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Ophthalmology Times EUROPE®

CUTTING-EDGE ADVANCEMENTS

OCTOBER 2020 VOL. 16, NO. 8

NOW IN A PRE-FILLED SYRINGE:

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Eylea®40 mg/ml solution for injection in a vial & Eylea®40 mg/ml solution for injection in pre-filled syringe (aflibercept) Prescribing Information.

(Refer to full Summary of Product Characteristics (SmPC) before prescribing).

Presentation: 1 ml solution for injection contains 40 mg aflibercept. *Vial:* Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. *Pre-filled syringe (PFS):* Each PFS contains 90 microlitres, equivalent to 3.6 mg aflibercept. **Indication(s):** Treatment of neovascular (wet) age-related macular degeneration (wAMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DMO) in adults and visual impairment due to myopic choroidal neovascularisation (myopic CNV). **Posology & method of administration:** For intravitreal injection only. Must be administered according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. Each vial or PFS should only be used for the treatment of a single eye. Extraction of multiple doses from a single vial or PFS may increase the risk of contamination and subsequent infection. The vial or PFS contains more than the recommended dose of 2 mg. The extractable volume of the vial (100 microlitres) or PFS (90 microlitres) is not to be used in total. The excess volume should be expelled before injecting. Refer to SmPC for full details. ***Adults:*** The recommended dose is 2 mg aflibercept, equivalent to 50 microlitres. For wAMD treatment is initiated with 1 injection per month for 3 consecutive doses. The treatment interval is then extended to 2 months. Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly to a minimum of 2 months during the first 12 months of treatment. There is no requirement for monitoring between injections. Based on the physician's judgement the schedule of monitoring visits may be more frequent than the injection visits. Treatment intervals greater than 4 months between injections have not been studied. For RVO (branch RVO or central RVO), after the initial injection, treatment is given monthly at intervals not shorter than 1 month. Discontinue if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. Treat monthly until maximum visual acuity and/or no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. Shorten treatment intervals if visual and/or anatomic outcomes deteriorate. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response. For DMO, initiate treatment with 1 injection/month for 5 consecutive doses, followed by 1 injection every 2 months. No requirement for monitoring between injections. After the first 12 months of treatment, and based on visual and/or anatomic outcomes, the treatment interval may be extended such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The schedule for monitoring should therefore be determined by the treating physician and may be more frequent than the schedule of injections. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, treatment should be discontinued. For myopic CNV, a single injection is to be administered. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease. The schedule for monitoring should be determined by the treating physician. The interval between 2 doses should not be shorter than 1 month. ***Hepatic and/or renal impairment:*** No specific studies have been conducted. Available data do not suggest a need for a dose adjustment. ***Elderly population:*** No special considerations are needed. Limited experience in those with DMO over 75 years old. ***Paediatric population:*** No data available. **Contraindications:** Hypersensitivity to active substance or any excipient; active or suspected ocular or periocular infection; active severe intraocular inflammation. **Warnings & precautions:** As with other intravitreal therapies endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract have been reported. Aseptic injection technique is essential. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients must report any symptoms of endophthalmitis or any of the above mentioned events without delay. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection; special precaution is needed in patients with poorly controlled glaucoma (do not inject while the intraocular pressure is ≥ 30 mmHg). Immediately after injection, monitor intraocular pressure and perfusion of optic nerve head and manage appropriately. There is a potential for immunogenicity as with other therapeutic proteins; patients should report any signs or symptoms of intraocular inflammation e.g pain, photophobia or redness, which may be a clinical sign of hypersensitivity. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors. Safety and efficacy of concurrent use in both eyes have not been systemically studied. No data is available on concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular). Caution in patients with risk factors for development of retinal pigment epithelial tears including large and/or high pigment epithelial retinal detachment. Withhold treatment in patients with: rhegmatogenous retinal detachment or stage 3 or 4 macular holes; with retinal break and do not resume treatment until the break is adequately repaired. Withhold treatment and do not resume before next scheduled treatment if there is: decrease in best-corrected visual acuity of ≥30 letters compared with the last assessment; central foveal subretinal haemorrhage, or haemorrhage ≥50%, of total lesion area. Do not treat in the 28 days prior to or following performed or planned intraocular surgery. Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection. In patients presenting with clinical signs of irreversible ischaemic visual function loss, aflibercept treatment is not recommended. Populations with limited data: There is limited experience in DMO due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections, concurrent eye conditions such as retinal detachment or macular hole, or in diabetic patients with uncontrolled hypertension. This lack of information should be considered when treating such patients. In myopic CNV there is no experience with Eylea in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions. **Interactions:** No available data. **Fertility, pregnancy & lactation:** Not recommended during pregnancy unless potential benefit outweighs potential risk to the foetus. No data available in pregnant women. Studies in animals have shown embryo-foetal toxicity. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last injection. Not recommended during breastfeeding. Excretion in human milk: unknown. Male and female fertility impairment seen in animal studies with high systemic exposure not expected after ocular administration with very low systemic exposure. **Effects on ability to drive and use machines:** Possible temporary visual disturbances. Patients should not drive or use machines if vision inadequate. **Undesirable effects:** *Very common:* Visual acuity reduced, conjunctival haemorrhage (wAMD phase III studies: increased incidence in patients receiving anti-thrombotic agents), eye pain. *Common:* retinal pigment epithelial tear (known to be associated with wAMD; observed in wAMD studies only), detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract (nuclear or subcapsular), corneal abrasion or erosion, increased intraocular pressure, blurred vision, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, increased lacrimation, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival or ocular hyperaemia. *Serious: cf. CI/W&P - in addition:* blindness, culture positive and culture negative endophthalmitis, cataract traumatic, transient increased intraocular pressure, vitreous detachment, retinal detachment or tear, hypersensitivity (during the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions), vitreous haemorrhage, cortical cataract, lenticular opacities, corneal epithelium defect/erosion, vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare, arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. As with all therapeutic proteins, there is a potential for immunogenicity. Consult the SmPC in relation to other side effects. **Overdose:** Monitor intraocular pressure and treat if required. **Incompatibilities:** Do not mix with other medicinal products. **Special Precautions for Storage:** Store in a refrigerator (2°C to 8°C). Do not freeze. Unopened vials and unopened syringe blisters may be stored at room temperature (below 25°C) for up to 24 hours before use. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** *Single vial or PFS pack:* £816.00 **MA Number(s):** EU/1/12/797/001-002. **Further information available from:** Bayer plc, 400 South Oak Way, Reading RG2 6AD, United Kingdom. Telephone: 0118 206 3000. **Date of preparation:** April 2020.

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Ophthalmology Times EUROPE

Glaucoma

Retina

Cornea

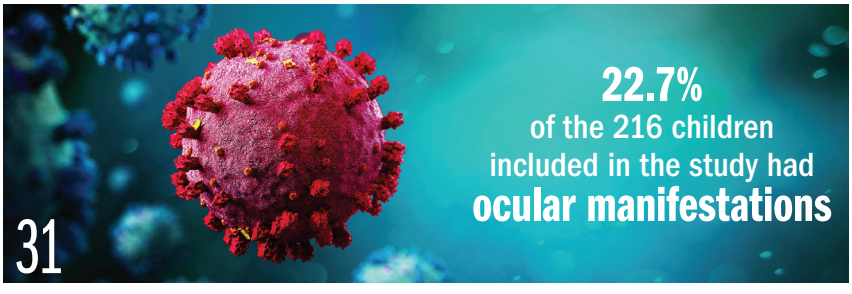
Paediatrics

Gene Therapy

Issue Feature

New Horizons in IOL Technology

Regulars



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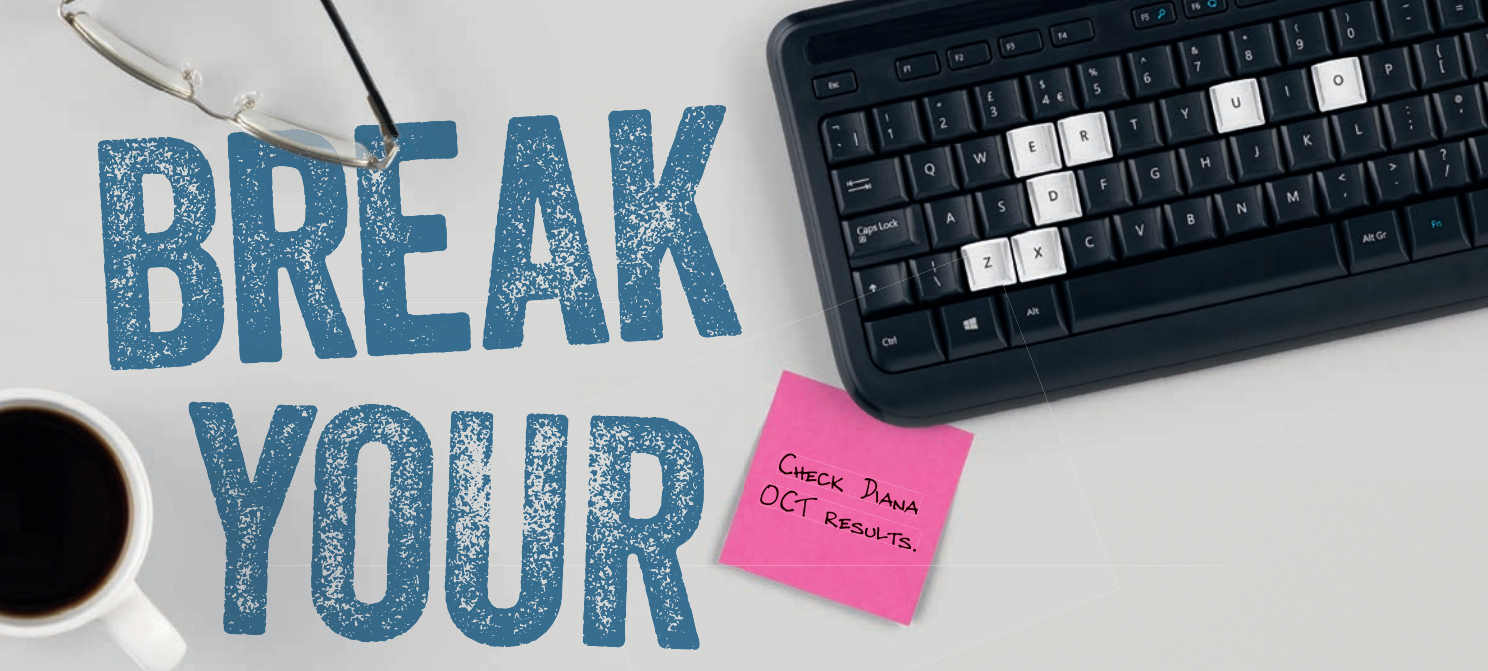

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DME, diabetic macular edema; OCT, optical coherence tomography. **1.** Nehmé A and Edelman J. Invest Ophthalmol Vis Sci 2008;49(5):2030–2038. **2.** Holekamp N. The role of corticosteroid implants in DME. Available at: http://retinatoday.com/2015/04/the-role-of-corticosteroid-implants-in-dme. Accessed March 2020. **3.** Campochiario PA *et al.* Am J Ophthalmol 2016;168:13–23. **4.** Malclès A *et al.* Retina 2017;37(4):753–760. **5.** Matonti F *et al.* Eur J Ophthamol 2016;26(5):454–459. **6.** Aknin I and Melki L. Ophthalmolgica 2016;235:187–188. **7.** Allergan. OZURDEX®. Summary of Product Characteristics. October 2019. **8.** Boyer SB *et al.* Ophthalmology 2014;121(10):1904–1914.

OZURDEX® (Dexamethasone 700 micrograms intravitreal implant in applicator) Abbreviated Prescribing Information

