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Ophthalmology Times Europe

Mission Statement: Ophthalmology Times Europe® is the independent source for current developments and best practices in European ophthalmology. It is the balanced and unbiased forum for ophthalmologists to communicate practical experience, clinical knowledge, discoveries and applications, thereby promoting improvements to medical practice and patient health.

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CUTTING-EDGE ADVANCEMENTS

Bonn, Germany

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“Despite over a decade of excellent outcomes, the ICL adoption rate is not as robust as might be expected.

—READ FULL STORY ON PAGE 25

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OZURDEX® is indicated for the treatment of adult patients with visual impairment due to diabetic macular oedema (DMO) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. Real world evidence is collected outside of controlled clinical trials and has inherent limitations including a lesser ability to control for confounding factors. OZURDEX® cannot be adequately controlled by medicinal products alone. Aphakic eyes with the active substance or to any of the excipients. Active or suspected ocular or conditions as described in the Summary of Product Characteristics. The patient intravitreal injection procedure should be carried out under controlled aseptic conditions. These patients should be closely monitored to allow for early diagnosis and not be retreated. Repeat dosing should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity also in the placebo group. Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not related to DMO, should not be retreated. In DMO and uveitis there is only very limited information on repeat dosing intervals less than 6 months. There is currently no experience of repeat administration in posterior segment non-infectious uveitis and visual impairment due to diabetic macular oedema (DME), cataract or neovascular age-related macular degeneration (nAMD). The rise in IOP is normally manageable with OZURdex medication. Corticosteroids should be used cautiously in patients with a history of glaucoma simplex and not be used in active or suspected uveitis, OZURDEX is not recommended in patients with macular oedema secondary to PDR with significant retinal neovascularisation. OZURDEX administration to both eyes concurrently is not recommended. Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or the inability to read. Repeat adverse events were increased intraocular pressure (IOP), cataract and conjunctival hyperaemia. Uncommon (≥1/1,000 to <1/100): migraine, necrotizing retinitis, endophthalmitis, glaucoma, retinal detachment, retinal tear, hypopyon of the eye, anterior chamber inflammation, anterior chamber flare, abnormal sensation in eye, eyelid protrusion, scleral hyperaemia, disease dislocation* (migration of implant) with or without central corneal edema, complications of cataract surgery and corneal decompensation. Adverse reactions considered to be related to the intravitreal procedure rather than the dexamethasone implant. Please refer to Summary of Product Characteristics for full information on side effects. OZURDEX is not recommended during pregnancy unless the benefit justifies the potential risk to the foetus. Lactation: Dexamethasone is excreted in human milk. No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast-feeding unless clearly necessary. Driving/Use of Machinery: Patients may experience temporary reduced vision after receiving OZURDEX by intravitreal injection. This should not occur or use machinery until this has resolved. Adverse Effects: In clinical trials the most frequently reported adverse events were increased intraocular pressure (IOP), cataract and conjunctival hyperaemia. Increased IOP with OZURDEX peaked at day 6 and returned to baseline levels by day 180. The majority of elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. 1% of patients (4/347 in DMO and 3/421 in RVO) had surgical procedures in the study eye for the treatment of IOP elevation. The following adverse events were reported for EYLEA: increased IOP, cataract, conjunctival hyperaemia, cosmetic intolerance, allergic hypersensitivity, conjunctival subcapsular, vitreous haemorrhage. In the majority of cases, these adverse events were related to the intravitreal injection procedure rather than the dexamethasone implant.
SPRING AHEAD: INNOVATIVE ADVANCEMENTS ON THE HORIZON

As we inch closer to spring, we hope the cutting-edge advancements featured in this month’s *Ophthalmology Times Europe*® will put a spring in your step.

First, we hear from Prof. H. Burkhard Dick on practical approaches to paediatric patients. Cataract surgery in children is challenging because of the likelihood of posterior capsule opacification. This can be overcome with primary posterior laser capsulotomy coupled with bag-in-the-lens technology (page 7).

Turning to glaucoma, Dr Felipe Medeiros discusses how the bimatoprost implant reduces intraocular pressure for 2 years or more. Physicians find that additional treatment is not required for many patients (page 12). Next, Dr Inder Paul Singh provides an update on simplifying glaucoma medical therapy for patients in the United States (page 13).

Shifting our focus to cornea, Dr Gerhard Garhöfer highlights a study targeting dry eye disease in postmenopausal women. Investigators find that oestradiol drops can ease signs and symptoms for 3 months (page 16).

In our cover story, Dr Redmer van Leeuwen and Dr Sjoerd Elferink touch upon ophthalmology’s role in the climate crisis. Lowering the carbon footprint of our clinical practices is a necessity (page 20).

With surgical updates, Dr Brett H. Mueller speaks to how a very-high-frequency ultrasound device provides a range of detailed intraocular measurements that enable highly accurate implantable collamer lens (ICL) sizing and placement. Such advancements make ICL an effective option for patients (page 25).

Dr Robert A. Sisk shares how an early-stage gene therapy study in patients with X-linked retinitis pigmentosa led to improved visual acuity, microperimetry sensitivity and foveal ellipsoidal zone status (page 30).

Presenters at the recent Angiogenesis, Exudation and Degeneration virtual conference provided new evidence about detecting retinal disease early, and predicting disease progression. Investigators also focused on finding cures for inherited retinal diseases (page 32).

Lastly, Dr Valérie Biousse provides a look at how retinal microvascular changes may not predict short-term ischaemic insults. A recent study found no evidence for a link between transient ischaemic attacks (TIAs) and changes in the eye (page 34).

Thanks for reading as always.

**MIKE HENNESSY JR.**
President and CEO of MJH Life Sciences®, parent company of Ophthalmology Times Europe®

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WHAT’S TRENDING

See what the ophthalmic community is reading on [Europe.OphthalmologyTimes.com](http://Europe.OphthalmologyTimes.com)
Paediatric cataract is a major cause of visual impairment in young patients. Although operating on congenital, early childhood or juvenile cataract can be challenging, in the hands of an experienced surgeon and a specialised team, the hurdles posed by the conditions of a developing eye can be overcome. The bane of the management of paediatric cataract, however, is posterior capsule opacification (PCO), which develops rapidly in the weeks and months after lens removal.

Close to or as much as 100% of young children will develop PCO as the most frequent complication in paediatric cataract surgery. Leaving the posterior capsule intact has been recognised for quite some time as a prerequisite in the pathogenesis of PCO and interventions on the posterior capsule have been introduced as a means to prevent or at least reduce the probability of PCO formation.¹

The introduction of the femto-second laser into cataract surgery has been—at least in our view, as pioneers of laser cataract surgery (LCS) in central Europe and with experience of close to 10,000 interventions now—a game changer in many respects, and I had the privilege to describe to readers of Ophthalmology Times Europe² in the November 2021 issue the potential of its employment in paediatric cataract surgery. Readers should be reminded that laser cataract surgery in children is, like so many interventions on our youngest patients, an off-label procedure.

**Primary posterior laser capsulotomy**

Posterior capsulotomy has been described as an option for reducing PCO formation in paediatric cataract patients. In our experience, primary posterior laser capsulotomy (PPLC) is a completely new approach, not least because an anterior vitrectomy is usually not necessary.

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**IN SHORT:**

Cataract surgery in children is challenging because of the likelihood of posterior capsule opacification. This can be overcome with primary posterior laser capsulotomy coupled with bag-in-the-lens technology.
This in turn reduces the risk of one of the most vicious complications of early childhood cataract surgery, aphakic glaucoma, significantly—in fact, to zero. Aphakic glaucoma is one of the most damaging and most difficult-to-manage forms of glaucoma.

In PPLC, the anterior hyaloid membrane of the vitreous stays intact and thus the influence of vitreous substances (which are discussed among the probable causes of aphakic glaucoma) is reduced to nil.

When undertaking LCS in paediatric patients, we perform capsulotomy with the laser (Figure 1); unlike in adult LCS, the lens is not fragmented because it can usually be removed by aspiration only.

Under general anaesthesia, the child is placed under the laser, then the smaller fluid-filled interface will be slowly and cautiously lowered towards the eye. After gently connecting with the ocular surface, the laser will perform anterior capsulotomy; when entering the clinical data in the platform’s software, we use the Bochum correction formula (described previously). Anterior capsulotomy is performed and small tags—which appear rarely—are gently removed manually.

The posterior capsule is meticulously polished; in paediatric cataracts, pupil dilation tends to be suboptimal. Ophthalmic viscosurgical device (OVD) is introduced sparingly to avoid pushing the posterior capsular too far back. The posterior capsule is elevated by OVD injection through a small opening in order to change its shape from concave to more convex.

