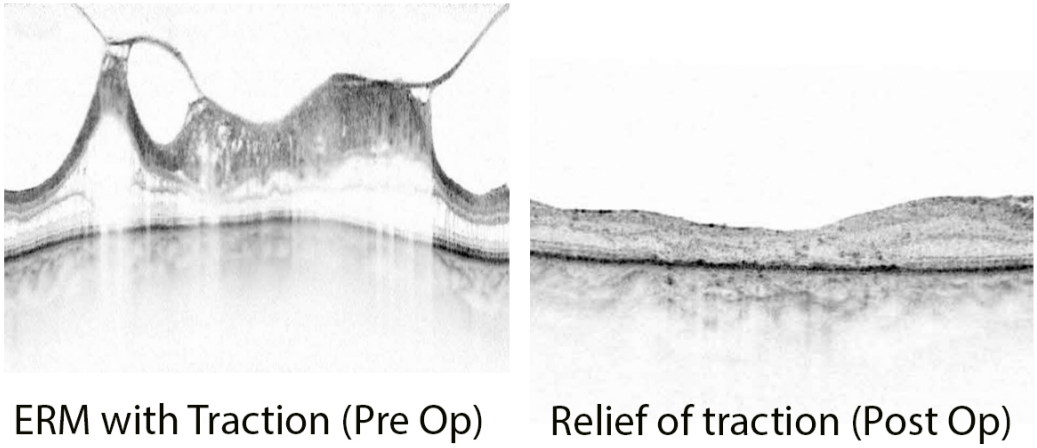
Conclusion:
Attainment of good outcomes in vitrectomy surgery depend in part on patient compliance. Triamcinolone acetonide–moxifloxacin injection is an effective method to control intraocular inflammation after vitrectomy surgery for epiretinal membranes associated with macular edema and not inferior to standard postoperative topical therapy.

It is particularly effective in reducing retinal thickness possibly from long acting steroid component. It is a promising substitute for standard eye drop therapy, especially for patients non-compliant (unable to fill medication for financial reasons or physical disabilities) with eye drop usage

IRB APPROVAL Yes



Administration of Trimoxi at the end of vitrectomy



Resolution of macular edema after trimoxi injection

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Tips and Tricks in the Management of Complications Associated With Autologous Retinal Transplants

- Ryan Shields, MD
- Tamer Mahmoud, MD, PhD

Objective:
To describe the most common complications associated with an autologous retinal transplant for macular hole repair

Purpose:
To describe the most common complications associated with an autologous retinal transplant, including graft dislocation, proliferative vitreoretinopathy, and subretinal perfluorocarbon liquid, and to demonstrate techniques in remedying each complication.

Methods:
A retrospective, consecutive case series on patients that underwent an ART and an associated surgical complication. Surgical videos were reviewed, and those with complications were identified.

Results:
Four surgical complications were encountered consistent with the global study results. Those included partial graft displacement, complete graft dislocation, sub-ART perfluorocarbon liquid (PFCL), and delayed proliferative vitreoretinopathy-associated retinal detachment (RDPVR). Surgical management of these complications included adjusting the graft at the time of PFCL removal, harvesting new graft with direct PFCL- silicone oil exchange, expression of PFCL from graft edge, and unimanual and bimanual graft harvesting and positioning under PFCL in RDPVR.

Conclusion:
As more surgeons employ ARTs to treat atypical macular holes, a satisfactory understanding of surgery-specific complications and techniques to treat those complications is indispensable.

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Macular Hole Surgery Results With Long-Acting Gas Tamponade and Internal Limiting Membrane Removal

- John Thompson, MD

Objective:
To evaluate the results of a single surgical technique in a large retrospective series of primary macular holes.

Purpose:
Multiple different surgical techniques, gas tamponade types and durations of prone positioning have been proposed to optimize the success of macular hole surgery. This study evaluated the results of macular hole surgery using the same technique with ILM removal and long-acting gas tamponade.