Presentation: Intravitreal implant in applicator. One implant contains 700 micrograms of dexamethasone. Disposable injection device, containing a rod-shaped implant which is not visible. The implant is approximately 0.46 mm in diameter and 6 mm in length. **Indications:** Treatment of adult patients: with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO), inflammation of the posterior segment of the eye presenting as non-infectious uveitis and visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. **Dosage and Administration:** Please refer to the Summary of Product Characteristics before prescribing for full information. OZURDEX must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended. Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk. Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated. In RVO and uveitis there is only very limited information on repeat dosing intervals less than 6 months. There is currently no experience of repeat administrations in posterior segment non-infectious uveitis or beyond 2 implants in Retinal Vein Occlusion. In DME there is no experience of repeat administration beyond 7 implants. Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Single-use intravitreal implant in applicator for intravitreal use only. The intravitreal injection procedure should be carried out under controlled aseptic conditions as described in the Summary of Product Characteristics. The patient should be instructed to self-administer broad spectrum antimicrobial drops daily for 3 days before and after each injection. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases. Advanced glaucoma which cannot be adequately controlled by medicinal products alone. Aphakic eyes with ruptured posterior lens capsule. Eyes with Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated intraocular lens and ruptured posterior lens capsule. **Warnings/Precautions:** Intravitreous injections, including OZURDEX can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aseptic injection techniques must always be used. Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay. All patients with posterior capsule tear, such as those with a posterior lens (e.g. due to cataract surgery), and/or those who have an iris opening to the vitreous cavity (e.g. due to iridectomy) with or without a history of vitrectomy, are at risk of implant migration into the anterior chamber. Implant migration to the anterior chamber may lead to corneal oedema. Persistent severe corneal oedema could progress to the need for corneal transplantation. Other than those patients contraindicated where OZURDEX should not be used, OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored to allow for early diagnosis and management of device migration. Use of corticosteroids, including OZURDEX, may induce cataracts (including posterior subcapsular cataracts), increased IOP, steroid induced glaucoma and may result in secondary ocular infections. The rise in IOP is normally manageable with IOP lowering medication. Corticosteroids should be used cautiously in patients with a history of *ocular herpes simplex* and not be used in active *ocular herpes simplex*. OZURDEX is not recommended in patients with macular oedema secondary to RVO with significant retinal ischemia. OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products. 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 other visual disturbances, consider evaluating for possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids. **Interactions:** No interaction studies have been performed. Systemic absorption is minimal and no interactions are anticipated. **Pregnancy:** There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus. **Lactation:** Dexamethasone is excreted in breast 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 Machines:** Patients may experience temporarily reduced vision after receiving OZURDEX by intravitreal injection. They should not drive or use machines until this has resolved. **Adverse Effects:** In clinical trials the most frequently reported adverse events were increased intraocular pressure (IOP), cataract and conjunctival haemorrhage*. Increased IOP with OZURDEX peaked at day 60 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 DME and 3/421 in RVO) had surgical procedures in the study eye for the treatment of IOP elevation. The following adverse events were reported: Very Common (≥ 1/10): IOP increased, cataract, conjunctival haemorrhage*. Common (≥1/100 to <1/10): headache, ocular hypertension, cataract subcapsular, vitreous haemorrhage*, visual acuity reduced*, visual impairment/disturbance, vitreous detachment*, vitreous floaters*, vitreous opacities*, blepharitis, eye pain*, photopsia*, conjunctival oedema*, conjunctival hyperaemia. Uncommon (≥1/1,000 to <1/100): migraine, necrotizing retinitis, endophthalmitis*, glaucoma, retinal detachment*, retinal tear*, hypotony of the eye*, anterior chamber inflammation*, anterior chamber cells/flares*, abnormal sensation in eye*, eyelids pruritus, scleral hyperaemia*, device dislocation* (migration of implant) with or without corneal oedema , complication of device insertion resulting in ocular tissue injury* (implant misplacement). (*Adverse reactions considered to be related to the intravitreous injection procedure rather than the dexamethasone implant). Please refer to Summary of Product Characteristics for full information on side effects. **Basic NHS Price:** £870 (ex VAT) per pack containing 1 implant. **Marketing Authorisation Number:** EU/1/10/638/001. **Marketing Authorisation Holder:** Allergan Pharmaceuticals Ireland, Castlebar Road, Westport, Co. Mayo, Ireland. **Legal Category:** POM. **Date of Preparation:** May 2019. UK/0288/2019

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ Adverse events should also be reported to Allergan Ltd. UK_Medinfo@allergan.com or 01628 494026

License and adverse events reporting may vary by country, please consult your local Summary of Product Characteristics. Date of preparation: March 2020 INT-OZU-2050058

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OCTOBER 2020 | Volume 16 Number 8
Ophthalmology Times EUROPE®

Autumn heralds a new season for ophthalmic innovation

***Mike Hennessy Sr**, Chairman/founder of* Ophthalmology Times Europe®*'s parent company, MJH Life Sciences*

The seasons may come and go, but one thing readers can count on from *Ophthalmology Times Europe*® is continued coverage of this month's virtual congresses of EURETINA and the European Society of Cataract and Refractive Surgeons (ESCRS). Be sure to watch our newsletter and website for updates.

In this month's issue feature, we begin with a look at new horizons in IOL technology. Prof. Ahmed Assaf speaks to the role of astigmatism in cataract surgery outcomes with premium IOLs. Calculating rather than predicting total corneal astigmatism gives a better outcome, he explains.

Next, Prof. Jorge Alió and Dr Piotr Kanclerz propose an alternative terminology as clarification of the current nomenclature for extended depth-of-field (EDOF) IOLs. It is important to differentiate between pure EDOF IOLs and hybrid multifocal-EDOF IOLs, they suggest. Dr Alice T. Epitropoulos highlights 1 month of postoperative follow-up in 40 eyes implanted with a spherical aberration-neutral monofocal toric IOL. The results show good refractive predictability, rotational stability and visual acuity outcomes consistent with the conclusion that the lens provides good depth of focus with excellent quality vision.

Turning to glaucoma and the use of optical coherence tomography angiography (OCTA), the jury may still be out. OCTA has become indispensable for managing macular degeneration and diabetic retinopathy, Dr Robert L. Stamper explains, and must become more sophisticated and evolved before it reaches its full potential for glaucoma specialists. Considering that blood vessels are the first severely affected structures in glaucomatous eyes, the hope is that OCTA might have better diagnostic sensitivity compared with standard OCT, he says.

We also hear from Dr Gaurang Patel, who discusses how IOP homeostasis could be a key to understanding the causes of glaucoma. New research is looking past just regulating the IOP and using gene therapy to help patients. Single-cell RNA sequencing reveals 12 cell types in trabecular meshwork.

In retina and our cover story, advances continue to transform the specialty. Drs Roberto Pinelli, Miorica Bertelli and Elena Scaffidi discuss harnessing the power of light in dry age-related macular degeneration (AMD). Photobiomodulation has been demonstrated to improve quality of vision in several patients suffering from dry AMD.

After a team of researchers at the University College London (UCL) Institute of Ophthalmology, London, started to explore the causes of malformed blood vessels in the eye, they discovered that a molecule called LRG1 (leucine-rich alpha-2-glycoprotein 1) was partly responsible. The team is now collaborating with Moorfields Eye Hospital, London, with the aim of moving toward clinical testing of new therapies that could improve disease outcomes in patients with a range of disorders including wet AMD, diabetes and cancer. Editor Caroline Richards speaks with Professors John Greenwood and Stephen Moss, who led the team at UCL, to find out more.

In cornea, Mr Richard Teofilo Atallah and Dr Richard D. Najac discuss the US debut of a topical antihistamine for allergic conjunctivitis, the first new therapy in nearly a decade, while Dr Caroline W. Wilson shares how researchers are looking for options to reduce corneal surface flora before and after surgery.

Focusing on the youngest of ophthalmologists' patients, a retrospective cross-sectional study conducted at Wuhan Children's Hospital in Wuhan, China, where the pandemic of the coronavirus disease 2019 (COVID-19) originated, found that children hospitalised with the virus presented with a series of onset symptoms that included fever, cough and conjunctival discharge, as well as eye rubbing and conjunctival congestion. Data could help to guide prevention and management of ocular disorders in children with COVID-19, researchers say.

We close out this October issue with an update on gene therapy. Dr Christopher D. Riemann shares how stem cells for dry AMD with geographic atrophy (GA) show promise in an early clinical study.

Please continue to stay safe and healthy this autumn.

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The role of astigmatism in cataract surgery outcomes with premium IOLs

Calculating rather than predicting total corneal astigmatism gives a better outcome

By Prof. Ahmed Assaf


Prof. Assaf

Patients judge the success of modern cataract and refractive surgery by the degree of spectacle independence they achieve. Distance vision after cataract surgery is taken for granted, so patients are usually disappointed when they need glasses for driving and watching TV.

The need for glasses after cataract surgery is often due to a residual refractive error, including spherical and astigmatic errors. However, accurate biometry with modern optical biometers can negate spherical errors. Astigmatism, mainly corneal in origin, is a common refractive error in the cataract age group.

Prior to surgery, corneal astigmatism of more than 0.75 D and of at least 1 D is found in 23.9% and 41.2% of patients, respectively.[1] Astigmatism can be addressed at the time of cataract surgery by toric IOL implantation or astigmatic keratotomies.

Effect of astigmatism on IOLs

Patients are also starting to request adequate intermediate and near vision without glasses after cataract surgery. Several presbyopia-correcting premium IOLs are available to address this issue. However, astigmatism greatly influences the function of these lenses and may result in patient dissatisfaction.[2,3]

Astigmatism reduces quality of vision, whether the patient receives a monofocal or a multifocal lens. In one study comparing the effect of astigmatism on the visual function of both types of IOLs—with astigmatism of 1.50 D or more—the corrected distance visual acuity and the distance-corrected intermediate visual acuity at 0.5 m were significantly worse in the multifocal IOL group than in the monofocal IOL group.[4]

The appropriate cut-off postoperative astigmatism to achieve optimal visual function is considered to be 0.5 D or less. Nevertheless, subjective perception of halos and glare after multifocal IOL implantation is correlated with the amount of postoperative residual astigmatism.[4]

If residual astigmatism is between 0.25 and 0.75 D—less than 1 D—the patient is usually satisfied and the quality of vision is not disturbed. However, if the astigmatism is beyond 0.75 D, the quality of vision is significantly decreased.

Residual astigmatism following cataract surgery

One of the leading causes of residual astigmatism after cataract surgery is the inaccurate preoperative measurement of corneal astigmatism. Most Placido topographers and keratometers measure corneal astigmatism based on anterior corneal radius measurements and assume that the posterior corneal surface has a fixed ratio of 82.2% to the anterior corneal surface.[5,6]

> Subjective perception of halos and glare after multifocal IOL implantation is correlated with the amount of postoperative residual astigmatism.

However, the principal planes of the anterior and posterior surfaces differ from one another, even in normal eyes. Furthermore, the posterior corneal surface might contribute to total corneal astigmatism, or total keratometry (TK), more than we thought.

The contribution of posterior corneal astigmatism to TK was explored by Koch et al. in 2012.[7] They showed continuous drift of the steep meridian on the anterior corneal surface from vertical to horizontal

IN SHORT

- ***The possibility of taking precise measurements of total corneal astigmatism enables more patients to be spectacle-free following cataract surgery.***

with increasing age, whereas the steep meridian on the posterior corneal surface remains substantially vertical and stable with age.

The magnitude of posterior corneal astigmatism showed no or weak correlation to the anterior corneal astigmatism if the axis on the anterior surface was oblique or horizontal. They concluded that anterior and posterior corneal astigmatisms are not necessarily correlated, and that posterior corneal astigmatism might alter the magnitude and axis of the TK astigmatism.

For accurate preoperative measurement of corneal astigmatism, it is essential to take posterior corneal astigmatism into account. Modern toric IOL calculators empirically predict this for more precise postoperative results. However, precision is achieved by measuring, not predicting.

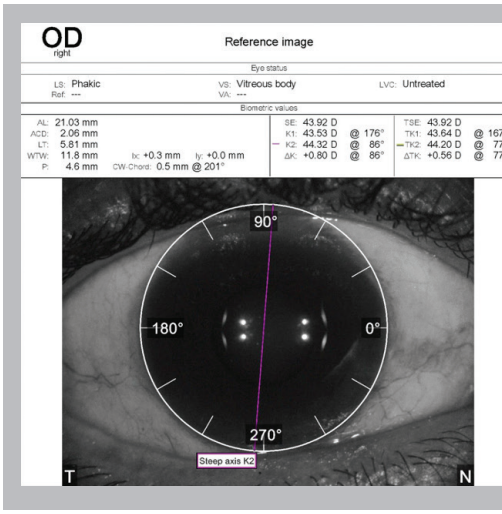
Measuring posterior corneal astigmatism

Tomography devices based on Scheimpflug images can measure posterior corneal astigmatism with moderate accuracy. Given that measurements must be converted to equivalent standard keratometry readings before using a biometry formula, it seems to be impractical for everyday refractive/cataract surgery.[5,6] I primarily rely on swept-source optical coherence tomography (OCT) biometry (IOLMaster 700; Carl Zeiss Meditec AG) because it allows for accurate measurement of corneal astigmatism on both the anterior and posterior surfaces.

This technology measures the curvature of the anterior corneal surface followed by corneal thickness: by fitting this measurement to the anterior corneal curvature, the posterior corneal curvature can be accurately calculated. Calibration is then applied to these posterior corneal surface curvature values to ensure that TK is compatible with the existing IOL power calculation formula and constants.[8]

Clinical case study

A 57-year-old man with astigmatism requested a presbyopia-correcting IOL. His delta K was +0.80 D, beyond the 0.75 D cut-off threshold noted on the previous page (see Figure 1). This amount of astigmatism needs to be corrected prior to implanting a multifocal premium IOL to obtain spectacle independence for distance and for near vision; based on this delta K, I should implant a multifocal toric IOL.



(FIGURE 1)
Clinical case study of a 57-year-old man with astigmatism who requested a presbyopia-correcting IOL.
(Photo courtesy of Dr Assaf)

However, if I consider the posterior corneal measurement, I can see that just to the right of this number, the delta TK is 0.56 D. In this case, the true amount of corneal astigmatism was less than expected when we measured the anterior corneal surface only. The delta K of 0.80 is not the true number; the true delta TK is 0.56 D.

Thus, I can implant a presbyopia-correcting IOL knowing that it will not interfere with the quality of vision of this patient's eye. There is no harm in leaving this amount of astigmatism because it is very low and will not affect visual quality with the presbyopia-correcting lens.

Conclusion

Now that we have devices that calculate total corneal astigmatism, cataract and refractive surgeons can make more precise measurements, which translates to more patients who have spectacle independence and better vision because we are targeting emmetropia closely. All in all, astigmatism should be measured, not predicted.

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Extended depth-of-field IOLs: Clarification of current nomenclature

It is important to differentiate between pure EDOF IOLs and hybrid MF-EDOF IOLs

By Prof. Jorge Alió and Dr Piotr Kanclerz


Prof. Alió

The increase in life expectancies and lifestyle changes have resulted in an increasing number of patients requesting spectacle-independent near and intermediate vision for their daily activities, aside from excellent distance vision. Presbyopia-correcting IOLs are also a treatment option for presbyopic patients who are not candidates for laser refractive surgery and do not want to rely on reading glasses. Over recent years, a wide spectrum of multifocal (MF) IOLs has been developed.