After lens removal under the operating microscope, the young patient is once again positioned under the laser. Primary posterior laser capsulotomy is performed after perfectly aligning the anterior and the posterior capsules. The laser shots are fired from posterior towards anterior.

**Bag-in-the-lens**
The bag-in-the-lens (BIL) implant or BIL lens is a foldable hydrophilic lens, which consists of a biconvex optic and two elliptical plane haptics and is prepared in a cartridge for implantation. In adults, it requires a main incision of about 2.8 mm, but a special BIL lens for paediatric eyes is commercially available, which is smaller than the one implanted in adult eyes and can be exchanged when the child is older.

As first described by Marie-José Tassignon in 2002, during the BIL technique with two well-centred capsulotomies of almost identical size, anterior and posterior capsules are placed in this special IOL’s flange for insertion. We implant the lens by aligning the lower haptic to the 6 o'clock/12 o'clock meridian. A small spatula is used to protect the IOL from going too deep into the anterior chamber during implantation.

![FIGURE 1: Overview of the operating theatre setting with the femtosecond laser (Catalys, Johnson & Johnson) beside the surgical microscope.](image)

The introduction of the femtosecond laser into cataract surgery has been a game changer. When the BIL lens is completely inserted and unfolded, the posterior haptics are placed behind the posterior capsule and the anterior haptics in front of the anterior capsule, which keeps both capsules...
in the “groove” that is so characteristic of this innovative type of IOL. This procedure allows perfectly centred and stable positioning of the lens (Figure 2).

Intraoperative use of acetylcholine ensures that the iris covers the haptics. In older children, we make sure the incisions are not leaking; in younger children we use a suture for watertight wound closure.

Minimal remnants of OVD will be resorbed over time.\(^5\) Postoperative care is as usual for paediatric cataract patients except for the additional postoperative application of pilocarpine 1% three times daily for 2 days starting directly at the end of the procedure.

PPLC is generally a safe and effective procedure; we have documented its excellent safety profiles after 6 months\(^6\) and our 2-year results are currently under review. The same can be said about the BIL technology. A recent publication demonstrated that this implant does not induce an elevated risk for postoperative cystoid macular oedema.\(^7\)

The superiority of secondary BIL implantation over ciliary sulcus implantation of an IOL in aphakic children, in terms of fewer adverse effects, best-corrected visual acuity and IOL centration, was recently described by Liu et al.\(^8\) Our opinion that cataract surgery has a great tool promising much lower PCO rates in children than could have been hoped for just a year ago is supported by a 2022 publication from Norway: in 50 eyes of 30 patients younger than 12 years at the time of operation, who had received a BIL since 2013, 92% had a visual axis free of PCO.\(^9\)

In our experience PCO occurs only if the capsule edges are not positioned in the optic groove between both haptics. This is promising data indeed. And yet, cataract surgery in children is always just the first step on the long and winding road to optical rehabilitation.

**REFERENCES**


**FIGURE 2:** Paediatric BIL with the anterior and posterior capsule within the “groove” of the optic (view through the microscope). (Images courtesy of Prof. Burkhard Dick)
With iStent inject® W, trabecular micro-bypass stents can deliver two stents on a single pass, through a single incision. This is particularly beneficial in patients with primary open-angle glaucoma, pseudo-exfoliation glaucoma, pigmentary glaucoma, or cataract surgery. The device is also beneficial for patients with intraocular pressure reduction and/or need for glaucoma medication reduction.

**References**

The longest-term real world clinical data of any Trabecular Micro-Bypass procedure demonstrates significant advantages for your patients:

### Long-term IOP Reduction

<table>
<thead>
<tr>
<th>Time</th>
<th>Eyes</th>
<th>Reduction in Mean IOP</th>
<th>Sustained Medication Reduction</th>
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<tbody>
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<td>4 years</td>
<td>57</td>
<td>46%</td>
<td>95% of eyes med-free</td>
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<tr>
<td>5 years</td>
<td>125</td>
<td>40%</td>
<td>71% reduction in mean medications</td>
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<tr>
<td>5 years</td>
<td>778</td>
<td>33%</td>
<td>81% of eyes med-free</td>
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### Improved OSD Symptoms

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<th>Reduction in %</th>
<th>Patients with Severe OSD Symptoms</th>
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<tbody>
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<td>3 months</td>
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<td>72%</td>
<td>72%</td>
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### Significant Improvement in OSDI Score

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<th>Patients</th>
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<td>24 months</td>
<td>505</td>
<td>57.6%</td>
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<tr>
<td></td>
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<td>48.9%</td>
<td>Cataract only</td>
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</table>

### Improved Quality of Life

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<td>Ocular Pain</td>
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<tr>
<td>Driving</td>
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Bimatoprost implant reduces intraocular pressure for 2 years or more
Physicians find that additional treatment is not required for many patients

By Lynda Charters

A Phase 3 clinical extension study of a bimatoprost implant (Durysta, AbbVie) showed that patients had sustained lowering of their IOP for 2 years or more with no additional treatment and no changes in their visual fields, according to the first author of the trial, Dr Felipe Medeiros.

Previous results from the Phase 1 and 2 clinical studies of the device, which is administered intracameral through a preloaded applicator with a 28-gauge needle, showed that the duration of its IOP-lowering effect had extended beyond the expected period of intraocular drug bioavailability.1,2

Investigators then conducted a 24-month, open-label, multicentre, long-term safety and efficacy extension study of patients with open-angle glaucoma or ocular hypertension who had received a bimatoprost implant in a Phase 3 trial and completed that study. A total of 200 patients were enrolled after completing one of two identically designed, 20-month, randomly assigned Phase 3 trials (ARTEMIS Studies 1 and 2).

The outcome measures of the extension study were both the number of patients who did not need additional (rescue) IOP-lowering treatment in the study eye for 2 or 3 or more years after the third implant administration during the ARTEMIS trial, and the IOP and visual field mean deviation in the study eye of these patients. The study is ongoing; the investigators have analysed all data available up to February 2021.

**Prolonged IOP-lowering effect may result from up-regulation of matrix metalloproteinases.**

**Major findings to date**
During the screening for the extension study, it was found that 69 of the patients had not received rescue treatment. “The data that were available for 54 patients showed that these patients remained untreated for 2 years or more after they received the third implant during the ARTEMIS trial, and data available for 18 patients showed that they had remained untreated for 3 years or more after the third implant in the ARTEMIS trial,” Dr Medeiros said.

In addition, the visual fields of the patients in the extension study who did not require rescue medication (i.e., 50 of those with controlled IOP for 2 years or more and 16 of those with controlled IOP for 3 years or more) remained stable.

The investigators theorised that the prolonged IOP-lowering effect may result from bimatoprost-stimulated up-regulation of matrix metalloproteinases, leading to sustained tissue remodelling of the outflow pathways. Clinical studies are continuing with the goal of obtaining a further understanding of the duration of effect of the bimatoprost implant and factors that predict a long-term response.1

Felipe Medeiros, MD, PhD
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Dr Medeiros is professor of ophthalmology and vice chair of technology in the Department of Ophthalmology at Duke University in Durham, North Carolina, United States. This article is adapted from Dr Medeiros’ presentation at the American Academy of Ophthalmology 2021 annual meeting, New Orleans, Louisiana, US. He is a consultant to Allergan, an AbbVie company.

REFERENCES
Simplifying glaucoma medical therapy for patients in the United States

Compounded medications are playing a central role in the process

By Dr Inder Paul Singh

Adherence with lifelong glaucoma therapy demands a great deal from our patients. They must be able to afford and acquire their medications, remember the daily dosing schedule, be able to tolerate the drops well enough not to skip doses and physically succeed in instilling the drops. This is a lot to ask of them, especially as they age and begin to have concomitant health problems or cognitive loss.

Numerous studies have shown that adherence declines with more complex regimens of more than one or two bottles. Various studies have shown that, when you add a second or third bottle with preservatives, such as benzalkonium chloride, the incidence of ocular surface disease (OSD) increases. Then, in a vicious cycle, patients with OSD become even less adherent.

More than ever, we are now beginning to appreciate the effect of compliance on long-term intraocular pressure (IOP) control in our glaucoma patients. Both the HORIZON study, looking at implantation of Hydrus Microstents (Ivantis) at the time of cataract surgery, and the LiGHT study, in which first-line selective laser trabeculoplasty (SLT) was compared with medical therapy, found that patients with the surgical/laser interventions were less likely to progress to needing incisional glaucoma filtration surgery. Even though we have medications that nominally provide the same IOP-lowering effect as SLT or minimally invasive glaucoma surgery (MIGS), we are not getting the full benefit of these medications because patients simply are not using them consistently. More MIGS and SLT is part of the answer, but there will always be patients who need to continue topical therapy instead of, or in addition to, these options.