Methods:
Vitrectomy was performed for primary macular holes in a retrospective, consecutive, single surgeon case series of 178 eyes with idiopathic macular holes. This included a small percentage of chronic and myopic macular holes. All eyes had removal of the perimacular ILM after staining with ICG. Prone positioning was maintained for 1-2 weeks with 5% - 16% perfluoropropane gas, depending on the size of the macular hole.

Results:
The macular hole was closed with one surgery in 175/178 eyes (98.3%) at 3 months and 177/178 eyes (99.4%) by the final exam. Mean visual acuity improved from 20/125 at baseline to 20/80 +2 at 1 year, 20/63 +2 at 2 years and 20/63 +1 by the final exam at a mean of 3.4 years (P<.001 between baseline and all postop visual acuities). The visual acuity improved 2 or more Snellen lines (0.2 logMAR) in 60% at 1 year, 70.6% at 2 years and 65.5% at the final exam. Visual acuity decreased 2 or more lines in 16.7% at 1 year, 8.2% at 2 years and 8.5% at the final exam. Visual acuity was 20/40 or better in 39.8% at 1 year, 48% at 2 years and 48% at the final exam. The visual acuity improved 2 or more lines in 69.3% eyes that were pseudophakic by the final exam from a mean of 20/125 at baseline to 20/50 -2 (P<.001). None of the eyes developed late reopening of the macular hole up to 12 years following surgery.

Conclusion:
Long-acting gas tamponade with ILM removal in eyes with a variety of macular hole sizes and durations assures a very high rate of macular hole closure, no late reopening of macular holes and excellent visual acuity results.

IRB APPROVAL Yes

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Interim Subretinal Gene Therapy Safety Results in Two Phase 1/2 Open-label, Dose-Escalation Clinical Trials to Treat Achromatopsia

- Lejla Vajzovic, MD, FASRS
- Alessandro Iannaccone, MD, MS, FARVO
- Audina Berrocal, MD FASRS
- Christine Kay, MD
- Mark Pennesi, MD/PhD
- Paul Yang
- Andreas Lauer, MD
- Ninel Gregori, MD
- Janet Davis, MD
- Byron Lam, MD
- Mauro Goldbaum, MD
- Bright Ashimatey, OD, PhD
- Feng Zhu
- Anne Fulton
- Efren Gonzalez, MD
- Rachel Huckfeldt
- Jason Comander
- Edward Averbukh, MD
- Eyal Banin
- Jessica Morgan, PhD
- Joseph Carroll, PhD
- Matthew Feinsod, MD
- Robert Sisk, MD, FACS, FASRS

Objective:
To report safety of AGTC-401 (rAAV2tYF-PR1.7-hCNGB3) and AGTC-402 (rAAV2tYF-PR1.7-hCNGA3) in Subjects with Achromatopsia (ACHM)

Purpose:
Achromatopsia (ACHM) is a congenital autosomal recessive retinal disease with cone photoreceptor dysfunction. Gene therapies, AGTC-401 and AGTC-402, are being developed to compensate for the mutated genes, *CNGB3 and CNGA3*, accounting for over 80% of ACHM. This is a report from two ongoing, Phase 1/2, open-label, dose-escalation clinical trial trials using recombinant AAV vectors.

Methods:
A macular subretinal injection (≤300 µL) of AGTC-401 (rAAV2tYF-PR1.7-hCNGB3, n=31) or AGTC-402 (rAAV2tYF-PR1.7-hCNGA3, n=24) was administrated in a study eye of 55 subjects, 5-69 years old (37 adults, 18 children). Subjects were sequentially assigned to 1 of 5 (*CNGA3*) or 6 (*CNGB3)* dose groups spanning from $4.0e^{10}$ to $3.2e^{12}$vg/ml. Safety results were evaluated by reported ocular and non-ocular adverse events (AEs), functional and microanatomical imaging-based outcome measures, and chemistry parameters.