Presbyopia-correcting IOLs can be divided into three broad categories: MF IOLs (including diffractive or refractive designs), extended depth-of-focus (EDOF) IOLs and accommodative IOLs (intracapsular or sulcus placed).[1] EDOF IOLs, or extended range-of-vision IOLs, are a relatively new technology in the treatment of presbyopia.

The basic optical principle is to create a single-elongated focal point to enhance the depth of focus, on the contrary to monofocal IOLs (in which light is focused on one single point) or MF IOLs (which has two or three discrete points). The idea of EDOF is not new.

Over 30 years ago, Nakazawa and Ohtsuki reported apparent accommodation in 39 eyes implanted with spherical IOLs.[2] The authors found that the depth of field in these cases was inversely proportional to the pupillary diameter. Since then, several optical strategies have been used to extend the depth of focus at both the cornea and lens plane.

However, the term EDOF should be limited to those IOLs in which a manipulation has been made in their aberrometry profile to enlarge the depth of field. Those IOLs which have a MF design and, on top of it, also offer a manipulated aberrometry optical profile, should be called 'hybrid EDOF IOLs'.

The first so-called EDOF IOL, which is really a hybrid EDOF (Tecnis Symfony, Johnson and Johnson Vision) was introduced into the European market in June 2014 and subsequently approved for use in the United States in 2016.[3] Since then, several EDOF-labelled IOLs, many of them not really based on the EDOF principle, have been released.

Optical models employed

Spherical aberration (SA) is associated with focal length difference between the central and marginal ray where the light enters in the lens (Figure 1A). For any given eye, the Zernike coefficients may vary widely, but a mean value of corneal spherical aberration is $+0.31 \pm 0.135$ µm for a 6-mm pupil size.[4]

It was shown that aspheric IOLs which effectively reduce spherical aberration improve the optical quality over spherical IOLs.[5] On the other hand, higher positive SA in eyes having received an aberration-free IOL results in a better distance-corrected near visual acuity than that following implantation of negative-SA IOLs (that have reduced corneal SA).[6] Similarly, intentional induction of SA within the IOL design can increase the depth of focus.

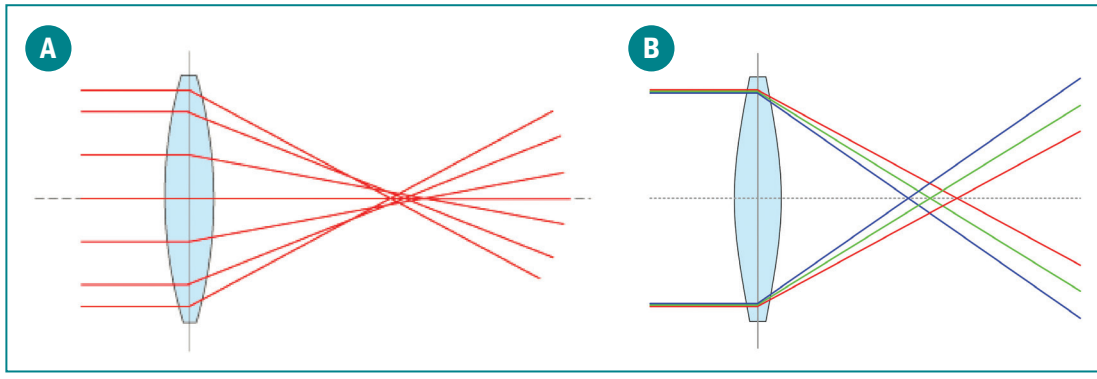
Chromatic aberrations (CAs) are associated with focal length difference between the visible spectrum of different colours of light (Figure 1B). The human cornea produces a CA, in which blue light is diffracted more than red light.

The optical design also has an impact: a refractive optic maintains the same CA of the cornea, so with this lens the final ocular CA will increase, as will the dispersion of the wavelengths. On the contrary, diffractive IOLs can reverse CA: red blends more than blue.

So, diffractive IOLs can minimise the CA in every eye. Achromatisation does not bring an extended depth-of-field improvement but rather an improvement in the contrast sensitivity function;[7] thus, diffractive could lead to an improvement of the

IN SHORT

- ***Clinicians and surgeons should be aware of the misleading use of the EDOF concept. The authors herein propose an alternative terminology and that lenses which have combined optical designs are referred to as 'hybrid IOLs'.***



(FIGURE 1) Spherical (A) vs. chromatic (B) aberrations. *(Reproduced with permission from https://commons.wikimedia.org/wiki/File:Lens-sphericalaberration.png and https://commons.wikimedia.org/wiki/File:Chromatic_aberration_convex.svg, CC licence.)*

contrast sensitivity and the quality of vision.[8]

The pinhole effect is another concept which allows a greater depth-of-focus to be obtained. In general, it could be stated that the smaller the pupil size, the greater the depth of field (and depth of focus).[9] Following this principle, the use of an opaque pinhole mask in a monofocal IOL enhances the depth of focus.

Moreover, the Stiles-Crawford effect could be additionally possible; it is believed that when an equal intensity of light enters near the centre of the pupil, it produces a greater photoreceptor response compared with the light entering the eye near the edge of the pupil.[10]

Confusion in the current nomenclature

EDOF IOLs provide a continuous range of focus without a clearly asymmetric IOL power distribution. This elongated focus is introduced to eliminate the overlapping of near and far images caused by traditional multifocal IOLs and the halo effect; ideally EDOF IOLs should enhance intermediate and near visual performance, while minimally affecting distance vision. In this way, EDOF IOLs differ from multifocal IOLs, in which the secondary out-of-focus images correspond to the additional foci and might induce halos.

Today, there is a relevant interest in the new models of presbyopic IOLs; several IOLs are marketed as EDOF IOLs. We encounter a confusion in the terminology; some of the so-called EDOF lenses are really MF lenses with low near-add power, in which part of the additional optical power has been withdrawn to avoid the overlapping of images and the consequent halos and glare.

We believe that it is necessary to clarify the current nomenclature and differentiate two types of EDOF IOLs: pure EDOF IOLs and hybrid MF-EDOF IOLs (Figure 2).[11] Pure EDOF IOLs are based on the spherical aberration-based optics or the pinhole effect, but have no multifocality.

The trade-off of inducing certain amounts of ocular aberrations is the potential degradation of quality of vision. This also limits their performance; their near vision capability is usually limited to about 1 dioptre.[12]

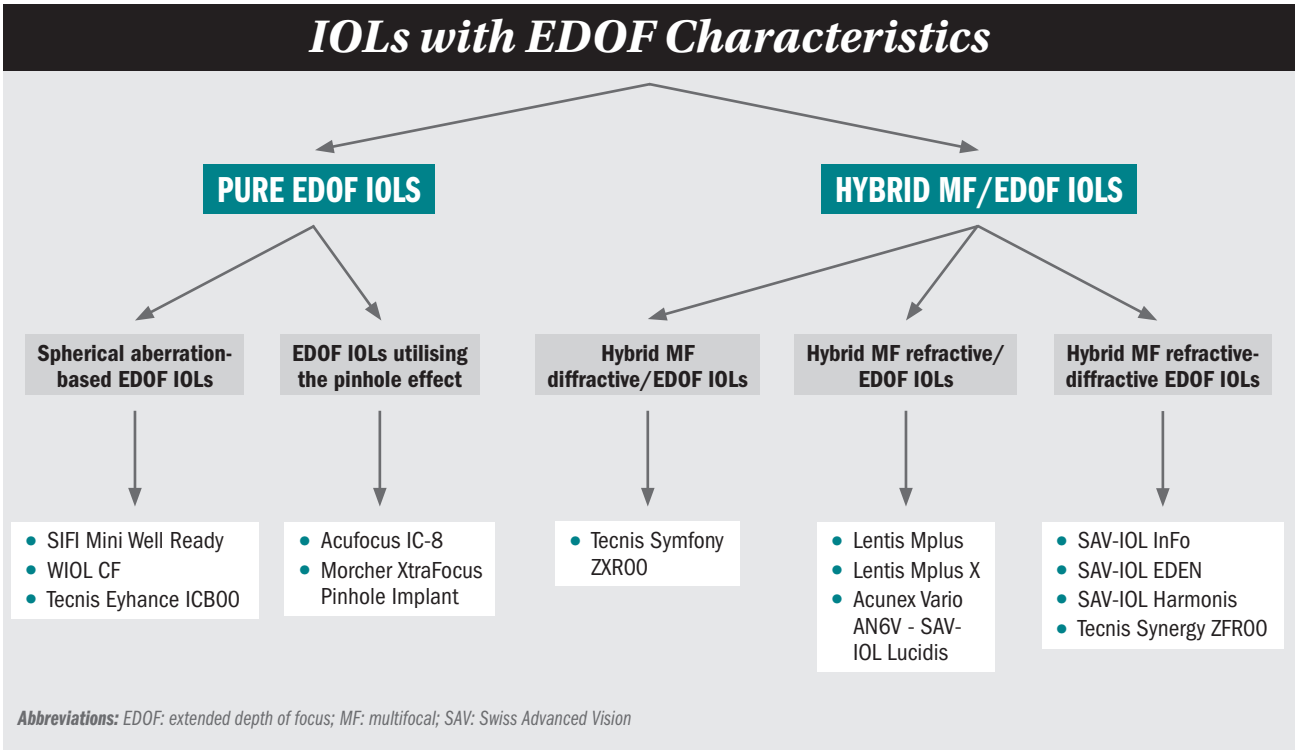
Those IOLs that have attempted to provide more are either no longer on the market, no longer available because the originator company has closed or they have produced very bad results. The reason for the latter is that for the first time we are able to see the retinal image quality with pyramidal aberrometry and the results are very different.

On the other hand, multifocality and EDOF characteristics are not exclusive of each other. A bifocal IOL may exhibit EDOF characteristics, likewise with an aspheric monofocal IOL or even a diffractive or refractive trifocal IOL. For example, the Tecnis Symfony is an IOL which combines an EDOF with multifocality. We propose naming such lenses 'hybrid MF-EDOF IOLs' (Figure 2).

> Those IOLs which have a MF design and, on top of it, also offer a manipulated aberrometry optical profile, should be called 'hybrid EDOF IOLs.'

To name a lens a pure EDOF IOL, the optical profile has to be continuous, without a change in the optical transition of the optical profile. This rule is equal for both the refractive and diffractive MF IOL models. All the lenses that employ correction of CAs, have a diffractive/diffractive-hybrid profile or an additional power to increase the near vision are not pure EDOF IOLs.

Hybrid MF-EDOF IOLs include diffractive-EDOF IOLs, refractive-



(FIGURE 2) Classification of IOLs having EDOF characteristics. *(Figure courtesy of Prof. Jorge L. Alió and Dr Piotr Kanclerz)*

EDOF IOLs and diffractive-refractive-EDOF IOLs. Some IOLs named as 'EDOF' are really only MF lenses with a low near-vision add and no EDOF component (an example of this confusing commercial terminology is the Zeiss LARA, whose neutral asphericity makes it a low-near vision add multifocal rather than an EDOF).

Optical bench reports and clinical outcomes

Several optical bench reports have shown that the EDOF lenses provide better optical quality on the whole addition range than MF and monofocal lenses. Nevertheless, assessment of the quality of vision and optical/refractive performance of EDOF IOLs can be challenging due to the wide array of procedures available for evaluation of these lenses.

In some cases, even if the optical laboratory benchmark study showed that an IOL has supreme optical properties, the results were not always correlated with patient satisfaction and spectacle independence in clinical trials. For example, the initial results of the WIOL-CF performance were presented in an observational study made by a Czech research group; they indicated excellent visual acuity for far and intermediate vision, and reasonably good near vision with minimal optical phenomena.[13]

Although the preliminary data were encouraging, recent investigations revealed a high rate of poor vision quality and a consistent pattern of spontaneous dislocation of the lens. The lens was withdrawn from the market and the company ceased commercial activities in October 2018.

For several other IOL types, the currently available clinical evidence is limited. The 2017 American Academy of Ophthalmology Task Force consensus statement on EDOF lenses requires:

1. A minimum of 100 patients with EDOF lenses;
2. Depth of focus defined as the interval of nonpositive defocus values with a mean visual acuity of at least 0.2 logMAR; and
3. A depth of focus set at least 0.5 D wider than for the monofocal control group at 0.2 logMAR.[14]

However, none of the currently published studies fulfills all the aforementioned requirements.

In practice, EDOF lenses provide excellent intermediate vision, but inadequate quality of vision for near distance.[12,15] We believe EDOF lenses should be used as monofocal lenses with a minor improvement for near vision; they can be expected to provide bad quality of near vision, while intermediate vision can be adequate.[12]

One of the ways to compensate the insufficiency in near visual acuity in patients with EDOF lenses is mini-monovision, or mix-and-match strategies with diffractive low-add lenses; nevertheless, using the mini-monovision may cause a decrease in far vision and additional halos from the low myopia in

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the contralateral eye.[16] If a patient requires good near vision with an IOL, we believe that they should receive a MF lens (a refractive and diffractive model) making the choice dependent on the patient profile and preferences.

It is not an easy task to make the IOL choice and this is why objective information based on aberrometer internal component information should be required. It is also important to develop a standardised objective means of measuring and reporting visual and refractive outcomes with these lenses, as a guide for clinicians in the future.

Neuroadaptation is a major concern in MF or EDOF IOLs; this process is time consuming and dependent on individual factors (of which some are unknown).[17] Pure EDOF lenses with a relevant amount of aberrations to improve near vision may be poorly tolerated by the patient, since although the brain is adapted up to a certain amount of aberrations over time, a sudden increase in aberrations may be problematic. Regarding photic phenomena the evidence is scarce, however, some studies have reported a lower intensity of photic phenomena in EDOF IOLs when compared with MF IOLs.[18]

Conclusion

There is a wide range of IOLs available on the market. A careful and thorough patient examination, taking into account IOL selection based on lifestyle and visual needs, is essential to avoid patient misunderstandings about the expected outcomes. In our recent article,[11] there is a biased used of the term EDOF, as some of the IOLs marketed with this name are only MF or hybrid MF/EDOF lenses.