In my practice, I typically prescribe a branded, commercially available glaucoma drug first and I may make this choice for the second bottle as well. These drugs have gone through rigorous United States Food and Drug Administration trials and are marketed accordingly. However, as the regimens get more complex with three to four medications, or if there are cost and adherence challenges with even two drops, I find that compounded fixed-combination glaucoma drops (Simple Drops, ImprimisRx) nicely address many of the factors that lead to poor adherence.

Although we have a few dual-drug combinations in the US, none of them include a beta-blocker with a prostaglandin analogue (PGA), and none include more than two agents. Using Simple Drops, as

IN SHORT:
Regimens of fixed-combination drops can help patient adherence with treatment, leading to improved IOP and lessening need for surgery.
the name implies, allows me to simplify the regimen for the patient to a single bottle once a day or one bottle each for morning and evening.

These drugs are compounded in a Pharmacy Compounding Accreditation Board-accredited 503A patient-specific pharmacy that follows many of the same high manufacturing standards as its 503B facility. Every batch is tested for potency, sterility and endotoxins, so I can be confident that my patients get a high-quality product.

**IOP fluctuation is the problem**

For many of our patients who are still progressing or have poorly controlled IOP on topical medications, the problem is not that the drops are not working; it is that their IOP is fluctuating with inconsistent use of the medication. The Advanced Glaucoma Intervention Study (AGIS) demonstrated that long-term IOP fluctuation of greater than 3.0 mm Hg is associated with visual field progression.⁷

Among AGIS patients with low mean IOP—those patients whose pressure looks fine when we see them in the clinic—fluctuations increase the risk of progression more than three-fold.⁷ Simplifying the regimen for these patients can boost adherence enough to stabilise them.

In a study I conducted, switching my patients to a 3-in-1 or 4-in-1 drop resulted in lower IOP across most patient types, particularly among those who were poorly controlled on their prior regimen of three bottles or more.⁸ Four patients in the study were able to avoid planned surgery.

One of these patients was a 43-year-old African American woman with advanced glaucoma who was still progressing on brimonidine/timolol (Combigan, Allergan), brinzolamide (Azopt, Novartis), and travoprost (Travatan, Alcon Laboratories). Her eyes were always red, and she told me she could not keep taking so many drops.

We discussed trabeculectomy, and I decided to put her on Tim-Brim-Dor PF (timolol 0.5%, brimonidine 0.15%, dorzolamide 2.0%, ImprisonRx) and stop the PGA to improve her ocular surface symptoms before surgery. At the next follow-up, her IOP was down to our target of 12 mm Hg, her eyes were not red and she was happy with the reduced drop burden. Four years later, she is still on this regimen and has been able to avoid filtering surgery.

**Clarity of cost and ingredients**

Another major reason for using compounded combination drops is that I know what to expect and what it will cost the patient. If I prescribe three separate medications to a patient, it is very hard for me to answer their very reasonable question, “How much is that going to cost?” in any sort of accurate or transparent way.

The cost to the patient could be $15 or $300, depending on their insurance coverage, co-pays and formulary requirements. Moreover, they are highly likely to get generic substitutions from the pharmacy.

The pH, viscosity and other aspects of the inactive vehicle ingredients can vary widely from one generic to another, greatly affecting the bioavailability and efficacy of the active ingredient and the tolerability and safety of the drop overall.⁹ 12 There can even be variability in the quality of the dropper bottle, causing drops to spill out too fast and the patient to run out of a 30-day supply in a much shorter period of time.

Finally, compounded drops also give me the ability to prescribe preservative-free formulations so the glaucoma medications are not contributing further to ocular surface toxicity. About half of our glaucoma patients have OSD,¹³ and those with concomitant OSD are more likely to experience adverse effects from topical glaucoma therapy, more likely to be non-adherent and more likely to progress.¹⁴ If we can minimise the effect on the ocular surface, we are also maximising the chances of success with later Xen implantation or filtration surgery if required.

If cost, compliance and generic substitution were not factors at all, I might prefer separate bottles of each branded medication. But we have to recognise that patients are not getting what we prescribe and are not consistently instilling what they do receive, with resulting IOP fluctuation and disease progression. A simplified regimen of compounded fixed-combination glaucoma therapy is a very welcome solution to these real-world problems.

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Dr Singh is in practice at the Eye Centers of Racine and Kenosha, Wisconsin, US. He is a consultant for many glaucoma companies, including Glaukos, ImprisonRx and Ivantis.

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Dry eye management has never been this easy. The new JENVIS Pro Dry Eye Report helps you perform comprehensive screenings, using the measuring results as a basis for diagnosing dry eye syndrome. The workflow is optimized for time saving and patient friendliness. All results are documented and summarized for you and your patient in a neat and easily understandable printout.

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Study targets dry eye disease in postmenopausal women

Investigators find that oestradiol drops can ease signs and symptoms for 3 months

By Louise Gagnon; Reviewed by Dr Gerhard Garhöfer

A novel treatment for dry eye disease (DED) in the form of topical oestradiol can reduce signs and symptoms of DED in postmenopausal women for at least 3 months, according to Dr Gerhard Garhöfer, associate professor at Medical University of Vienna, Department of Clinical Pharmacology, Vienna, Austria.

Dr Garhöfer served as lead investigator for a randomised, controlled, parallel-group study of the therapeutic formulation of oestradiol candidate RP101 (Redwood Pharma).

“Sex hormone receptors or oestrogen receptors have been found to be present on the ocular surface in several tissues, such as the conjunctiva, cornea and Meibomian glands,” Dr Garhöfer said. “The pronounced contrast in dry eye prevalence between men and women, especially women who are postmenopausal, points towards an involvement of sex hormones in the disease process. Furthermore, anti-oestrogen treatment seems to disrupt tear production.”

RP101 contains 17-beta-estradiol as the active ingredient and a sterile isotonic thermogelling (IntelliGel) solution as the drug delivery system. This thermosensitive, supramolecular hydrogel becomes a gel at eye temperature, allowing for a long period of residency on the ocular surface and thus permitting sustained drug delivery.

Dr Garöfer and his co-investigators enrolled 104 patients in the study, with 77 completing the study according to the protocol. Five patients requested withdrawal, 21 withdrew due to adverse events and one patient withdrew for other reasons.

The study aimed to determine the optimal dosing regimen of RP101 and to evaluate its safety in postmenopausal women with moderate-to-severe DED. The four arms of the study included 0.05% twice daily, 0.1% morning and vehicle (isotonic thermogelling solution) in the evening, 0.1% twice daily and a control group who received the vehicle twice daily. The total treatment period was 3 months.

Investigators used Schirmer’s test II and grading of corneal fluorescein staining, taking measurements at baseline and at various points during treatment: Day 14, Day 30, Day 60 and Day 90 (treatment completion). Patients reported outcomes for various DED symptoms via the Symptom Assessment Questionnaire in Dry Eye (SANDE) and the Visual Analogue Scales (VAS).

Corneal fluorescein staining score significantly decreased during the 3-month treatment period (P < 0.001 vs baseline). Investigators found no significant difference between treatment groups. The staining of the inferior cornea, however, showed a significantly
more pronounced reduction in the highest-dose group compared with vehicle \((P = 0.0463)\).

Schirmer’s test II showed an increase in tear production, reaching maximum effect after 90 days of treatment. “Schirmer’s Test II increased significantly after 14 days of treatment in the active groups and after 1 month of treatment in the control group and remained significantly elevated until the end of the study,” Dr Garhöfer explained.

The SANDE symptom score, a frequently used standardised questionnaire for assessing the severity and frequency of dry eye symptoms, showed a decrease at the end of the treatment period in all groups. Moreover, patient-reported outcome via VAS in all four treatment arms showed a decrease in symptoms of DED, such as foreign body sensation; burning/stinging; itching; pain; sticky feeling; redness; and tearing.

The eye drops were well tolerated on the ocular surface and showed a favourable safety profile. “Most treatment-related adverse events were eye-related and mostly mild or moderate,” Dr Garhöfer said. “The most frequent … (more than 5% in at least one treatment group) were blurred vision; eye pain; eye irritation; ocular hyperaemia; eyelid swelling; or foreign body sensation. All these adverse events had resolved at the end of the study.”

According to Dr Garhöfer, at this time therapy data are limited to use in postmenopausal women. “Further studies are needed to investigate whether other target populations would benefit from topical oestrogen treatment.” He added that the next step will be a Phase 3 study, which will be designed based on the data obtained from the Phase 2 study.