Results:
Across both trials, 3 drug-related serious adverse event (SAE) cases were seen in children at the highest dose level [$3.2e^{12}$vg/mL, CNGA3 (N=2) and CNGB3

(N=1)], which was assessed to be a dose-limiting toxicity (DLT) dose level in children. Uveitis and posterior segment changes were seen clinically and further detected and characterized by wide-field fundus imaging in 3 children (Figure 1, 2), one of whom also developed subretinal fluid in the untreated fellow eye. No DLTs were observed at any dose level in adults. At dose levels below the DLT in adults and children, both drugs had a favorable safety profile and none of the 3 SAEs in this group were deemed drug-related [macular hole related to subretinal surgery (n=1); steroid-induced elevated IOP resolved after glaucoma surgery (n=2)]. Most AEs were Grade 1 or 2 (except one Grade-3 anterior chamber inflammation). All intraocular inflammatory AEs were controlled with oral, intravenous, periocular and/or topical steroids. Steroid-related IOP elevations were seen in 24 subjects (47.1%) and were non-serious and controlled with IOP-lowering agents in 22 (91.7%). Immunological T-cell and antibody tests to AAV and genes *CNGA3* or *CNGB3* were not associated with safety findings.

Conclusion:

In ACHM, AGTC-401 and AGTC-402 gene therapy was safe and well-tolerated up to and including the second highest dose ($1.1e^{12}$vg/mL). For adults, the highest dose ($3.2e^{12}$vg/mL) also was tolerated. For children, the highest dose resulted in intraocular inflammation considered to be dose limiting toxicity that responded well to adjusted steroid regimens. Wide-field imaging studies aided in identification and characterization of some unique SAE findings and should be advocated as an outcome measure for both efficacy and safety reasons, especially in pediatric trials where participants' cooperation is more limited.