We propose an alternative terminology and naming lenses that have combined optical designs as 'hybrid IOLs'. Clinicians and surgeons should be aware of this misleading use of the EDOF concept.

Future research will continue towards finding a balance between quality of vision, extended depth of focus and dysphotopsias. Counselling and advice is needed in order to ensure satisfactory outcomes – both for the patient and the surgeon.

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Spherical, monofocal IOL is offering treatment options for ophthalmologists

Lens delivers effective astigmatic correction and more, study results show

By Cheryl Guttman Krader;

Reviewed by Dr Alice T. Epitropoulos

Early real-world experience with the spherical aberration-neutral monofocal toric IOL enVista MX60T (Bausch + Lomb) shows that it delivers predictable, stable correction of refractive astigmatism. It also provides an improved range of vision with excellent image quality, according to Dr Alice T. Epitropoulos, clinical professor of ophthalmology at The Ohio State University Wexner Medical Center in Columbus, Ohio, United States.

In a presentation at the American Society of Cataract and Refractive Surgery 2020 virtual annual meeting in May, Dr Epitropoulos reported outcomes achieved in 40 consecutive eyes of 33 patients implanted with the SA neutral monofocal toric IOL. Thirty-one eyes were targeted for distance (77.5%) and the refractive target in nine eyes was for monovision (22.5%).

> Despite having an essentially plano refraction postoperatively, patients who were targeted for distance had a surprising amount of intermediate and near vision with this monofocal lens.
>
> – Dr Alice T. Epitropoulos

At 1 month post-surgery, manifest refraction spherical equivalent (MRSE) was about 0.5 D target in 93% of eyes targeted for distance and 78% of those targeted for monovision. Results from functional testing showed that 77% of eyes had uncorrected visual acuity (UCVA) of 20/30 or better at distance and intermediate, and J3 or better at near.

"It is interesting that, despite having an essentially plano refraction postoperatively, patients who were targeted for distance had a surprising amount of intermediate and near vision with this monofocal lens. It is also worth noting that quite a few of the eyes in this series had either a history of refractive surgery or ocular comorbidities," said Dr Epitropoulos, who also works in private practice at Ophthalmic Surgeons and Consultants of Ohio in Columbus.

"It seems that by preserving the cornea's natural positive corneal SA because of its zero SA aspheric optic, the enVista toric IOL can give patients the best of both worlds in terms of good depth of focus and sharper quality of vision," Dr Epitropoulos said.

Study results

Seven of the patients in the series underwent bilateral surgery. Dr Epitropoulos performed all the procedures. She noted that surgery was delayed for several patients while they were treated for existing ocular surface disease so that reliable topography and keratometry measurements could be obtained for surgical planning.

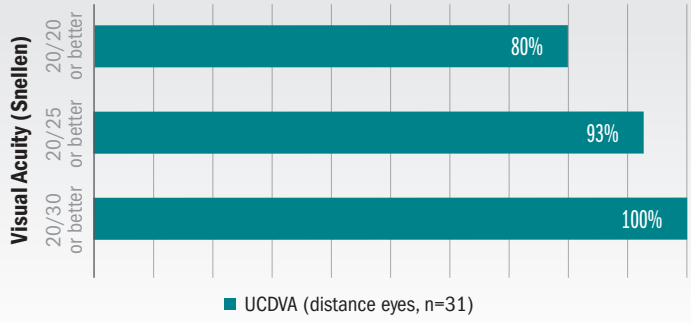
IOL power calculations were performed using the Barrett Universal II (90%) or SRK-T (10%) formulas. Cylinder power (IOL plane) ranged from 1.25 to 5 D (mean 2.06) and was calculated based on the enVista toric calculator.

At 1 month postoperatively, mean MRSE was reduced from -1.41 D preoperatively to -0.44 D and average cylinder was reduced from 1.22 D preoperatively to 0.19 D. MRSE averaged -0.26 D (mean targeted MRSE -0.4D) among eyes targeted for distance and -1.03 D (mean targeted MRSE –1.43D) for the monovision eyes.

IN SHORT

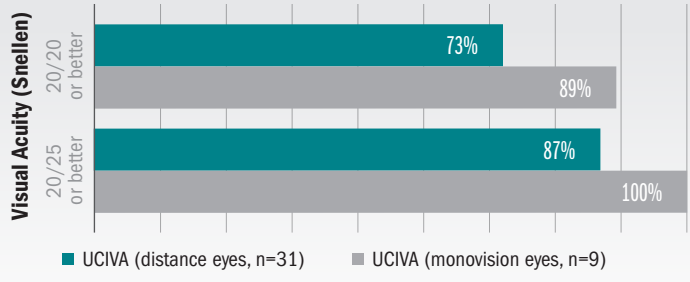
- ***Results from 1 month of postoperative follow-up in 40 eyes implanted with a spherical aberration-neutral monofocal toric IOL show good refractive predictability, rotational stability and visual acuity outcomes consistent with the conclusion that the lens provides good depth of focus with excellent quality vision.***

Uncorrected Distance Visual Acuity



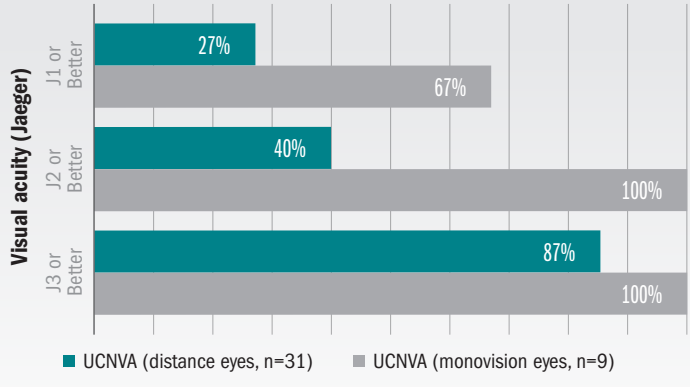
(FIGURE 1) Uncorrected distance visual acuity in patients' eyes 1 month after surgery. Average UCDVA: 20/21.

Uncorrected Intermediate Visual Acuity



(FIGURE 2) Uncorrected intermediate visual acuity in patients' eyes 1 month after surgery. Average UCIVAs were 20/20 (distance eyes) and 20/16 (monovision eyes), demonstrating increased depth of field.

Uncorrected Near Visual Acuity



(FIGURE 3) Uncorrected near visual acuity in patients' eyes 1 month after surgery. Average UCNVAs were J2.5 (distance eyes) and J1 (monovision eyes). Average MRSE was -0.26 D for distance eyes and -1.03 D for monovision eyes. Despite having near plano refraction postoperatively, patients had surprising amount of near VA for a monofocal IOL. *(Charts courtesy of Dr Alice T. Epitropoulos)*

In the subgroup targeted for distance, distance UCVA was 20/30 or better in 100% of eyes and 20/20 or better in 80% (see Figure 1). Intermediate UCVA was 20/25 or better in 87% of the 31 eyes that had been targeted for distance and in 100% of those targeted for monovision (see Figure 2). Near UCVA was J3 or better in 87% of eyes targeted for distance and J2 or better in 100% of eyes targeted for monovision (see Figure 3).

"Keep in mind that our average MRSE for monovision was only about 1 D. Our results reinforce that patients who choose monovision do not require as much anisometropia when using this lens," Dr Epitropoulos said.

Measurement of lens alignment showed that the toric IOL had excellent rotational stability. In all eyes, lens rotation between postop and both 1 day and 1 month was 5° or less.

"This result is similar to the outcome in the FDA clinical study where less than 6% of lenses rotated more than 5 degrees," Dr Epitropoulos said.

Choosing a toric IOL

Options for correcting astigmatism during cataract surgery are important considering the prevalence of astigmatism and its effect on visual quality, Dr Epitropoulos said.

"Approximately one-third of all patients who present for cataract surgery have at least 1 D of corneal astigmatism," she said. "Left untreated, as little 0.5 D of astigmatism can affect the quality of uncorrected vision. Therefore, it is surprising that only 7% of all cataract procedures include implantation of a toric lens."

In 2020, three monofocal toric IOLs were available in the US. The enVista toric IOL, which was approved in 2018, is the newest of the three platforms.

"Its SA neutral aspheric optic is one feature that sets the enVista apart from the other monofocal toric IOLs," Dr Epitropoulos said. "In addition, the enVista toric IOL is the only toric IOL option on the market that is available in a toric power to treat astigmatism as low as 0.9 D at the corneal plane."

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OCTA in glaucoma: The jury is still out

Diagnostic and monitoring advancements in glaucoma need to be fine-tuned

By Lynda Charters;

Reviewed by
Dr Robert L. Stamper


Dr Stamper

Optical coherence tomography angiography (OCTA), a relatively new imaging procedure, can do many things. It can generate 70,000 B-scans per second, identify differences among them, block saccadic movements and correct fixation loss. The user can look at a static structure sequentially to derive the presence of movement in the macular blood vessels, with the movement being detected by an algorithm.

Describing this and other advantages of the technology, Dr Robert L. Stamper, distinguished professor of clinical ophthalmology and director emeritus of the Glaucoma Service at University of California, San Francisco, United States, said: "Motion detection makes the image sharper and artificial intelligence applied provides a useful image." OCTA has become indispensable for managing macular degeneration and diabetic retinopathy. In fact, it is almost the standard of care, Dr Stamper commented, because of its ability to differentiate the capillary plexi and their status in all the retinal layers and their possible connections.

Dr Stamper explained that in glaucoma, two retinal areas are considered. One—in the macula—is the superficial macular capillary plexus, which is the area that feeds the retinal nerve fibre layer or the axons of the ganglion cells.

The other is the radial peripapillary capillaries. This comprises the vascular mid-layer of the optic nerve. Dr Stamper demonstrated that initially, the capillaries are relatively evenly distributed.

Early in the disease, the capillaries begin to drop out and this progresses to generalised capillary loss in advanced glaucoma in the peripapillary capillary plexus. The deep capillaries are present despite the advance of the disease. Current imaging devices can quantify the capillary density by ocular sector and facilitate follow-up over time.

The hope for OCTA

Dr Stamper explained that OCTA must become more sophisticated and evolved before it reaches its full potential for glaucoma specialists. Considering that blood vessels are the first severely affected structures in glaucomatous eyes, Dr Stamper pointed out, the hope is that OCTA might have better diagnostic sensitivity compared with standard OCT.

Clinicians also want OCTA to shed light on the pathophysiology of the disease. Specifically, he speculates as to whether the source is mechanical, such that the optic nerve is being pushed back, or whether the vessels are dropping out first.

"The thought was that OCTA might provide a way of distinguishing between primary open-angle glaucoma and normal tension glaucoma, which is often associated with some vascular issues," Dr Stamper explained. He recounted that previous OCTA studies have shown the following:

- **The vessel density is reasonably repeatable but more variable than the standard OCT thickness of the nerve fibre layer;**
- **The presence of a posterior subcapsular cataract markedly reduces the ability to measure the vessel density;**
- **The vessel density is correlated with the findings on indocyanine green angiography and declines with age, and;**
- **The decline seems to be accelerated in glaucoma.**

"The most important technologic ability is that OCTA can detect movement. It knows where vessels are, but the shortfall is that it does not provide information about how much is flowing through those vessels or how rapid the flow is," he explained. In addition, the dropout of radial peripapillary capillary density and superficial macular capillary density is well correlated with standard OCT and visual field measurements. OCTA images can distinguish between the normal retinas and those with early glaucoma.