“Our data show that all dosages of RP101 were safe and improved signs and symptoms of DED at the end of the observation period,” he said. “We think the topical approach would make the most sense in dry eye patients as it can reach higher levels on the ocular surface while not needing high plasma levels, which would be the case when oestrogen is given systemically.”

Dr Garhöfer did point out, however, that the thermosensitive hydrogel solution that served as a control in the study also had an impact on signs and symptoms of DED. He said that systemic oestrogen is not a preferred option to treat DED in postmenopausal women because it has been linked to serious systemic adverse effects. He concluded, though, that “with a topical formulation, systemic uptake of oestradiol is very low, which limits the risk of systemic side effects.”

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Dr Garhöfer has no financial disclosures to declare related to this content.
CASE OF THE MONTH

Lenticule Extraction with SMILE in low myopic patients – a case study

By Bostjan Drev, MRCP, FRCS, FRCOphth

EXCHANGE OF EXPERIENCE

Findings from various studies along with anecdotal observations point to growing patient interest in refractive surgery, and this trend is expected to continue.1,2 Most patients seeking refractive surgery are younger (20 to 40 years old), the vast majority are myopes, and low myopia (< -3.0 D) accounts for the largest proportion of the myopic population.1,3

We acquired a VisuMax femtosecond laser (Carl Zeiss Meditec AG; Jena, Germany) in April 2015 and began to offer Lenticule Extraction with SMILE (Carl Zeiss Meditec AG, Jena, Germany) to treat myopia and myopic astigmatism soon after. Today SMILE accounts for approximately 92% of our myopic procedures. The following case illustrates the great outcomes that are achieved using Lenticule Extraction with SMILE to treat low myopia and highlights some of the features that make it our refractive procedure of choice for nearly all patients with myopia.

CASE HISTORY

A 30-year-old male who works as a car maintenance supervisor presented for a refractive surgery consultation. The patient had been using contact lenses to correct low myopia, but dust at his workplace caused problems with his contacts and he had stopped wearing them about 6 months earlier. The patient said he enjoys cycling, football, and martial arts. He was motivated to have refractive surgery because he wanted freedom from glasses at work, and he was particularly interested in SMILE because of his enthusiasm for contact sports. The patient underwent a comprehensive ophthalmic evaluation. His visual acuity and refractive data are shown in the table and maps from Scheimpflug imaging (Pentacam, OCULUS Optikgeräte GmbH; Wetzlar, Germany) are shown in the figure.

Table. Preoperative and postoperative data

<table>
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<tr>
<td>Refraction*</td>
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<td>+0.50 -2.5/15°</td>
</tr>
<tr>
<td>OD</td>
<td>-1.00 -0.75/175°</td>
<td>+0.75 -0.50/87°</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloplegic</td>
<td>-0.25 -2.00/8°</td>
<td>-0.25 -0.75/175°</td>
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* Preop refractions are done twice; postop refractions are from autorefractor

Figure. Preoperative (top row) and postoperative (bottom row) maps from Scheimpflug imaging

All options for refractive surgery and their individual risks and benefits were discussed with the patient, and he confirmed his interest in SMILE. The procedure was planned using the following parameters: cap thickness 140 μm, cap diameter 7.90 mm, incision position 90°, incision angle 40°, optical zone 7.0 mm, and minimum side cut 20 μm. The input for refractive correction was -0.50 -2.50/10° OD, -1.00 -1.00 cyl/177° OS. The cylinder correction was increased from the subjective refraction by -0.25 D OU and the axis OS was set at 177°, midway between the first and second examinations. The measured sphere values from the subjective refractions were used because the values from the cycloplegic refraction were lower than from the subjective refraction.

The procedure was completed successfully, and the patient commented about its speed and comfort. Data collected from follow-up after 1 day, 1 month, and 18 months show his very good results and stability of the refractive and functional outcomes (Table). The patient expressed his satisfaction at all visits, nothing that he was especially pleased about the rapid recovery and freedom from glasses and contact lenses.

DISCUSSION

Our clinic has built a reputation as a center of excellence for SMILE based on word-of-mouth referrals from happy patients, and the patient in this case who
presented with a specific interest in SMILE is typical of our refractive surgery population. Approximately three-fourths of patients inquire about SMILE at the initial consultation. Nevertheless, all suitable options are discussed so that patients understand the pros and cons of each procedure. Great outcomes can be achieved with SMILE and also with excimer laser refractive surgeries. However, Lenticule Extraction with SMILE is a minimally invasive procedure associated with fast visual recovery. Compared to LASIK, SMILE offers benefits of a larger functional optical zone, potentially less dry eye, and freedom from flap-related complications. Dry eye has become a growing problem among adults of all ages, and the potential for flap dislocation is a particular concern for active adults, such as the patient in this case, who enjoys contact and other sports that put him at risk for traumatic eye injury.

Published reports document that SMILE for low myopia is safe and predictably effective. Over the past 6 years, we have performed more than 2000 cases of SMILE to correct SE between -0.75 D and -12.0 D, of which approximately 40% of cases were low myopia (-0.75 to -3.00 D) with or without astigmatism. Analyzing our SMILE outcomes, we found very good results across all groups of eyes stratified by level of myopic error.

**SURGICAL DETAILS**

When treating low myopia, I use a cap thickness of 120 to 140 μm and the lenticule through a 2.6 to 2.8 mm incision at 12 o’clock, although I make two incisions in some cases. Optical zone size varies from 6.50 to 7.50 mm and is made as large as pachymetry allows to maximize achieved lenticule thickness. I initially changed the default setting for side cut minimum edge thickness from 15 to 25 μm when I first started treating low myopia; after gaining experience in these cases, I set the edge thickness to 20 μm for cases with SE < -2.0 D.

Based on outcomes analyses, our initial SMILE nomogram was adjusted to achieve greater refractive accuracy, and we now correct 10% above the subjective refraction when treating eyes with ≥ -2.0 SE or when treating lower levels of myopia in younger patients. The target refraction is +0.50 D for patients aged 18 to 25 years, 0.0 D for patients aged 26 to 38 years, and slight monovision for patients older than 38 years (-0.5 D to -0.75 D in the non-dominant eye, depending on the patient’s professional activities and lifestyle).

Using the original VisuMax laser good centration and cyclotorsion adjustment is achieved with attention to proper patient positioning and “verbal anesthesia” to help the patient fully relax. I also place a reference mark on the peripheral cornea when treating >1.5 D of Cylinder, and adjust for cyclotorsion if needed. The new VISUMAX 800, which was launched in October 2021, incorporates a centration aid to support surgeons with this critical step and cyclotorsion alignment is done by digitally rotating the shooting pattern instead of manual alignment.

Following is my approach to lenticule dissection and extraction. Using a small hook, I open the incision and then create an entrance to the upper layer from the lateral (temporal) side to two-thirds of the distance to the center of the incision. Then, I look for the edge of the lenticule in the middle of the incision, go under the lenticule, and open the lower plane from the center to the opposite (nasal) side. After finding both interfaces, I gently separate the upper lenticule interface followed by the lower interface. When I am certain that the edges are free, I grasp the lenticule in the center with a micro-forceps and slowly extract it. Finally, I always check that the edges are smooth. These steps are technically the same regardless of level of myopia, but the correct application is most important for low myopia. Surgeons should find it reassuring to know that the site on the lenticule that is most susceptible to tears, its edges, are at least as thick if not thicker in low myopia cases compared to medium or high myopia.

**CONCLUSION**

Within the population of patients interested in refractive surgery, low myopes represent a large potential pool that can be offered the benefits of SMILE. After performing 2,000+ Lenticule Extraction procedures with SMILE, I can say with confidence that surgeons who adopt SMILE will be gratified by the results and rewarded with patients like the gentleman in this case who are thrilled with their outcome and act as a referral source for building practice volume.

References


Bostjan Drev, MRCP, FRCS, FRCOphth specializes in cataract and refractive surgery and is in private practice at Vidim Eye Surgical Center, Celje, Slovenia.

Media placement sponsored by Carl Zeiss Meditec AG
The Dutch Working Group on Sustainable Ophthalmology was founded in 2019. The aim of this group is to promote the transition to a sustainable clinical practice within our medical specialty. The group promotes research, provides information and coordinates action.

Based on current guidelines and scientific consensus, and respecting patient safety, the group has written directions for the safe and sustainable implementation of common ophthalmological procedures. Examples are intravitreal injections, cataract surgery and patient gowns during surgery.

The Dutch Ophthalmological Society has adopted and recommended these best practices, which are being adopted in a growing number of hospitals. Recently, Dutch health insurance companies have shown interest in promoting these best practices.