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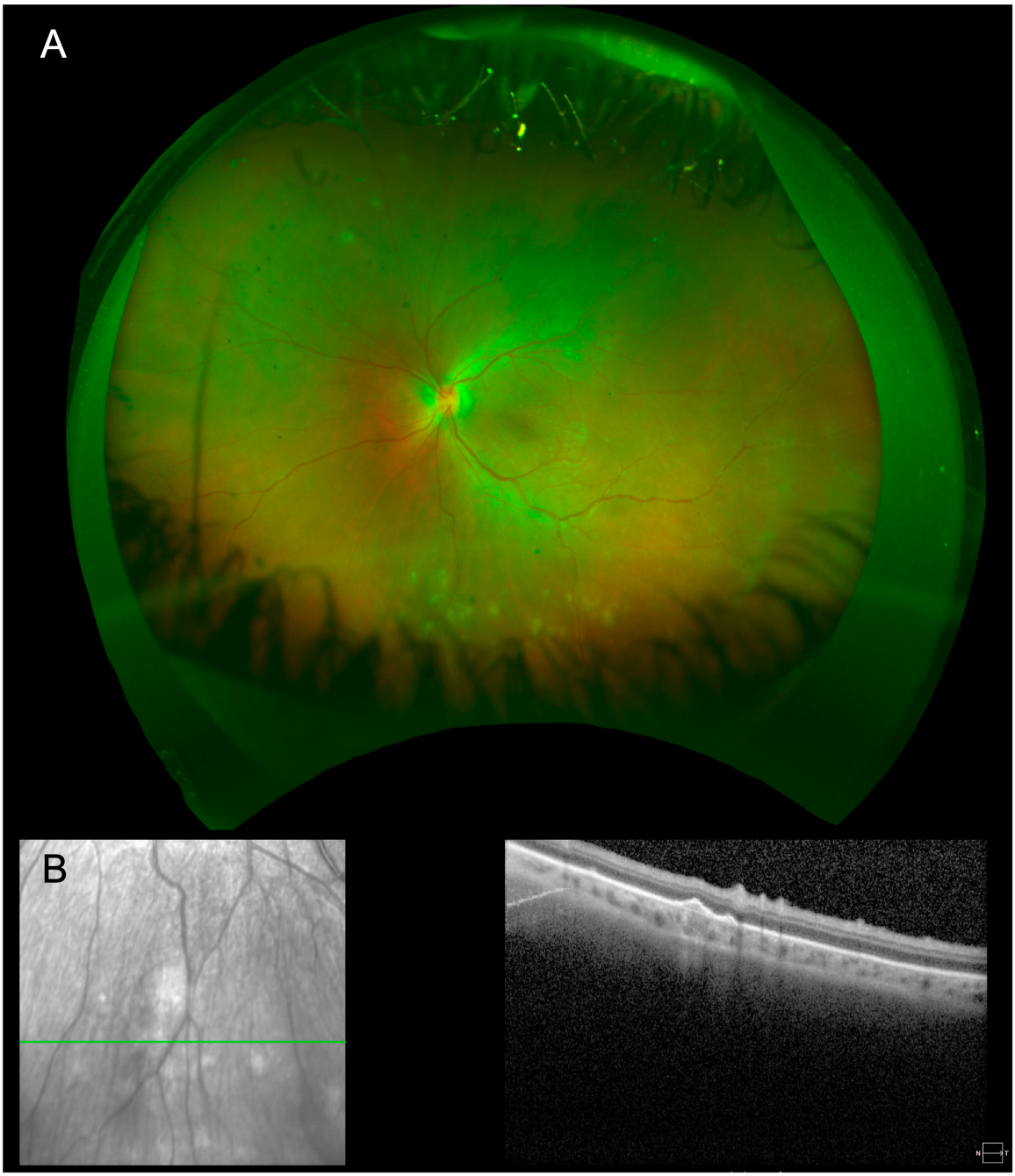
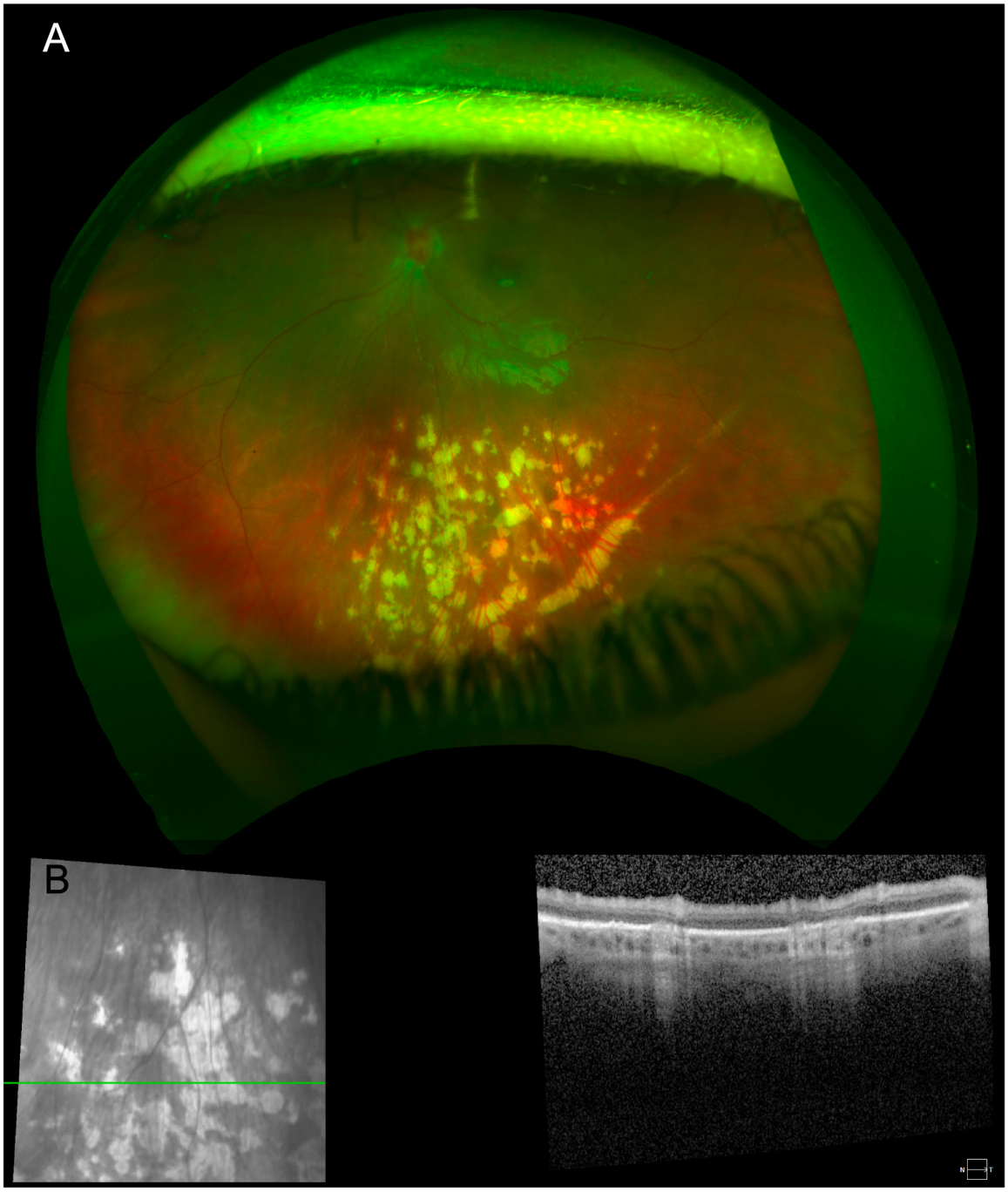