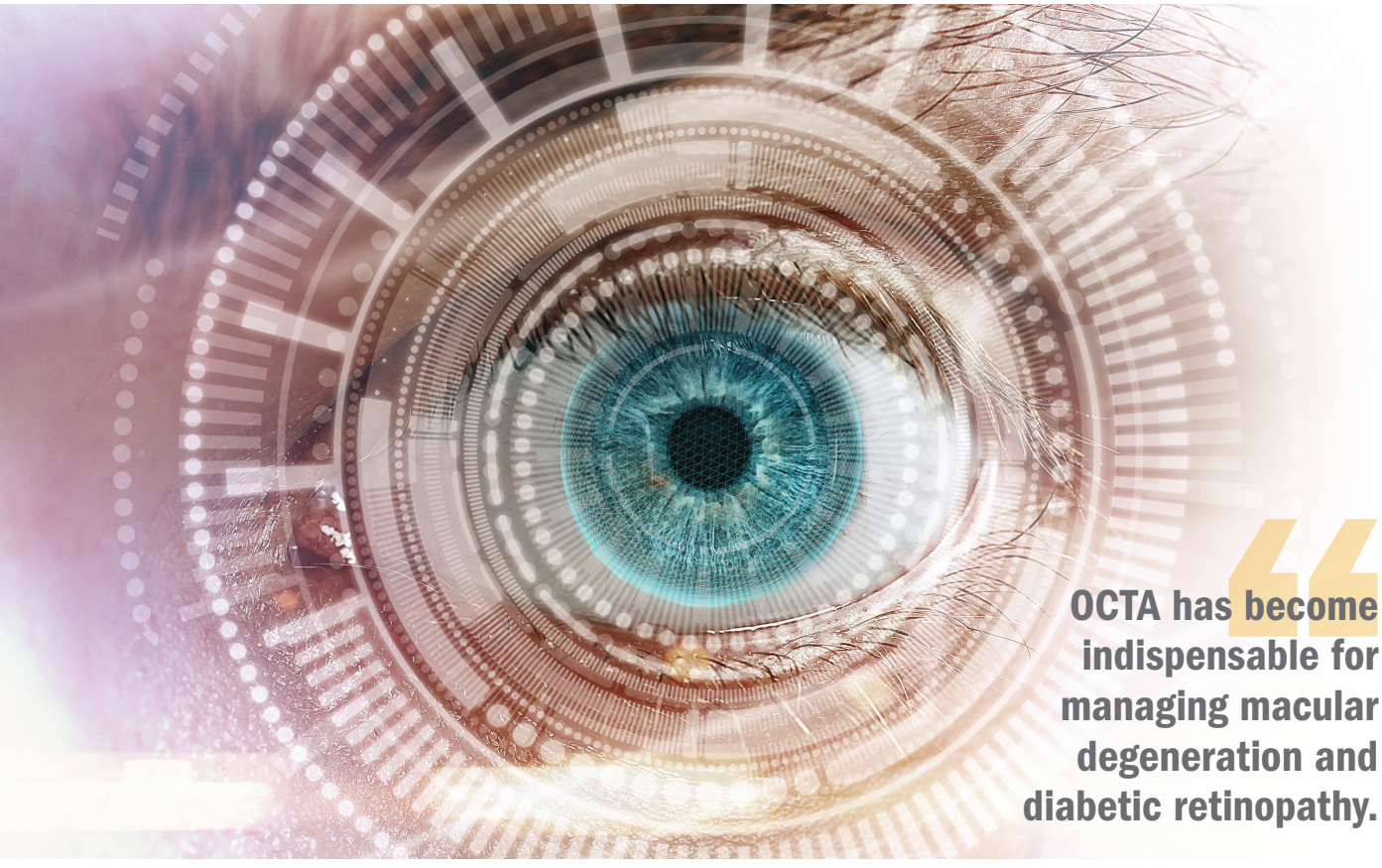
Defects an issue

When a defect is present in the macular area, this almost always shows up on the 10-2 visual fields.

The hope was that these problems in the vessels would appear on OCTA images before they appeared

IN SHORT

- ***Optical coherence tomography should provide key information about glaucoma with future technological iterations.***



> **OCTA has become indispensable for managing macular degeneration and diabetic retinopathy.**

on standard OCT images.

"Unfortunately, the diagnostic ability of OCTA in the macular and peripapillary areas is worse than the nerve fibre layer measurement in both the macular area and the peripapillary area," Dr Stamper said. "It appears that the ganglion cell complex or the thickness of the three anterior retinal layers declines before the changes are apparent in the macular density profile. The vessel, therefore, may not be the primary change."

Interestingly and unfortunately, after successful glaucoma surgery, almost no change is seen in the OCTA images. However, one positive finding that has become apparent is that a baseline reduction in the capillary density is associated with a higher risk of visual field progression.

Using OCTA, Dr Stamper and his colleagues evaluated the macular and peripapillary areas in 25 patients with open-angle glaucoma and 25 patients with normal-tension glaucoma. He observed that the vessels in those areas decreased with glaucoma severity. "Unfortunately, in this preliminary study, we found no difference between the two groups," Dr Stamper pointed out.

Conclusion

Considering the hopes for the usefulness of OCTA, Dr Stamper noted that OCTA does not have better diagnostic sensitivity. It does not show earlier changes compared with standard OCT images; it does not definitively provide information about the pathophysiology or evolution of glaucoma; and as of now, the technology does not differentiate between primary open-angle glaucoma, high-pressure glaucoma and normal-tension glaucoma. Dr Stamper and his colleagues are now evaluating a large patient group, which may provide some additional information.

"OCTA offers an interesting new window into various layers of retinal circulation in a variety of conditions and is most useful in the conditions around the macula," he pointed out. "The technology still has not shed light on the long-suspected feeling that normal-pressure glaucoma has a different pathophysiology than primary open-angle glaucoma."

It remains unclear as to whether OCTA offers improvement or additional information over standard OCT for glaucoma diagnosis or monitoring, Dr Stamper added. He also offered the additional caveat that the technology is new and with improvements in sensitivity and specificity along with better interpretation of findings, more information about glaucoma will be forthcoming.

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Image courtesy of peshkova @Adobe Stock

Early experience with the aspheric CT LUCIA 621P IOL. Host of design features add up to reliable optical performance

By Rüdiger Schmid, MD, FEBO

The "perfect" IOL for modern cataract surgery would predictably provide excellent visual acuity and quality of vision outcomes in routine and challenging cases. To achieve those goals, an IOL would need to be made of a highly biocompatible clear material, be easy to deliver using a preloaded injector system, center well within the capsular bag, feature a large optical zone matching the mesopic pupil size for the average cataract age patient, and have a high tolerance to the adverse effects of potential decentration.

Considering its design and our early clinical experience, the CT LUCIA 621P, a new monofocal aspheric IOL from Carl Zeiss Meditec and an enhancement of LUCIA 611P, seems to meet these criteria.

CT LUCIA 621P DESCRIPTION

The CT LUCIA 621P is a single-piece implant with step-vaulted haptics and a 6.0 mm optic that has a sharp posterior edge and innovative aspheric design (ZEISS optic technology), which as described below, is the most outstanding feature of this new lens.

The CT LUCIA 621P is made of a glistening-free hydrophobic acrylic material with a heparin-coated surface* and is available in versions with or without blue light filtering (621P and 621PY, respectively). Compared with hydrophilic acrylic IOLs, hydrophobic acrylic lenses are associated with less posterior capsule opacification and are much less prone to develop opacification.[1,2] The development of PCO is further limited by the sharp posterior optic edge of the CT LUCIA 621P. The material of the 621P has a Abbe number of 51, indicating lower chromatic aberration resulting into better optical quality with pseudophakic lenses.[3]

The CT LUCIA 621P comes preloaded in a new proprietary single-use injector system (BLUESERT™) that allows for an easy and safe cataract surgery workflow. The injector is a user-friendly device designed for reproducible IOL delivery into the capsular bag through a 2.2 mm incision. It features a silicone plunger that avoids damage to the IOL and advances with less force than needed using a previous generation injector system. A spring mechanism allows for comfortable injection resistance, and a latching of the inner section prevents rejection once the plunger has been depressed in the front section of the cartridge.

Unfolding of the CT LUCIA 621P IOL in the capsular bag is facilitated by its heparin-coated surface.* Yet, the lens unfolds in a gentle and controlled manner that enables its positioning. The sophisticated optic-haptic junction with its relatively rigid and enlarged step-vaulted haptics socket (Figure 1) together with the length and biomechanics of the haptics act to maintain stable IOL centration.

Figure 1. Schematic illustration of the CT LUCIA 621P optic-haptic junction

ZEISS OPTIC (ZO) ASPHERICITY CONCEPT

ZEISS optic (ZO) technology differentiates the CT LUCIA 621P from other aspheric IOLs. It combines the performance benefits of SA-correcting and SA-neutral designs in order to provide excellent image quality with a high tolerance to decentration (Figure 2).[4]

In addition, the CT LUCIA 621P optic is designed for optimum performance at pupil sizes of 4 to 5 mm, which corresponds to the pupil size of persons in the age range of most cataract patients. Aspheric IOLs with varying amounts of negative SA were introduced to compensate for positive corneal SA and thereby improve mesopic vision and contrast sensitivity relative to spherical IOLs. With decentration, however, optical quality with an SA-correcting IOL deteriorates due to an increase in coma.[5]

Thanks to the design of modern implants and with good surgical technique, postoperative IOL decentration can be minimized. Nevertheless, decentration arising because of a poorly sized, shaped, or positioned cap-

* Fragment of heparin used in IOL surface coating with no pharmacological, immunological or metabolic action.

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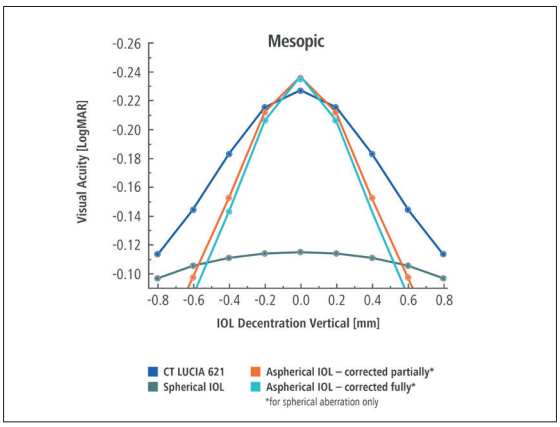


Figure 2. LogMAR visual acuity in mesopic light condition vs vertical IOL decentration

sulorhexis, zonular insufficiency, or aberrant capsular contraction remains a concern considering the number and prevalence of factors that predispose to these situations. Pseudoexfoliation, which is associated with zonule weakness, difficulty with capsulorhexis creation, and capsular contraction, appears to be the most common risk factor for IOL decentration.[6]

The ZEISS optic features a central zone (~3.5 mm) that has negative SA, balancing the positive SA of the natural cornea to optimize contrast sensitivity. Because it takes into account the posterior corneal surface, however, the CT LUCIA 621P has less negative SA in its central zone than other aspheric, aberration-correcting IOLs. Then, moving from the edge of the central zone to the periphery, the SA of the CT LUCIA 621P optic changes from negative to positive, giving the IOL improved tolerance to the negative impact of decentration on visual quality.

Findings from optical bench studies measuring visual acuity and visual quality show that the CT LUCIA 621P has better overall decentration tolerance under both photopic and mesopic conditions compared to aspheric IOLs that partially or fully compensate for SA.7 In addition, the CT LUCIA 621P had better peak visual acuity under mesopic conditions at myopic defocus compared with fully and partially SA-correcting aspheric IOLs.[7] This latter finding suggests that visual acuity for patients implanted with the CT LUCIA 621P should be less impacted by post-surgery residual refraction.

CLINICAL EXPERIENCE

We have had the opportunity to use the CT LUCIA 621P IOL in our clinic since June 2020 and implanted it in 10 eyes within the first few months of its availability. Both the intraoperative experience and patient outcomes have been very positive. Delivery of the preloaded lens was very smooth using the new injector system. Although the posterior haptic appeared slightly crumpled in some cases, it recovered its normal shape within seconds thanks to the material's elasticity, and we saw no visible evidence of damage. Lens positioning was excellent, consistent with our experience using previously available CT LUCIA IOLs (Figure 3).

We targeted a refraction of -0.5 D in most eyes implanted with the CT LUCIA 621P IOL, because in our experience this slightly myopic objective refraction is most suitable for older patients. Biometry was done with the IOLMaster 700 with total keratometry, and the Barrett True K formula was used. Good refractive predictability was achieved in this initial series of eyes. Patients were satisfied with their visual acuity and quality of vision after surgery, even in cases where the IOL seemed to be slightly decentered, which occurred mainly in relation to an irregular pupil. No patients have reported positive or negative dysphotopsia.

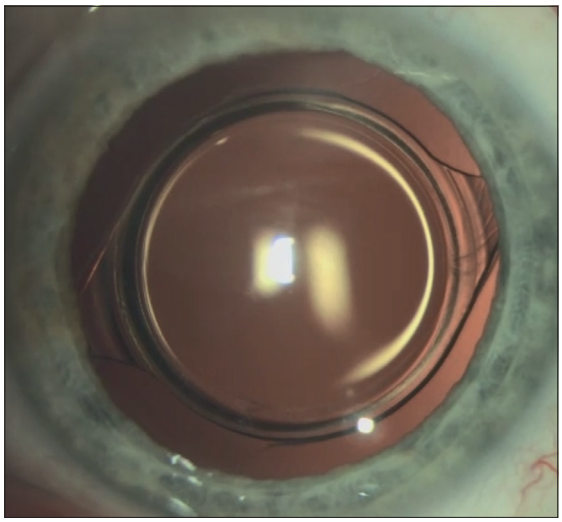


Figure 3. Slit lamp image of the well centered CT LUCIA 621P

CONCLUSION

The features of the CT LUCIA 621P IOL, including its intraoperative handling characteristics, excellent refractive predictability, stability in the capsular bag, and consistently good visual outcomes, make it a good option to use as our standard IOL for cataract surgery patients with a monofocal lens. In addition, because of the benefits of the ZEISS optic concept, the CT LUCIA 621P IOL is now our implant of choice even in more complicated cases where there is a concern about risk for potential lens decentration.

Dr. med. Rüdiger Schmid FEBO is Senior Consultant at accuratis. Practice for Refractive Eye Surgery, Ulm & Augenkompetenzzentren Dillingen (Donau) Consultant to ZEISS.

IOP homeostasis could be key to understanding causes of glaucoma

Single-cell RNA sequencing reveals 12 cell types in trabecular meshwork

By Lynda Charters;

Reviewed by Dr Gaurang Patel

Dr Patel

Until now, IOP elevations have been managed medically or surgically, but the most recent research is looking below the surface to get to the root causes of glaucoma.

Scientists at Regeneron Pharmaceuticals and Duke University have been collaborating to do just that and have identified 12 cell types that are involved in regulating the IOP as well as mapping region-specific expression of the candidate genes involved.

According to Dr Gaurang Patel, lead author of the study, glaucoma is a leading cause of irreversible blindness.

"It occurs when increased pressure inside the eye damages the optic nerve," Dr Patel said. "Current treatments alleviate that pressure, but it's not fully known how it increases. We set out to identify the molecular structure of an area of the eye that helps regulate pressure."

Importantly, while conventional treatments lower IOP and slow progression of the glaucoma, the progression of the visual field damage continues. Dr Patel and colleagues wanted to look past this to determine the 'hows and whys' of dysregulation of the conventional outflow pathway in glaucoma.