Intravitreal injections (IVIs) have revolutionised ophthalmology. With ever-increasing numbers of injections and a shift from reusable to disposable instruments, waste production has also soared.

Initially, I accepted the disposable custom-pack with plastic bowls, speculum, cotton buds and drape. However, seeing the overflowing waste bins after an afternoon of injections, I became frustrated.

I critically reviewed the literature on IVI procedures and concluded that we could do without drapes and forceps. In consultation with the supplier, we omitted all plastic trays and bowls and replaced the polypropylene cover sheet with a crepe-paper wrap (see Figure 1). This allowed for a much smaller plastic package. In this way we reduced waste from 135.5 to 66.5 g per IVI and costs by 20%.

In combination with the recycling of paper and clean plastics, the carbon footprint of a single IVI decreased from 0.68 kg CO₂ to 0.17 kg CO₂. Performing 50 injections a day, the daily savings equate to 25.5 kg CO₂, the equivalent of driving 116 km in a car.

This reduced IVI set has been adopted by the Dutch Ophthalmological Society and is being implemented in more and more hospitals. With over 400,000 annual injections nationwide,1 this small revision represents a large step forward in sustainable ophthalmology.

**A call to action**

Last September, over 200 scientific medical journals simultaneously published a “Call for emergency action to limit global temperature increases, restore biodiversity and protect health.” Participating journals ranged from the *New England Journal of Medicine* to the *Croatian Medical Journal* and from the *Lancet* to the *Medical Journal of Australia*. In this paper, editors call for governments and
leaders to act on keeping the global temperature rise below 1.5°C and on restoring nature.

The science is unequivocal: a global increase of 1.5°C above the pre-industrial average and the continued loss of biodiversity risk catastrophic harm to health. Climate change is already impacting health in a myriad of ways, including death and illness from increasingly frequent extreme weather events such as heatwaves, storms and floods; the disruption of food systems; increases in zoonoses and food-, water- and vector-borne diseases; and mental health issues.

Furthermore, climate change is undermining many of the social determinants for good health, such as livelihoods, equality and access to healthcare and social support structures. Despite the world’s necessary preoccupation with COVID-19, we cannot wait for the pandemic to resolve before taking action and should act now to rapidly reduce greenhouse gas emissions.

**What have ophthalmologists got to do with this?**

The healthcare sector is a major contributor to greenhouse gas emissions. It is estimated that healthcare’s climate footprint is equivalent to 4.4% of global net emissions (2 gigatons of CO₂ equivalent). If the health sector were a country, it would be the fifth largest emitter on the planet. So, the healthcare system itself contributes to a decline in public health.

This message has been heard by leaders in the field. During the recent COP26 UN Climate Change Conference in Glasgow, a group of 50 countries, including the UK, the US, Germany and the Netherlands, committed to develop climate-resilient and low-carbon healthcare systems.

Previously, a target of net zero greenhouse gas emissions in the year 2030 was adopted by the UK National Health Service. In the Netherlands, all major players in the healthcare sector signed a Green Deal, committing to a 50% reduction in carbon footprint by the year 2030.

Important sources of healthcare carbon emissions are energy consumption, medication, disposables and patient travel (Figure 2). Although we are a small medical specialty, ophthalmology contributes significantly to all these components. We have the highest surgical volumes in medicine and use energy-consuming operating rooms (ORs); we increasingly use single-use products; we prescribe large amounts of (single-dose) eye drops; and we invite many patients to our clinics.

**So, what can we do?**

**Air conditioning in the operating room**

Are the highest ventilation standards really necessary for small-incision eye surgery? In the Nether-
lands, the recommendation for the OR air ventilation system for cataract surgery is an air change rate of at least six times per hour. We should turn off the air conditioning when the OR is not in use. This may seem obvious, but it is not common practice in many hospitals.

Research shows that shutting down OR ventilation during off-duty periods does not appear to result in an unacceptably high particle count or microbial contamination of OR air, 30 minutes after the system is restarted. Using an Eco-mode in OR air conditioning will save not only greenhouse gas emissions, but also money.

A critical factor is the source of electricity. The air conditioning accounts for more than 90% of the total energy use of the OR, so it is paramount to choose a renewable energy source instead of fossil-based energy. We should push our hospital management to buy 100% green energy.

**Waste in cataract surgery**

One phaco procedure in the UK produces around 130 kg CO$_2$, equivalent to a car ride of 500 km. More than 50% of this is due to procurement. More recent data are not available, but the use of disposables has grown, adding to clinical waste production. Disposable instruments can account for 10–20 times as much waste as reusable items. All clinically contaminated waste must be incinerated or burned, which produces large amounts of greenhouse gases.

It is feasible to lower the carbon footprint of cataract surgery. This has been shown by the Aravind Eye Care System in southern India. Aravind performs around 1,000 surgeries per day. They generate 250 g waste and nearly 6 kg CO$_2$ equivalents in greenhouse gases per phacoemulsification (Figure 3).

This carbon footprint is approximately 5% of that in the UK, with comparable visual acuity outcomes. Many differences can account for this low carbon footprint, including efficient, high-volume logistics and the reuse of instruments, protective equipment and medicines.

These differences do not affect infection prevention. In fact, the endophthalmitis risk after a phaco in Aravind is 0.01%, which is lower than the 0.04% in the US. This fact can partly be explained by the standard...
dard use of intracameral moxifloxacin in Aravind. Ironically, this drug is not registered in the United States because of the lack of adequate randomised controlled trials.

Rigid adherence to single-use material creates an excessive amount of surgical waste at a high cost, with no proven benefit in postoperative endophthalmitis risk. Given the huge number of cataract operations worldwide, changes in the materials used will bring great environmental benefits.

In the past two decades, operating theatres have transformed into disposable theatres; in every surgical specialty the majority of what is used is disposable. The same holds for cataract surgery, where we have witnessed the transition to disposable I/A handpieces, disposable phaco-cartridges, disposable incision blades and preloaded IOLs.

Some colleagues argue that disposables are safer than reusables and should therefore be promoted. However, this claim has not been substantiated. The debate about disposable versus reusable surgical instruments should be settled by evidence. And the evidence shows that waste, greenhouse gas emissions and a shortage of commodities are a threat to future generations. As long as there is no evidence that disposable instruments are safer for our patients, their use should be discouraged, not promoted.

Recently, a large survey among more than 1,300 US cataract surgeons and nurses showed that 93% believe that operating room waste is excessive and should be reduced. More specifically, 78% believe that we should reuse more supplies and 87% want medical societies to advocate for reducing the surgical carbon footprint. Assuming comparable costs, 79% of surgeons preferred reusable over disposable instruments.

**Medication**

It is important to consider the “reduce-reuse-recycle” rationale for medication use in ophthalmology as well. Tauber et al. showed that in cataract surgery a lot of medication used pre- and intraoperatively is discarded. Discarded topical eye drops were the most costly, averaging 148 US dollars per case. Reasons for discarding these medications could be a lack of counselling for patients and lack of medication labelling, facility policies, and noncompliance with burdensome state requirements.

The largest component of pharmaceutical waste in the study of Tauber was antibiotic drops. As noted by the authors, given the lower rate of endophthalmitis after cataract surgery with the use of intracameral antibiotics, the use of antibiotic drops with cataract surgery is likely to decrease. One should consider whether postoperative antibiotic eyedrops are still necessary when perioperative intracameral antibiotics are used.

In many clinics it is policy to throw medication away after is has been opened for a single patient. But it is important to examine the justification of these policies.

Chambers showed that this justification is not scientifically based but rather a misinterpretation of the evidence. He explained that manufacturers of multiple-dose ophthalmic products are required (by the Federal Register) to use an antimicrobial preservative. This antimicrobial preservative minimises the chances of injury to the patient should a contamination event occur. This additional protection also enables the drug product to be admin-
istered to multiple different patients until the bottle’s stated expiration date. Every ophthalmologist should consider whether it is possible to reuse multi-dose medication.

**Transport**

The COVID-19 pandemic has shown that remote care of patients via telemedicine is possible.15 Telephone calls and video visits can be used to review test results, check on medication adherence or triage patients, and can replace check-ups for oculoplastic, neuro or paediatrics. Remote care can save greenhouse gas emissions.

Another lesson from the COVID-19 pandemic is that online meetings and conferences are feasible. Online meetings have pros and cons, but they certainly cause less greenhouse gas emissions than long-distance travel.16 So, why not stick to virtual international meetings?

Social interactions are undeniably important, but a national gathering to watch lectures and discussions abroad may be a reasonable alternative for many attendants.17 Thousands of ophthalmologists flying abroad to attend a medical congress is not sustainable and not justifiable in these times.