Hazy vitreous and inferior white pigmented epithelium lesions at 1 month.



At 5 months, vitreous cells resolved and RPE lesions became atrophic areas.

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Surgery Symposium 7
Scleral-Fixated Carlevale IOL: The Ultimate Solution

- Stratos Gotzaridis, MBBS, MD

Objective:
The ultimate solution to sceral fixated IOL with an IOL specially designed for this purpose

Purpose:
To report the clinical outcomes of the use of a novel specially designed scleral fixated intraocular lens, the Carlevale intraocular lens (carlevale IOL, Soleko, Italy) for the correction of aphakia in the absence of capsular support of variable etiology.

Methods:
This retrospective, non-comparative study included 169 eyes of 169 consecutive patients who underwent 3-port pars plana vitrectomy and scleral fixation on Carlevale IOL. Inclusion criteria were at least 12 months' follow-up period, patients > 18 years old who underwent vitrectomy and Carlevale IOL placement for aphakia and inadequate capsular support.

Results:

- The median follow-up period of 9 months (range 6-18 months). Mean postoperative BCVA at the last follow-up visit was 20/25 (0.09 ± 0.1 LogMAR), improving from a mean baseline BCVA of 20/80 (0.58 ± 0.49 LogMAR), a statistically significant change (p = 0.0001). Regarding the postoperative complications, a transient rise in the IOP was observed in 28 patients (16.5%) and mild vitreous hemorrhage was observed in the immediate post-operative period in eight eyes (4.7%) and it spontaneously resolved within 3 weeks. All patients demonstrated a nice IOL position at the end of the follow-up without IOL capture. None of the patients required re-operation.

Conclusion:
The present study represents the largest to date in evaluating the use of carlevale IOL in patients with aphakia and inadequate capsular support. The technique is safe and provides excellent post-operative IOL fixation without IOL capture in any of the patients studied.

IRB APPROVAL No - no IRB or exemption