According to Dr Patel, using single-cell RNA sequencing, a high-throughput process that analyses the RNA molecules expressed by genes, the team identified 12 distinct cell types in the trabecular meshwork (TM) and surrounding tissue.

"The TM is a specialised area of eye tissue that acts like a membrane, regulating fluid outflow. If the eye is a sink, the trabecular meshwork is its drain," he said. "How the drain gets 'clogged,' leading to high IOP and eventually the vision loss of glaucoma, is not known. Better understanding of this very complex tissue may help lead to future treatment approaches for glaucoma."

The investigators obtained the expression profiles of 17,757 genes from 8,758 cells in eight human donor eyes. By so doing, they identified two expression patterns, i.e., myofibroblast- and fibroblast-like, from the cells in the TM, which is the primary outflow pathway in the eye.

> While conventional treatments lower IOP, the progression of the visual field damage continues.

They also found Schwann cell and microphase macrophage signatures in the TM. Schlemm's canal (SC) is the other primary component in the outflow pathway and it had a combination of lymphatic/blood vascular gene expression. They localised select glaucoma-related genes to the specific cell populations in the outflow tract.

Other expression clusters were found in cells in tissues adjacent to the TM and SC in the unconventional uveoscleral outflow pathway.

"From the most abundant to the least, the cell signatures included Schwann cell-like; TM1 fibroblast-like; smooth muscle cell; TM2 myofibroblast-like melanocyte; macrophage; pericyte; vascular endothelial cell; T cell/natural killer cells; lymphatic-like endothelial cell; myelinating Schwann cell; and epithelial cell clusters," the investigators reported.

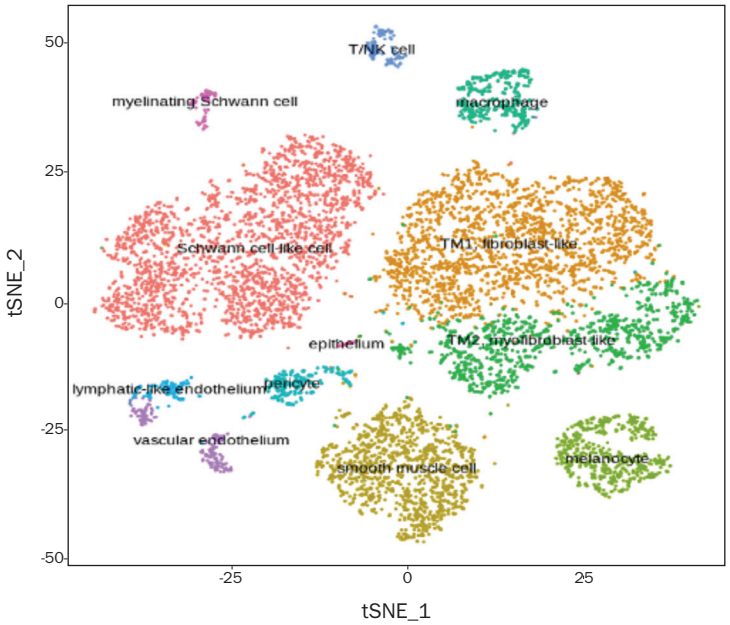
Gene involvement

Many genes have been found to be involved in glaucoma. The investigators looked at a few to determine which cell clusters they were present in. For example, the mutations in the *MYOC* gene cause glaucoma and the formation of angiopoietin-like 7, a protein which has an elevated expression level in the aqueous in glaucomatous eyes.

In the current study, "*MYOC* was highly expressed in TM1, TM2 and smooth muscle clusters, and was expressed at high levels in the TM and at lower levels in the ciliary muscle, Schlemm's canal and scleral

IN SHORT

- ***New research is looking past just regulating the IOP and using gene therapy to help patients.***



Abbreviation: t-SNE: t-distributed stochastic neighbour embedding

◀ (FIGURE 1) The 12 cell types identified in the study are shown in this chart. *(Chart courtesy of Dr Gaurang Patel)*

fibroblasts. Similarly, angiopoietin-like 7 was found in both TM1 and TM2 clusters, but the expression was more limited," they reported.

The importance of this study is that the genes that are relevant in glaucoma were mapped to the genes in the conventional outflow pathway.

The identification of 12 distinct cells types in and near the conventional outflow pathway emphasises the diversity of the cells that are actively engaged in regulating the outflow function and IOP control.

The current findings may pave the way for developing novel glaucoma drugs for newly identified targets in glaucoma.

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Harnessing the power of light in dry age-related macular degeneration

Photobiomodulation is a non-invasive treatment which offers improved vision

By Drs Roberto Pinelli, Miorica Bertelli and Elena Scaffidi

Dr Pinelli

Photobiomodulation (PBM) is the application of monochromatic light to the body with the aim of repairing tissues and reducing inflammation, oedema and pain.[1] It has been used for 20 years for the treatment of musculoskeletal pain, injury and dysfunction; to aid wound healing; to improve acute muscle performance and reduce muscle damage after exercise;[1] and for neuropathic pain, lymphoedema and oral mucositis.[2–4]

Several studies in the past 5 years have shown encouraging results using PBM to treat eye diseases including age-related macular degeneration (AMD),[5,6] retinopathy of prematurity and diabetic macular oedema.[1,7–9] PBM does not worsen the disease, has no side effects and is completely non-invasive.[10,11]

There is no currently approved treatment or cure for the dry form of AMD, which affects 80% of individuals with AMD and tends to progress more slowly than the wet type.[10]

Light waves

PBM is not a heat therapy but is more akin to photosynthesis in plants, in that light, in the far red and near-infrared spectral range, can stimulate cells and lead to a cascade of photochemical reactions.

What happens first is that the low-powered light is absorbed locally by cytochrome c oxidase. Mitochondrial energy is then produced by releasing oxygen, which results in increased ATP concentration and reduced oxidative stress.

This photochemical reaction activates enzymes and second messengers, which lead to a cellular and, indirectly, a systemic response in tissues that have not absorbed photons.[5,12,13] Mitochondrial dysfunction and oxidative stress play a key role in many macular diseases, so PBM is of use in acute and chronic eye diseases.[1,5,10]

We offer nine PBM therapy cycles within approximately 1 month. During the procedure, a medical device with light-emitting diodes stimulate cellular function and improve energy production.

Each cycle of therapy delivers wavelengths in the range of 590–850 nm for 4 minutes per eye. Clinical outcomes are determined immediately after the final cycle, after 3 months and after 6 months, using optical coherence tomography (OCT) imaging, the Amsler grid, the Pelli-Robson chart, a Snellen chart and a Jaeger chart.

Case study

Nine PBM cycles were administered over 1 month to a patient with dry AMD, after which OCT showed reduced drusen and the patient obtained subjectively improved vision (see Figure 1). The patient also experienced less eye strain, more colour contrast, higher definition and better far and near uncorrected visual acuity.

Contrast sensitivity improved from 1.8 to 2.0 log units. Outcomes remained stable at the 6-month follow-up (see Figure 2).

This case demonstrated a successful non-invasive treatment with improved quality of vision in dry AMD. Irradiation could therefore offer a new non-invasive, adverse-effect-free means of stimulating retinal stem cells to regenerate.

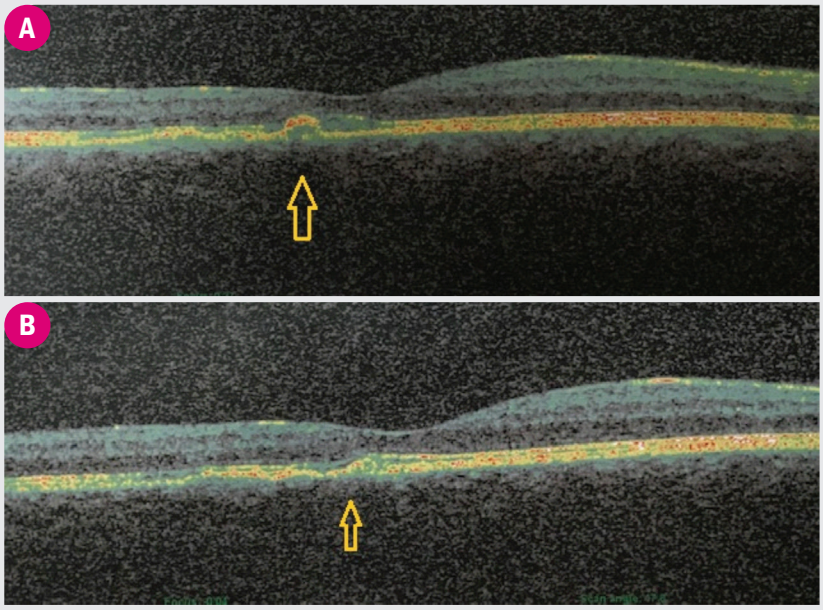
Conclusion

To date, there are no approved treatments for many retinal diseases. With its ability to promote cellular regeneration using light waves, PBM has resulted in better visual acuity, contrast sensitivity and a less-damaged macular profile in several patients with dry AMD.

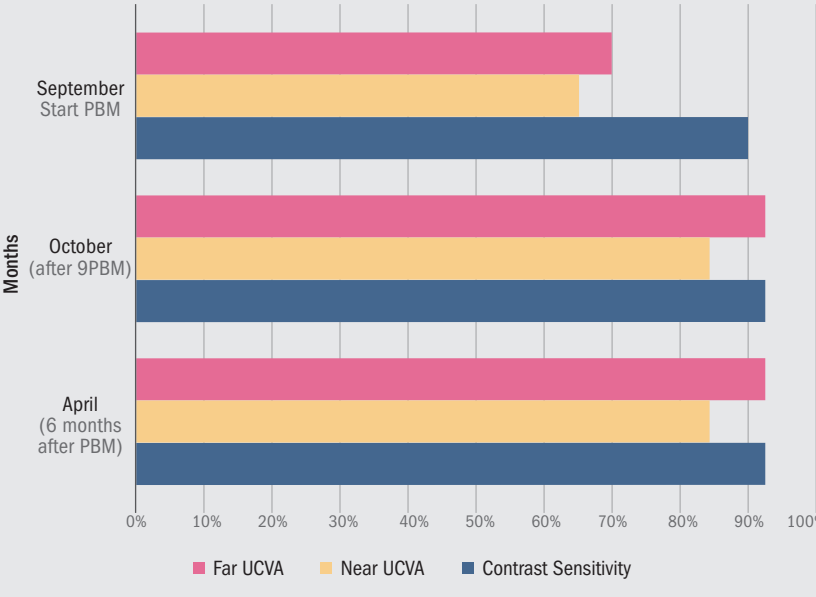
Overall, these results are encouraging. Our protocol seems to offer an extremely promising approach to prevent visual acuity from worsening and to promote tissue repair in dry AMD. Moreover, this method has the advantage of being entirely non-invasive.

IN SHORT

- ***Photobiomodulation has been demonstrated to improve quality of vision in several patients suffering from dry AMD.***



(FIGURE 1) Macula before treatment (A) and 6 months after treatment (B).



(FIGURE 2) Far and near uncorrected visual acuity (UCVA) and contrast sensitivity before treatment and 6 months later. *(Images courtesy of Dr Pinelli)*

According to this hypothesis, irradiation at certain wavelengths can regenerate retinal cells. Thus, modulated light can offer a novel valid therapeutic approach for dry AMD, which has the potential to facilitate the repair of damaged tissues in the retina and promote survival and functions of epithelial cells within the retinal pigmented epithelium.[14]

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The role of LRG1 in disease mechanisms

Novel monoclonal antibody can halt the growth of abnormal blood vessels

***By Caroline Richards, editor of* Ophthalmology Times Europe®**

Prof. Moss

Prof. Greenwood

After a team of researchers at the University College London (UCL) Institute of Ophthalmology (IoO), London, started to explore the causes of malformed blood vessels in the eye, they discovered that a molecule called LRG1 (leucine-rich alpha-2-glycoprotein 1) was partly responsible. They realised that if they could block the function of this molecule, they might be able to improve the formation of blood vessels.

The team is now collaborating with Moorfields Eye Hospital, London, with the aim of moving towards clinical testing of new therapies for patients with a range of disorders including wet age-related macular degeneration (AMD), diabetes and cancer. I spoke with Professors John Greenwood and Stephen Moss to find out more.

» WHAT PROMPTED YOUR RESEARCH INTO LRG1?

Our research began in 2005, when Prof. Mark Gillies, a clinical colleague from Sydney, Australia, invited us to join the MacTel Project, a new international consortium set up by the Lowy Medical Research Institute to understand the mechanism behind the rare retinal condition macular telangiectasia type 2, or MacTel. The disease leads to a permanent loss of central vision.

The MacTel Project provided us with almost one million pounds over 5 years, funding which enabled us to see which genes and biological mechanisms were involved in abnormal vessel formation in the retina. This was a hallmark feature of MacTel.

It led to us identifying the gene *LRG1*, which we found was implicated in the growth of abnormal blood vessels. We realised that LRG1 might be a factor not just in MacTel, but in other eye conditions and diseases. At the time, there were fewer than ten publications on it, and almost nothing was known about its function.

» WHAT DID YOU DO AFTER FINDING YOUR TARGET?

We developed a function-blocking humanised monoclonal antibody against the LRG1 protein, 'Magacizumab'. It has already been through preclinical testing and it looks extremely promising.

More recently, we have generated a Fab fragment (an antigen-binding fragment) from our antibody: 'MagaFab'. Rather like how Lucentis (ranibizumab, Novartis), the Fab fragment of anti-tumour drug Avastin (bevacizumab, Roche), is used for retinal disease, our aim is for Magafab to be used in eye conditions, with Magacizumab having systemic applications.