**In conclusion**

Healthcare professionals are continuously trying to improve the quality of care as well as keeping the healthcare system affordable and accessible for future generations. If we do not lower the carbon footprint of our clinical practices, we will compromise the healthcare systems of our children and grandchildren.

We should evaluate our own actions, both private and professional, and take into account their carbon footprints. Only by doing so do we act according to the oath we swore: primum non nocere (first do no harm).

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Very-high-frequency ultrasound improves ICL sizing precision

Advancements in imaging make ICL an effective option for patients

By Dr Brett H. Mueller

Implantable collamer lens (ICL) implantation is reversible, spares the cornea from permanent change, and expands the treatment range up to -20 D for patients with myopia and up to 6 D for those with astigmatic myopia. Additionally, ICL implantation can produce excellent outcomes: in United States Food and Drug Administration clinical trials of the Visian Toric ICL (STAAR Surgical) in patients with mean myopia of -9.37 D and mean astigmatism of +1.95 D, 82% of the eyes were 20/20 or better uncorrected, and 54% of the eyes were 20/16 or better uncorrected.

In a more recent retrospective study of my Visian Toric ICL patients, 87% of eyes achieved postoperative spherical equivalent of 0.5 D or less. These features and outcomes are among the reasons why I am an enthusiastic ICL devotee, and why I recommend these implantable lenses even to patients with low myopia, in contrast to many of my peers, who relegate them to patients who fall outside of approved LASIK parameters.

ICL sizing

Despite over a decade of excellent outcomes, the ICL adoption rate is not as robust as might be expected. Many consider lens sizing limitations to be among the factors responsible for under-utilisation. The most widely used ICL sizing method entails obtaining white-to-white (WTW) measurements and plugging the data into the Online Calculation and Ordering System. This combination results in the correct-size ICL in most cases, but it is also associated with rare, high-risk outlier outcomes.

Phakic lenses occupy the space between the posterior surface of the iris and the anterior surface of the crystalline lens. Because of the limited space here, and the need for aqueous humour to pass through, it is critical to measure this area accurately before surgery.

Precise sizing of the ICL is crucial because it affects the vault. Ideally, the size of the vault should be about 250–750 μm. If a vault is less than 250 μm, there is a risk of anterior subcapsular cataract formation. A vault greater than 750 μm risks pupillary block glaucoma and crowding of the angle, with possible iris chafing and resultant loss of pigment.

Very-high-frequency ultrasound

My practice is among the first in the US to adopt an innovative very-high-frequency ultrasound (VHFUS) device—the ArcScan Insight 100 (ArcScan)—that, among other things, improves the precision of ICL sizing. The device can image behind the iris, clearly visualising the sulcus (the space between the iris and the ciliary body).

Although traditional ultrasound

IN SHORT:

A very-high-frequency ultrasound device provides a range of detailed intraocular measurements that enable highly accurate ICL sizing and placement.
Biomicroscopy (UBM) can visualise this space as well, the Insight 100 obtains exceptional resolution and repeatability. The device maintains a consistent perpendicularity and distance from the eye with a robotically controlled 50 MHz ultrasound transducer and automatic focal depth settings. The Insight 100's measuring calipers are accurate to within 0.12 mm laterally behind the iris.

Each preoperative imaging scan set includes seven meridians to cover the desired area of the lens footplate location. In addition to determining the exact lateral space, the resulting images can be used to detect the presence of ciliary cysts or other pathologies, aiding surgical planning.

High-risk outcomes are rare in refractive surgery practices, but because of the sizing challenges and the unlikely—though possible—event of pupillary block glaucoma or cataract formation, the first 24 hours after ICL implantation can be stressful.

Surgeons like me, who perform a high volume of ICL procedures, have had the experience of implanting a lens that is too small or too large, then having to remove the lens or do an ICL exchange. The ArcScan system essentially eliminates that concern and enables me to offer this excellent refractive surgery option to my patients with a high degree of confidence in both its efficacy and its safety.

Eliminate outliers

As I mentioned, external ocular measurements are still the criteria most often used to determine ICL size. However, there are many more factors beyond WTW measurements that need to be considered. For instance, in addition to sulcus-to-sulcus measurements, the Insight 100 can measure anterior chamber depth; anterior chamber angle; angle-to-angle; anterior chamber width measured scleral spur to scleral spur; angle recess-to-angle recess lens rise; sulcus-to-sulcus; sulcus-to-sulcus lens rise; and ciliary body inner diameter.

The goal of these measurements is to reduce lens exchange to a very rare event. Once we secure the detailed intraocular measurements and input them into the ArcScan digital template, we upload the data to the London Vision Clinic free online ICL sizing calculator (www.iclsizing.com), which uses a dedicated nomogram to predict the vault for each ICL size.

This process has enabled us to eliminate the outliers. The nomogram factors in the inner ciliary body diameter, as well as the lens rise, the scotopic pupil size and the lens power. When we have those four measurements, we can reduce the scatter of the post-vault by a factor of four, according to Dr Dan Reinstein, who is responsible for the ICL sizing nomogram and much of the research behind the ophthalmic VHFUS measurement technology.

The Insight 100’s ICL sizing capability eliminates the risk of size-related complications by selecting a lens based on direct

**Figure 1.** The ArcScan Insight 100 can measure anterior chamber depth; anterior chamber angle; angle-to-angle; anterior chamber width measured scleral spur to scleral spur; angle recess-to-angle recess lens rise; sulcus-to-sulcus; sulcus-to-sulcus lens rise; and ciliary body inner diameter.
measurements of the posterior chamber. By producing VHFUS images instead of those captured by analogue UBM systems—or WTW measurements—accuracy is assured to within 1.0 μm at the cornea and 0.12 mm laterally behind the iris.

Retrospective study
We performed a retrospective study looking at our ICL patient cohort to assess the accuracy and predictability of utilising the Insight 100 in conjunction with the London guide available online. Analysis of the first 86 eyes of 160 ICL patients identified for this study revealed that we were able to get within 300 μm—half the thickness of a cornea—of the predicted ICL vault size 97% of the time with the ArcScan system.

Eliminating the outliers has enhanced our confidence in this procedure even further, and we believe that surgeons who have been on the fence about offering ICLs to their patients will be more likely to include these lenses in their armamentarium if concerns about high-risk outliers are eradicated. Surgeons will often use ICLs only if a patient is not a LASIK candidate, but we offer ICLs to any patient with myopia or astigmatic myopia who falls within the approved treatment parameters—even those who have lower prescriptions.

We are not afraid of encountering high-risk outcomes because we are confident about the accuracy and precision that we achieve with the Insight 100. Based on my experience with the ArcScan Insight 100, I believe that VHFUS will become the gold standard of ICL sizing. And with our ability to predict the ICL vault to this level of accuracy, I anticipate that there will be further adoption of ICLs by refractive surgeons.

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REFERENCES
The vast majority of patients undergoing cataract surgery today receive a monofocal intraocular lens (IOL), and results with these implants are excellent overall. However, there are many material and design issues that affect the intraoperative delivery and clinical performance of any IOL. Therefore, IOL manufacturers have continued to refine and update their technologies with the aim of improving surgical handling and clinical outcomes.

In 2016, Carl Zeiss Meditec AG (Jena, Germany) introduced the CT LUCIA 611P/PY IOL as a successor to the CT LUCIA 601P. The CT LUCIA 611P/PY retained all of the desirable material and optical characteristics of the previous lens but was designed with modifications to the optic-haptic junction to optimize centration and postoperative stability.

Specifically, the CT LUCIA 611P/PY IOL is a single-piece, hydrophobic acrylic monofocal lens with a heparin-coated surface that comes preloaded in the BLUEJECT™ injector (Carl Zeiss Meditec AG). The IOL features the patented ZO (ZEISS Optic) asphericity design (Carl Zeiss Meditec AG), also referred to as a non-constant aberration aspheric optic. This approach provides improved vision by more closely representing the optics of the human eye. Furthermore, the IOL has a 6.0 mm optic with a 360° square edge design that inhibits lens epithelial cell migration. Step-vaulted haptics of the CT LUCIA 611P/PY maximize optic contact with the capsular bag to further limit the development of posterior capsule opacification.

We have implanted the CT LUCIA 611P/PY over the past 4 years with excellent results, and it is our preferred monofocal IOL. However, we were interested in conducting a formal comparative study to document its handling and clinical outcomes. For this purpose, we chose to compare the CT LUCIA 611P/PY to another commonly used single-piece hydrophobic acrylic monofocal IOL, the TECNIS-1 ZCB00 (Johnson & Johnson Surgical Vision). We were particularly interested in evaluating our intraoperative experience with the two IOLs. We hypothesized we would find differences between the two IOLs associated with material differences and because the CT LUCIA 611 P/PY comes preloaded while the TECNIS-1 IOL must be manually folded and loaded into an injector system.