Importantly, in the context of eye disease, we have learnt that inhibiting LRG1 improves clinical outcomes and reduces lesions in animal models of ocular disease. It does this totally independently of vascular endothelial growth factor (VEGF), which is the key target for most ocular treatments, such as Avastin and Eylea (aflibercept, Regeneron Pharmaceuticals). This means we have identified a completely separate pathway that may explain why some patients do not respond to current treatments.

» COULD YOU TELL ME ABOUT THE PROCESS OF DEVELOPING THE ANTIBODY?

It took us 4 years to generate the antibody and then engineer it so it could be used in patients without causing an immune response.

In preclinical studies, the full-length antibody caused an acute inflammatory response in the eye. There is always a risk that a protein may cause some inflammation, but this was a real puzzle for us, because antibodies being injected into the eye have a long history of being very safe and non-toxic.

We thought this would set us back, but then we got some seed-funding through the UCL Technology Fund, which enabled us to produce the Fab fragment, thus removing the unneeded half of the molecule which we thought might be eliciting the inflammatory response.

This time, preclinical studies yielded no adverse events. In addition, since MagaFab is a smaller molecule, more of it can be contained in solution, which means you can inject a larger, longer-lasting dose.

We have also been researching its role in cancer, as well as collaborating with scientists working on lung disease, colitis and vascular inflammation, where LRG1 is also emerging as a contributing factor in disease progression. In particular, we have shown that our antibody reduces the growth of many solid tumours, and enhances the effectiveness of existing therapies such as cytotoxics and the new immunotherapies.

We would like to see some clinical benefit for the large cohort of wet AMD and diabetic eye disease non-responders.

– Prof. Stephen Moss and Prof. John Greenwood

» HOW DOES LRG1 AFFECT VASCULATURE AND THUS LEAD TO DISEASE?

LRG1 seems to affect the capacity of a blood vessel to mature and stabilise. When blood vessels grow, pericytes crawl along the endothelial cells which line the vessel wall.

Through interactions between these two cell types, the new vessels stabilise and the junctions between them start to become impermeable. If you disrupt this interaction, the vessels fail to stabilise and instead retain an immature and abnormal, leaky characteristic.

We think LRG1 affects the pericytes by preventing crosstalk, so blood vessels remain fragile and haemorrhagic; indeed, if we inject the molecule into the eye as the vasculature is developing, it disrupts the vessels and prevents them from growing normally. In diseases we have looked at, ranging from diabetic eye disease to cancer, LRG1 is switched on in the affected blood vessels.

This might explain why, in nearly every disease you look at, vessels do not grow normally. This opens up the possibility that LRG1 may be involved in the early stages of diabetes, where pericytes are one of the first cell types to be affected.

We know that the gene gets switched on very early in diabetes – you suddenly see levels go shooting up, even before you start to see the pathology, which is very interesting. And our studies show that LRG1 is certainly involved in the later, proliferative stage of diabetes. In fact, in both proliferative diabetic retinopathy and wet AMD, when we look in the eyes of patients, we find high levels of LRG1.

» WHAT IS NEXT WITH YOUR RESEARCH?

We would like to see MagaFab succeed in the early-stage trials by showing that it is safe and can be tolerated in patients. Ultimately, however, we would like to see some clinical benefit for the large cohort of patients with wet AMD and diabetic eye disease who either do not respond to current treatments or respond poorly. Given how common these diseases are, if our therapy is able to meet the needs of a significant number of those patients, it has the potential to impact hundreds of thousands of people globally.

The fact that so many patients do not respond to anti-VEGF treatment indicates that processes other than the VEGF pathway are important. The same is true for cancer, which can bypass the VEGF pathway.

However, we think that because of what we know about the mode of action of the LRG1 molecule, diabetic patients may be more likely to benefit. This is because more of them fail to respond to anti-VEGFs than for wet AMD: around 50% non/poor responders in the early, diabetic macular oedema stage. We have evidence that our therapy might be good at that point, as well as later on, when you have new vessel formation.

This also raises the possibility—and this is speculation—that MagaFab would be beneficial in other eye diseases where abnormal vasculature is a problem, such as retinopathy of prematurity and inherited diseases such as Coats disease and familial exudative vitreoretinopathy.

If we can prove it is safe in the eye, then these can all be investigated. Outside of ophthalmology, we are hoping to take the full-length antibody (which is safe in the rest of the body) to cancer trials.

We have created PanAngium Therapeutics, a spin-out company, which is about to seek its first series A funding from external investors for the ophthalmic work. That would enable us to scale-up production of MagaFab and then design and embark on appropriate early-stage clinical trials, probably starting two years from now.

We will be relying on our Moorfields colleagues and the information they have about patients to identify the inclusion and exclusion criteria for potential participants into the trial. A visual acuity test will be our primary outcome measure – this is the gold standard, although we will also be measuring a number of secondary outcomes. These include optical coherence tomography scans to look at retinal thickness and, potentially, adaptive optics scanning laser ophthalmoscopy to detect vessel structure.

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Topical antihistamine for allergic conjunctivitis make debut in USA

First new therapy in nearly a decade is found to quickly quell ocular itching

By Mr Richard Teofilo Atallah and Dr Richard D. Najac


Mr Atallah


Dr Najac

The United States Food and Drug Administration (FDA) recently approved the first prescription-only topical ocular formulation of the second-generation antihistamine cetirizine, available as a 0.24% ophthalmic solution (Zerviate, Nicox Ophthalmics; licensed to Eyevance Pharmaceuticals) for the treatment of ocular itching associated with allergic conjunctivitis. The antihistamine demonstrated robust efficacy in three randomised, double-masked, placebo-controlled clinical trials using the conjunctival allergen challenge (CAC) model among patients with allergic conjunctivitis.

Two of the trials that evaluated onset and duration showed that the drug solution led to statistically and clinically significantly less ocular itching versus vehicle at 15 minutes and 8 hours after treatment.[1] The ophthalmic solution breaks the 10-year drought since the last approval for allergic conjunctivitis treatment, with the twice-daily drops hitting the market in March 2020.

Cetirizine hydrochloride (Zyrtec, Johnson & Johnson Consumer) is recognised as the number one oral antihistamine allergy treatment recommended by allergists, with 23 years on the market and countless doctor and patient years of experience.[2] Based on its vast track record of therapeutic success and safety in different formulations, the industry sought to develop cetirizine as an ophthalmic solution.

Background

Allergic conjunctivitis affects at least 30% of Americans.[3] Reactions range anywhere from mild—making it merely a self-limiting nuisance—to the other end of the spectrum, when allergies become a debilitating disease, significantly impairing patients' quality of life. Stimuli, whether tree and grass pollens, animal hair and dander, or any number of other environmental insults, manifest in the familiar cascade of ocular symptoms that include itching, redness, chemosis, tearing and eyelid swelling.

Thanks to the vast work being done around ocular surface disease and dry eye—along with fine-tuning of diagnostic and treatment algorithms—awareness among eye care specialists to diagnose and treat the "red eye" is improving. Allergic conjunctivitis is a frequent and substantial piece of the puzzle when it comes to finding the root cause of ocular surface disease.

Patients with allergies typically have bilateral signs and symptoms, with the most common ocular symptoms being itching, burning, redness and tearing. Allergic conjunctivitis is often associated with swelling, an important area of differentiation from dry eye disease. Eversion of the lower lid is highly advised to assess the extent of chemosis.

Allergy cycle

In response to an allergen, the process of conjunctivitis has an early acute phase followed by a late phase. Allergens interact with immunoglobulin E, which is bound to sensitised mast cells that in turn activate increased histamine and subsequent degranulation.[4] The release of histamine and other proallergic mediators during the acute phase induces itching, vasodilation and vascular leakage.

This is followed by ocular redness, chemosis and lid swelling. Mast cells then synthesise, releasing cytokines, chemokines and growth factors, which kicks off a cascade of inflammatory events. During the final late-phase reaction, eosinophils, neutrophils and macrophages infiltrate conjunctival tissues.[5,6]

The commonly used and approved treatments for ocular allergies include antihistamines and mast cell stabilisers, or both; and these agents act to reduce the signs and symptoms of the early-phase reaction.[7,8]

IN SHORT

- ***Cetirizine ophthalmic solution 0.24% is a therapeutic with an ability to quickly quell ocular itching for patients experiencing allergic conjunctivitis. There have been no safety concerns identified with cetirizine treatment.***

ORA-CAC MODEL KEY TO ESTABLISHING DRUG EFFICACY

IT HAS BEEN a struggle for researchers to measure allergic conjunctivitis in a controlled environment. There is a huge amount of variability owing to numerous factors such as allergen, subject, season and weather,[1] resulting in different symptomatic responses and a range of severity.[2] The Ora conjunctival allergen challenge (CAC) model circumvents these concerns, inducing a moderate to severe allergic reaction in a controlled and reproducible manner.[3]

In the Ora-CAC model, all subjects undergo a screening procedure whereby they demonstrate reproducible moderate to severe allergic responses. This model is an established method approved by regulatory agencies to determine therapeutic efficacy in the relief of allergic signs and symptoms. Numerous studies have demonstrated the clinical efficacy of therapeutics for the indication of allergic conjunctivitis using this model.

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Ocular form of cetirizine

Cetirizine is a second-generation antihistamine (highly selective H1 receptor antagonist) that binds competitively to histamine receptor sites to reduce swelling, itching and vasodilation. Two Phase 3 efficacy studies revealed strong and similar anti-itch efficacy of cetirizine ophthalmic solution 0.24% compared with vehicle (using the CAC model).

The single-centre (study one) and multi-centre (study two), double-masked, randomised, vehicle-controlled, parallel group CAC studies were conducted over approximately 5 weeks and four study visits. Patients with moderate and severe symptoms were enrolled in the trials and study two required patients to have more severe allergic conjunctivitis symptoms.

Subjects were screened for an allergen response at visits one and two and then randomised at visit three. Approximately 100 subjects were randomly assigned in each study. The primary efficacy end points were ocular itching and conjunctival redness 15 minutes and 8 hours post-treatment, post-CAC.

Quells itching fast

Investigators administered cetirizine 15 minutes or 8 hours before CAC and subjects had significantly lower ocular itching at all time points post-CAC ($P<0.0001$) compared with vehicle in both studies. The investigators' assessment of conjunctival redness was significantly lower after cetirizine treatment compared with vehicle at 7 minutes post-CAC and at both 15 minutes and 8 hours post-treatment in both studies ($P<0.05$).

Numerous secondary end points, ocular and nasal, were also examined. It should be noted that the most robust treatment differences were observed in study two, where patients were required to have more severe symptoms in order to be included ($P<0.05$). There were no safety concerns for cetirizine ophthalmic solution 0.24%.

Comfort is key

For added comfort, cetirizine ophthalmic solution 0.24% is designed with Hydrella, which includes glycerin and hydroxypropyl methylcellulose, ingredients commonly found in lubricant drops. Patients in the FDA trials reported a mean comfort score of less than 1 at all time points (on a scale of 1-10, with 1 being the most comfortable). The solution is also formulated with a neutral pH of 7.0, similar to the natural tear film.

Eye-care providers now have a solution for patients with allergic conjunctivitis experiencing disruptive ocular itching. The drop form of cetirizine ophthalmic solution 0.24% gives them a chance to greatly improve patients' quality of life with an effective and targeted approach. Notably, unlike some oral antihistamines, the new formulation did not cause drowsiness.

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Is topical moxifloxacin the best choice prior to cataract surgery?

Researchers are looking for options to reduce corneal surface flora in patients

By By Lynda Charters;

Reviewed by Dr Caroline W. Wilson

Dr Wilson

The use of topical moxifloxacin instilled onto the ocular surface before cataract surgery may not be effective for reducing the corneal surface flora in most patients, according to Dr Caroline W. Wilson, an ophthalmology resident at the Department of Ophthalmology and Visual Sciences at University of Iowa Hospitals and Clinics in Iowa City, Iowa, United States.

Traditionally, perioperative topical antibiotics have been administered to prevent endophthalmitis following cataract surgery. Previously, surgeons prescribed antibiotics for use preoperatively and/or postoperatively to reduce rates of infection.

"With the increasing popularity of intracameral antibiotics, questions have arisen about the utility of continuing use of topical antibiotics before and after surgery," Dr Wilson said. "Many published studies have shown the equal efficacy of topical and intracameral antibiotics."

The use of intracameral antibiotics has gained popularity because of the reduced treatment burden for patients. Dr Wilson and colleagues also wondered if the benefits of intracameral drugs extended beyond just decreasing the treatment burden (i.e., how do perioperative antibiotics affect the health and biome of the ocular surface?)

Dr Wilson recounted that some studies have shown that use of pre- and postoperative antibiotics has no proven benefit over topical antiseptics and intracameral antibiotics in the prevention of endophthalmitis.[1] In addition, increasing the frequency and the duration of time of antibiotics use does not reduce the flora on the conjunctiva.[2]

There is also concern about the induction of antibiotic resistance with repeated use of the drugs. The European Society of Cataract and Refractive Surgeons went so far as to recommend that preoperative antibiotics not be used.

Investigation

To look further into this area of uncertainty, Dr Wilson and colleagues wanted to determine what the effect of a short course of moxifloxacin actually had on the ocular surface flora before surgery and if bacterial resistance was induced after a few days of treatment.

The investigators conducted a prospective study in which study eyes were treated four times daily with moxifloxacin for 3 days preoperatively and control eyes received no antibiotic preoperatively. They collected conjunctival swabs, one on the day surgery was scheduled and the second on the morning of the surgery before applying an antiseptic. The swabs were sent for culturing, speciation by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry and drug sensitivity patterns, Dr Wilson said.