Clinical study design
Our IRB-approved clinical trial included the first eye of 100 patients representing two consecutive cohorts. The first 50 eyes received the CT LUCIA 611P/PY and the next group of 50 eyes were implanted with the TECNIS-1 IOL. Although patients enrolled in the study were not randomized to IOL assignment, the two study groups were well-matched with respect to age and preoperative biometric characteristics.

One surgeon (Dr. Sri Ganesh) performed all of the procedures using the same technique and phacoemulsification unit. A video shows implantation of the preloaded CT LUCIA 611P/PY (Figure 1). The TECNIS-1 IOL was delivered using the UNFOLDER Platinum 1 Series Screw-Style Inserter (Johnson & Johnson Surgical Vision). Emmetropia was the refractive target for all cases. Intraoperative evaluations included measurement of unfolding time. Difficulties with injection or other delivery complications were also noted. In addition, clinical outcomes were recorded at follow-up examinations scheduled at 1 day, 2 and 6 weeks, and 6 and 12 months after surgery.

Clinical study results
We found that the mean intraoperative unfolding time was significantly shorter (p< 0.00) for the CT LUCIA 611P/PY IOL compared to the TECNIS-1 (12.93 ± 3.80 vs 35.16 ± 10.50 seconds, respectively). Otherwise, all surgeries were completed uneventfully without complications.

No complications were encountered in either study group during follow-up to 1 year, and no eye needed Nd:YAG laser capsulotomy to treat PCO. Refractive
outcomes were excellent in both groups, and assessments of visual function and quality, including uncorrected and best corrected distance visual acuity, contrast sensitivity, Objective Scatter Index, and modulation transfer function, were similar in the two groups.

Mean total higher order aberrations, coma, and spherical aberration were also similar comparing eyes implanted with the CT LUCIA 611P/PY and TECNIS-1 IOLs. However, mean internal spherical aberration and internal coma values, which derive from the IOL, were significantly higher in the TECNIS-1 group.

Discussion
Comparison of the intraoperative handling of the CT LUCIA 611P/PY and TECNIS-1 IOLs was a focus of our study, and the results showed a benefit of the preloaded CT LUCIA 611 P/PY IOL for reducing unfolding time and problems with IOL delivery. Not only does the need for additional manipulation during implantation raise the possibility of causing IOL damage, but it can also increase the risk for additional complications, including damage to the capsular bag, that can compromise a successful outcome.

Cases of improper unfolding related to adhesion of the haptics to the optic have been described with acrylic IOLs and have been suggested to be related to insufficient OVD in the injector cartridge or improper IOL loading. Theoretically, differences in unfolding behavior between the two IOLs might also reflect differences in material and surface coating. Faster unfolding of the CT LUCIA 611P/PY relative to the TECNIS-1 may also be enabled by the higher glass transition temperature of the CT LUCIA’s hydrophobic acrylic material (13.8°C vs 11-12°C).

The findings in our study are consistent with those reported for the CT LUCIA 611P/PY by other cataract surgeons. In a study including 29 eyes followed up to 6 months after surgery, Stepanov et al. concluded that the CT LUCIA 611P/PY was safe and easy to implant. In addition, they found it had good in-the-bag centration and patients benefited with stable refractive outcomes and visual acuity. Borkenstein and Borkenstein reported outcomes for a series of 54 patients (96 eyes) followed for up to 1 year after implantation of the CT LUCIA 611P/PY. They also highlighted the IOLs centering in the bag and its positional and refractive stability along with an encouragingly low rate of PCO and attributed the performance of the CT LUCIA 611P/PY to the construction of its optic-haptic junction. In a separate study focusing on eyes with pseudoxfoliation syndrome that are at risk for IOL decentration, the same investigators again reported that the CT LUCIA 611P/PY had excellent refractive stability during follow-up of 10 months after cataract surgery.

Looking ahead
We have been very satisfied with the results achieved using the CT LUCIA 611P/PY. Consistent with its history of continually improving its surgical technology, Carl Zeiss Meditec AG more recently introduced the CT LUCIA 621P. Available in Europe since October 2020 and coming soon to the Asia-Pacific region, the CT LUCIA 621P comes preloaded in a new single-use injector system (BLEUESERTM), but the IOL itself is made of the same material as 611P/PY with same design features.

Trusted colleagues who have been implanting the CT LUCIA 621P are very enthusiastic about the performance of the new injector system. Because of their feedback and our experience with the CT LUCIA 611P/PY, we are now looking forward to implanting the CT LUCIA 621P that represents the next generation of a time-tested hydrophobic acrylic monofocal IOL platform.

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Dr. Brar and Dr. Ganesh are paid consultants to Carl Zeiss Meditec AG. The study described in this article was an investigator-initiated trial conducted by them independently.

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Novel gene therapy offers vision gains for X-linked RP
Sub-retinal injection of adeno-associated virus is showing promising results

By Lynda Charters; Reviewed by Dr Robert A. Sisk

AGTC-501 (Applied Genetic Technologies Corporation), a novel gene therapy in development for the potential treatment of X-linked retinitis pigmentosa (RP), has shown an acceptable safety profile and visual function improvements at higher doses, according to Dr Robert A. Sisk, director of paediatric vitreoretinal surgery and director of ophthalmic genetics at Cincinnati Children’s Hospital and the Cincinnati Eye Institute, Ohio, United States.

Patients with X-linked RP, an inherited retinal disease that begins in childhood, experience night blindness, progressive loss of peripheral vision and eventual loss of central vision. Affected patients currently have access to only one approved treatment, voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics), which represents about 1% of RP.

AGTC-501 trial
Dr Sisk outlined the safety and efficacy findings of a Phase 1/2 study of AGTC-501, a recombinant adeno-associated virus (AAV) 2 vector, for X-linked RP resulting from mutations in the RPGR gene, which accounts for 10% of RP cases. This study was a 12-month open-label, dose-escalation trial that included 29 male patients aged 6 years and older with the RPGR mutation.

All patients were treated with one sub-retinal injection in the study eye. The first nine patients received peripheral retinal injections as part of a safety assessment, which was the primary outcome, and the rest of the patients were treated centrally.

Dr Sisk stated that the safety assessment also included immunological responses to the AAV capsid and the RPGR proteins expressed. Key secondary outcomes included visual function, measured by microperimetry (Macular Integrity Assessment), and retinal structure status, seen on optical coherence tomography (OCT).

There were no serious adverse events related to the treatment. The initial surgical approach resulted in four peripheral retinal detachments related to dosing targeting the peripheral retina. The detachments did not occur when the central retina was targeted.

Grade 1 to 2 intraocular inflammation developed in about 20% (5/29) of patients, but all cases were reported as resolved. About one-third of the patients had intraocular pressure (IOP) elevations related to corticosteroid use, and all have resolved without IOP-related morbidities. The immunological results did not suggest safety concerns.

Regarding vision, in the 20 patients who received injections targeting the central retina, Dr Sisk noted that “the

IN SHORT:
An early-stage gene therapy study in patients with X-linked retinitis pigmentosa led to improvements in visual acuity, microperimetry sensitivity and foveal ellipsoidal zone status.
mean visual acuity improved about five letters compared with the untreated fellow eyes”.

Dr Sisk reported that the microperimetry sensitivity improved at Month 12 in all centrally dosed patients across the central 36 points, which corresponds to the most anatomically and functionally intact areas in the patient population. He also noted that the US Food and Drug Administration (FDA) has accepted a change of seven or more decibels in five or more loci in the central microperimetry as clinically meaningful.

During the course of the study, the investigators observed that patients without foveal ellipsoid zone (EZ) integrity before the treatment did not have improved microperimetry. When these patients were excluded from analysis, 50% of patients were responders to treatment. Another two patients also had significant improvements in microperimetry compared with the untreated fellow eye.

An analysis based on the status of the macular EZ showed that seven of the 20 patients who were centrally treated had no EZ before or after the AGTC-501 injection. In the 13 patients with a macular EZ at baseline, nine had recovery of the EZ 3–6 months after treatment, and six of the nine had an improved EZ at 12–18 months.

In the other four of the 13 eyes with a macular EZ, all had incomplete EZ recovery at 12 months. Dr Sisk reported positive associations between anatomical improvements in the EZ band and functional microperimetry sensitivities.

**Optimising outcomes**

In addition to avoiding treatment targeting the peripheral retina, patient selection is paramount to achieve the best results. “Advanced disease with absence of baseline microperimetry or a foveal EZ line precluded meaningful microperimetry or visual benefits,” Dr Sisk said.

Clinical trials of AGTC-501 for the potential treatment of X-linked RP are continuing. The Skyline trial is an expansion of this Phase 1/2 clinical trial, and the Vista trial is a Phase 2/3 safety and efficacy clinical trial.

“The 12-month results of the study of AGTC-501 to treat X-linked RP showed acceptable safety outcomes and vision and microperimetry improvements at higher doses,” Dr Sisk said. “In addition, we observed an encouraging anatomical correlate of EZ improvement.”

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This article is adapted from Dr Sisk’s presentation at the American Academy of Ophthalmology 2021 annual meeting, New Orleans, Louisiana, US. Dr Sisk is a consultant to AGTC.

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Angiogenesis, Exudation and Degeneration 2022: Spotlighting major advances in retinal diagnostics and therapies

By Lynda Charters

Many of the recent advances in retina have focused on getting to the root of the causes of visual degeneration in the major retinal diseases at the cellular level.

The Angiogenesis, Exudation and Degeneration 2022 virtual conference sponsored by the Bascom Palmer Eye Institute, Miami, Florida, United States, was at the forefront of this movement.

Presenters at the conference, a two-day event spanning 11 and 12 February, provided new evidence about detecting geography atrophy and wet and dry age-related macular degeneration (AMD) early and predicting disease progression. Investigators are also focused on finding cures for inherited retinal diseases.

Here are just a few of the groundbreaking technologies discussed at the conference.

**Disease detection/progression using optical coherence tomography**

OCT is an important tool for detecting AMD, and both its limitations and benefits were evaluated in disease diagnosis, patient management and progression. One example was the application of deep learning models for detecting AMD specific features and predicting progression to late-stage AMD. Dr Emily Chew reported that deep learning used to evaluate OCT images is highly accurate for predicting progression to the late disease stage in either neovascular disease or geographic atrophy (GA).

Swept-source OCT angiography (OCTA), Dr Seung-Young Yu reported, is valuable for staging diabetic retinopathy based on an optimal combination of nonperfusion areas seen on OCTA and the macular ganglion cell/inner plexiform layer thickness, which she described as a novel strategy.

**Current and new therapies**

Researchers reviewed the results achieved with the currently available anti-vascular endothelial growth factor (VEGF) therapies, those that are in the pipeline, and those that have been approved recently.

A sampling of these included an emerging therapy for nonexudative AMD, as reported by Dr David Boyer. This drug, Xiflam (InflammX Therapeutics), works by inhibiting connexin43, thus stopping the initiation of the inflammatory cascade in its tracks in AMD and diabetic retinopathy.

A second treatment, an investigational subretinal implant, the California Project to Cure Blindness Retinal Pigment Epithelium (CPCB-RPE1, Regenerative Patch Technologies), to treat advanced dry AMD, was associated with some increases in vision, as reported by Dr Amir Kashani.

Dr Glenn Jaffe reported on avacincaptad pegol (Zimura, Iveric Bio) in the GATHER1 trial. Results indicated that the 2-mg dose of the drug slowed growth of GA lesions secondary to AMD in the central area and fovea, as well as in each quadrant surrounding the central area.
GA, also studied in the DERBY and OAKS Phase 3 trials, was shown to respond to pegcetacoplan (Empaveli, Apellis Pharmaceuticals) administered monthly and every other month in the OAKS study and the drug was more efficacious in patients with baseline extrfoveal lesions. In the DERBY trial, the drug did not meet its primary endpoint, according to Dr David Lally.

The Phase 2 part A results of the KALAHARI Study found that THR-149 (Oxurion), a plasma kallikrein inhibitor, was safe and well tolerated when up to 3 injections were administered to patients with diabetic macular oedema (DMO), according to Dr Arshad M. Khanani. The high dose will move forward in trials.

The Phase 3 KESTREL and KITE studies evaluated brolucizumab for treating DMO. The 100-week results showed that the drug was comparable to results achieved with aflibercept (Eylea, Regeneron) with fewer injections needed with the 6-mg dose along with robust anatomic improvements, Dr Carl Regillo reported.

**Recent approvals**
The approval of the Port Delivery System (PDS) with ranibizumab (Susvimo, Roche/Genentech), caused excitement this year with its demonstrated positive results. Dr David Eichenbaum reported that device maintains the visual and anatomic outcomes over 3 years of treatment and beyond, and patients with neovascular AMD expressed a strong preference for implantation of the device over monthly anti-VEGF injections.

Another exciting advance was the approval of faricimab (Vabysmo, Genentech), reported by Dr Charles Wykoff. This treatment has the potential to have a three-pronged effect: inhibition of the disease processes of wet AMD and DMO, improvement of visual acuity (VA), and reduction of the patient treatment burden.

Dr Thomas Ciulla reported on the first drug approved for drug delivery into the suprachoroidal space. Xipere (triamcinolone acetone injectable suspension 40 mg/ml, Clearside) was approved to treat macular oedema, the first therapy for macular oedema associated with uveitis.

**Gene therapy**
Netherlands investigators led by Dr Carel Hoyng have gotten to the root cause of Stargardt disease with the development of an RNA therapy that can stop the progression of the disease. Antisense oligonucleotides, a new area of drug development, prevent the gradual decline in vision that characterises Stargardt disease by binding to the targeted RNA. These synthetic RNA molecules work to restore the proteins that are affected by the disease.

Another drug for Stargardt disease is tinlarebant (LBS-008, Belite Bio), a retinal binding protein 4 antagonist, was reported by Dr Quan Dong Nguyen to be safe and well tolerated in adolescent patients with Stargardt disease. In addition, patients for whom VA data were available had improvements ranging from 5 to 10 letters in at least one eye. The improvements were associated with reduced autofluorescence.

Scientists, clinicians and healthcare experts explored developing pharmacotherapies as well as best clinical practices for management of exudative diseases of the eye.

Visit the website to watch interviews with investigators as they discuss the findings presented at Angiogenesis.
Retinal microvascular changes may not predict short-term ischaemic insults

Study found no evidence for link between TIAs and changes in the eye

By Lynda Charters;
Reviewed by Dr Valérie Biousse

About a quarter to half a million people in the United States have a transient ischaemic attack (TIA) annually. Of these, approximately 10% are estimated to go on to have a stroke during the subsequent 90 days.

A cohort study was undertaken (FOTO-TIA) to determine whether retinal microvascular findings were helpful for predicting strokes and cardiovascular events in patients who presented with a suspected TIA. The first author of the study, Dr Valérie Biousse, professor of neuro-ophthalmology at the Emory Eye Center in Atlanta, Georgia, US, reported that the retinal changes seen in patients with suspected TIAs in the emergency department do not improve the ability to predict future ischaemic events (i.e., stroke and cardiovascular events) during the ensuing 90 days. This is despite the fact that retinal microvascular findings are independent risk factors that differentiate TIAs and strokes from mimics.

**Study outline**

Adults with a National Institutes of Health Stroke Scale score of three or less were admitted for observation to three emergency departments for an accelerated diagnostic protocol for a suspected TIA or stroke. Non-mydriatic fundus photographs were obtained prospectively for all patients and reviewed for retinal microvascular findings, which included retinal haemorrhages; cotton wool spots; retinal emboli/occlusions; hard exudates; or microaneurysms.

The investigators noted that, of the 395 study patients (median age 57 years; 55% women; 64% Black), 34 (9%) had retinal microvascular findings. A total of 154 patients completed the 90-day follow-up evaluation. Within this time frame, three (0.8%) of the 395 patients had a stroke, three (0.8%) had a recurrent TIA and none had a cardiovascular event.

“All the patients who had a stroke or recurrent TIA had an ABCD2 score over three, compared with 70% of the other patients ($P = 0.25$),” Dr Biousse said. (The ABCD2 score is a tool to improve the ability to predict the risk of short-term stroke after a TIA.) Importantly, none of the patients who had a stroke or recurrent TIA had microvascular findings, compared with the 9% of patients who already had microvascular findings ($P = 0.59$).

Non-mydriatic fundus photographs were reviewed for retinal microvascular findings.

The investigators concluded that this study did not show any evidence that retinal microvascular findings in patients with suspected TIA in the emergency department would improve the short-term predictability of future ischaemic events. They pointed out that the study was underpowered because the incidence of short-term stroke was much lower than they had anticipated. They credit this largely to the improved accelerated diagnostic protocol among the patients.

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This article is adapted from Dr Biousse’s presentation at the American Academy of Ophthalmology 2021 annual meeting in New Orleans, Louisiana, US. Dr Biousse has no financial interest in this subject matter.
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