The results showed that coagulase-negative staphylococcal species were the most frequently identified on the ocular surface in both study groups. Among the patients who instilled moxifloxacin for 3 days preoperatively, 52% had ocular surface bacterial growth on the day of surgery, as did 100% of the control patients as expected.

"We saw that the antibiotics do work half of the time," she commented. "Interestingly, three (17.6%) of the patients treated with moxifloxacin had flora resistant to the drug after the 3 days of use".

"Topical moxifloxacin instilled before cataract surgery does not effectively reduce the ocular surface flora in most patients," Dr Wilson concluded. "Further, bacterial resistance may be inducible in as little as 3 days of the topical antibiotic use."

Dr Wilson suggested future studies examine preoperative antibiotics' effect on the efficacy of intracameral drugs against bacteria.

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Dr Wilson has no financial interest in this subject matter.

The ocular manifestations of COVID-19 in children in Wuhan, China

Retrospective study in hospitalised patients revealed conjunctival symptoms

By Lynda Charters

A retrospective cross-sectional study conducted at Wuhan Children's Hospital in Wuhan, China, where COVID-19 originated, found that children hospitalised with the virus presented with a series of onset symptoms that included fever, cough and conjunctival discharge, as well as eye rubbing and conjunctival congestion. The patients' systemic clinical symptoms or cough were associated with the ocular symptoms.

A consideration for the investigators was that most reported cases were adults and little is known about ocular manifestations in infected children. "Compared with adults, COVID-19 in children could be very different in terms of exposure history, clinical characteristics and ocular manifestations," they said.

In light of this, they conducted a retrospective clinical study on the clinical and ocular characteristics of paediatric patients hospitalised with COVID-19. Children with confirmed severe acute respiratory syndrome coronavirus disease between 26 January and 18 March 2020 were included. The main outcomes were the onset of clinical symptoms and duration, ocular symptoms and need for medication.

Findings

The investigators found that 22.7% of the 216 children (median age, 7.25 years) included in the study had ocular manifestations, including conjunctival discharge, eye rubbing and conjunctival congestion. "Children with systemic symptoms or cough were more likely to develop ocular symptoms, which were mild, and recovered or improved with minimal eye drops or self-healing," they reported. The investigators published their results in *JAMA Ophthalmology*.[1]

Almost 90% of children had a family member with confirmed or suspected COVID-19. The most common symptoms among symptomatic children were fever in 37.5% and cough in 36.6%; 43.1% had no systemic or respiratory symptoms.

All children with mild (46.8%) or moderate (53.2%) symptoms recovered. Of the 22.7% with ocular symptoms, nine had ocular complaints that were the initial manifestations of COVID-19 including conjunctival discharge (55.1%), eye rubbing (38.8%) and conjunctival congestion (10.2%).

A few had ocular pain (8.2%), tearing (4.1%) and eyelid swelling (8.2%). Two patients (4.1%) had allergic conjunctivitis before the COVID-19 pandemic. Children with systemic symptoms or with cough were more likely to develop typically mild ocular symptoms.

"These data could help guide prevention and management of ocular disorders in children with COVID-19," the authors concluded.

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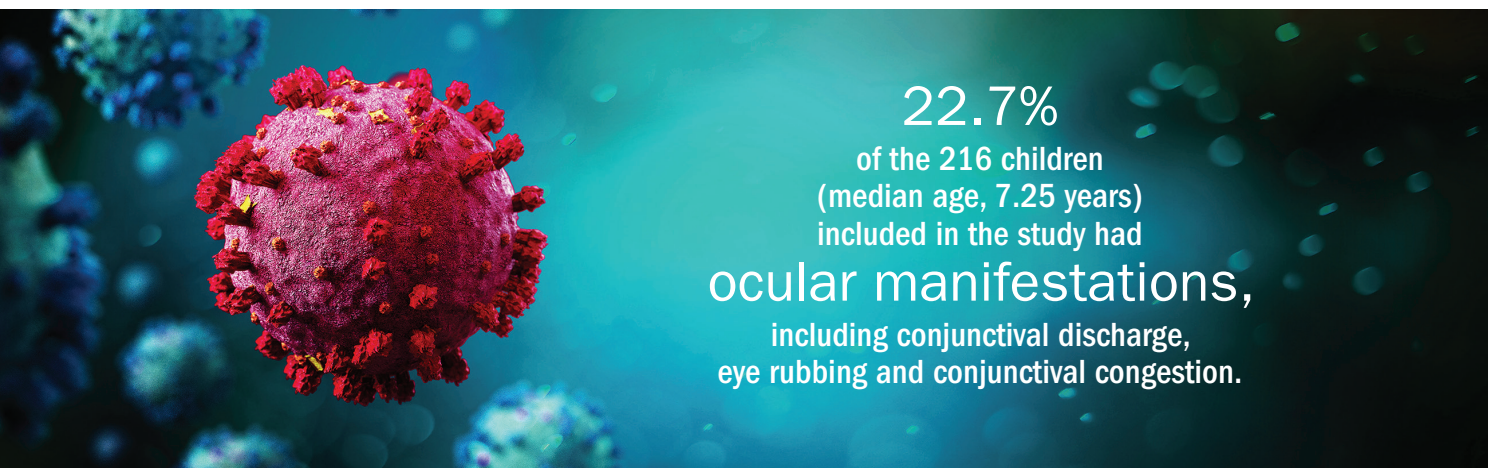

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Stem cells for dry AMD with GA show promise in early clinical study

Patients underwent short-course, systemic immunosuppression before procedure

By Michelle Dalton;

Reviewed by Dr Christopher D. Riemann

Dr Riemann

Subretinal transplantation of human embryonic stem cell-derived retinal pigment epithelial (RPE) cells in patients with age-related macular degeneration (AMD) and geographic atrophy (GA) appears to be well tolerated, according to Dr Christopher D. Riemann of Cincinnati Eye Institute and University of Cincinnati in Ohio, United States. During the Association for Research in Vision and Ophthalmology virtual annual meeting, he presented interim results of a Phase II/IIa trial investigating OpRegen for the treatment of dry AMD with GA.

OpRegen is administered as a cell suspension; initially this was in a balanced salt solution but now it is provided in a thaw-and-inject formulation using CryoStor 5. The US Food and Drug Administration has granted OpRegen fast track designation.

RPE cell replacement is important because loss of RPE cells impairs drusen clearance, leading to the development of macular degeneration and corresponding central vision loss. The trial's primary objective was to assess the safety and tolerability of the subretinal transplantation of stem cell-derived RPE cells in patients with dry AMD and GA. The secondary objective looked at the cells' survival and possible effects of OpRegen treatment by assessing changes in retinal structure and function.

Study design and procedure

In the trial, patients with advanced dry AMD and GA were divided into 4 cohorts. Cohorts 1, 2 and 3 included 12 legally blind patients (visual acuity, < 20/200); cohort 4, which will include patients with better visual acuity and smaller atrophy (average visual acuity, 20/125), is still recruiting, with 5 of 12 patients enrolled. (See Table 1 for full cohort data.)

Patients underwent short-course, perioperative systemic immunosuppression prior to the procedure. The eyes with the poorest vision received subretinal implants with 50,000 to 200,000 OpRegen cells in suspension either through standard pars plana vitrectomy and retinotomy or using the gyroscope therapeutics Orbit subretinal delivery system (SDS).

"The Orbit subretinal delivery system is a new surgical procedure using novel instrumentation," Dr Riemann said. "A sclerotomy is created, [and] a special cannula is placed tangentially into the suprachoroidal space and advanced posteriorly toward the target area in the macula, adjacent to the geographic atrophy."

When the target area is reached, "a screw drive advances a needle through the choroid into the subretinal space," he said. Next, a leading balanced salt solution subretinal bleb is created.

> RPE cells impairs drusen clearance, leading to the development of macular degeneration and corresponding central vision loss.

"Once we confirm a subretinal bleb, we turn a valve and switch from balanced salt solution to cells and deliver the OpRegen into the subretinal space," Dr Riemann said. "The subretinal injection is accomplished without a vitrectomy or retinotomy."

Efficacy results

Patients in cohorts 1, 2 and 3 had no marked, sustained reductions in visual acuity. The five patients in cohort 4, however, had improved vision up to the 1-year follow-up period, including one patient

IN SHORT

- ***The primary objective of a Phase II/IIa trial was to assess the safety and tolerability of subretinal transplantation of stem cell-derived RPE cells in patients with dry AMD and GA.***

Table 1. ***Study Design and Population***

PARAMETER	COHORTS 1-3	COHORT 4 (ONGOING)
Subretinal dose delivered	Cohort 1: 50,000 cells Cohorts 2-3: Up to 200,000 cells	Up to 200,000 cells
Surgical approach (PPV and retinotomy or Orbit SDS)	12 patients, PPV and retinotomy	3 patients, PPV and retinotomy; 2 patients, Orbit SDS
GA size—central reading assessment	≥ 1.25 mm^2 and ≤ 17 mm^2	≥ 4 mm^2 and ≤ 11 mm^2
Mean GA area	12.7 mm^2	7.9 mm^2
Mean age	78.3 years	74.6 years
Historical GA growth	Not available	Square root/year > 0.25 mm
Cataract status	Not defined	Pseudophakic or phakic with Orbit SDS

Abbreviations: PPV: pars plana vitrectomy; SDS: subretinal delivery system; GA: geographic atrophy.

(TABLE 1) Phase II/IIa trial cohort data. *(Chart data courtesy of Dr Christopher D. Riemann)*

who experienced a 10-letter gain that was sustained for 15 months.

"Improvements in drusen retinal outer layers and retinal pigment epithelium within the area of OpRegen transplant were observed and have persisted in some patients," Dr Riemann said. "Asymmetrical progression of geographic atrophy in the treated areas has been observed. The change in the total area is trending toward slower growth in treated versus fellow eyes. Better visual acuity and improved reading speed have been observed in some early cohort patients and all cohort 4 patients after OpRegen."

Adverse events

There was no acute or delayed inflammation or increases in intraocular pressure, but all patients reported at least one adverse event (AE). For systemic AEs, asthenia and malaise were reported by four patients. "Subretinal pigmentation was common and presented in 11 out of 17 patients," Dr Riemann said. "[Although] the significance of this remains unclear, we believe it may represent a potentially positive finding as evidence of long-term survival of the subretinally-transplanted OpRegen cells."

Of note, among patients who received vitrectomy and retinotomy, one had a retinal detachment (successfully repaired) and 13 of 15 patients developed or experienced an exacerbation of an existing epiretinal membrane; one resulted in a temporary reduction in vision and required a vitrectomy, after which vision was restored.

"[Although] visual acuity improved after the peeling, the need for the vitrectomy to remove the epiretinal membrane is important," Dr Riemann said. "Though the cause of these epiretinal membranes remains unclear, we felt as if a possible etiology may have been migration of the OpRegen cells through the retinotomy in the vitreous cavity post transplantation, and this was an important underlying reason for us to explore the Orbit SDS for transplantation of the OpRegen cells without a vitrectomy or retinotomy."

Neither of the two cohort 4 patients operated on with the SDS have developed epiretinal membrane, macular pucker, lamellar hole, retinoschisis or retinal detachment. However, patients in the SDS group developed small, asymptomatic subretinal haemorrhages that resolved on their own. The significance of this AE is unknown.

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This article is adapted from Dr Riemann's virtual presentation at ARVO 2020. He has no financial disclosures related to this content.

High-definition imaging system launched

Quantel Medical has announced the launch of an imaging system, Mosar, which features a high-definition camera, screen and computer, and can be used with its retinal laser, Easyret. The system is designed to enhance retinal laser treatment procedures and follow-up of patients, according to the company, and offers three modes of use:

- **A co-observation teaching mode for live viewing of laser procedures;**
- **An advanced mode allowing the operator to import diagnosis images; prepare, print and record advanced treatment reports including fundus and diagnosis images; and take pictures or record treatment videos for presentation and training purposes; and**
- **A library mode, to manage all the generated images, videos and treatment reports which can be exported on a USB drive or a local network.**

The device has received a CE Mark and is approved by the United States Food and Drug Administration.

Automated diagnostic platform wins CE approval

Geneva-based start-up Mikajaki has announced the limited initial roll-out of a diagnostic system designed to automate and optimise the entire eye diagnostic and testing process.

The company said the CE-Marked platform, Eyelib, should improve operating efficiency at eye clinics and health institutions by delivering better quality of care, reducing waiting times, improving patient access and lowering costs. The device uses proprietary digital technologies, robotics and artificial intelligence to deliver "comprehensive eye health pre-diagnosis and patient triage", according to the company.

The firm has signed contracts with more than 15 European ophthalmic centres and ophthalmic device manufacturers. In a press release, Mikajaki stated that the product is self-operating and requires minimal human interaction, has advanced reporting capability "that goes far beyond traditional data points and charting tools" and is "telemedicine-ready".

Moorfields quadruples cataract operations

Moorfields Eye Hospital quadrupled the number of cataract operations taking place in a single week in September to help clear surgical waiting lists, which have been significantly affected by COVID-19.

To make the 'cataract drive' possible, theatres at Moorfields Private only provided emergency surgeries that week to free up more theatre space. The surgery day process was also adapted, which enabled patients to spend just over an hour on site, as opposed to the usual longer times.

The project was supported by over 90 St John ambulance first-aider volunteers who assisted patients with pre-operative assessments, accompanied them during their surgery and helped with their discharge. The company Alcon supplied IOLs and other equipment to the hospital.

It is likely the initiative will take place again in the coming months as the pandemic continues, Moorfields told *Ophthalmology Times Europe®*.

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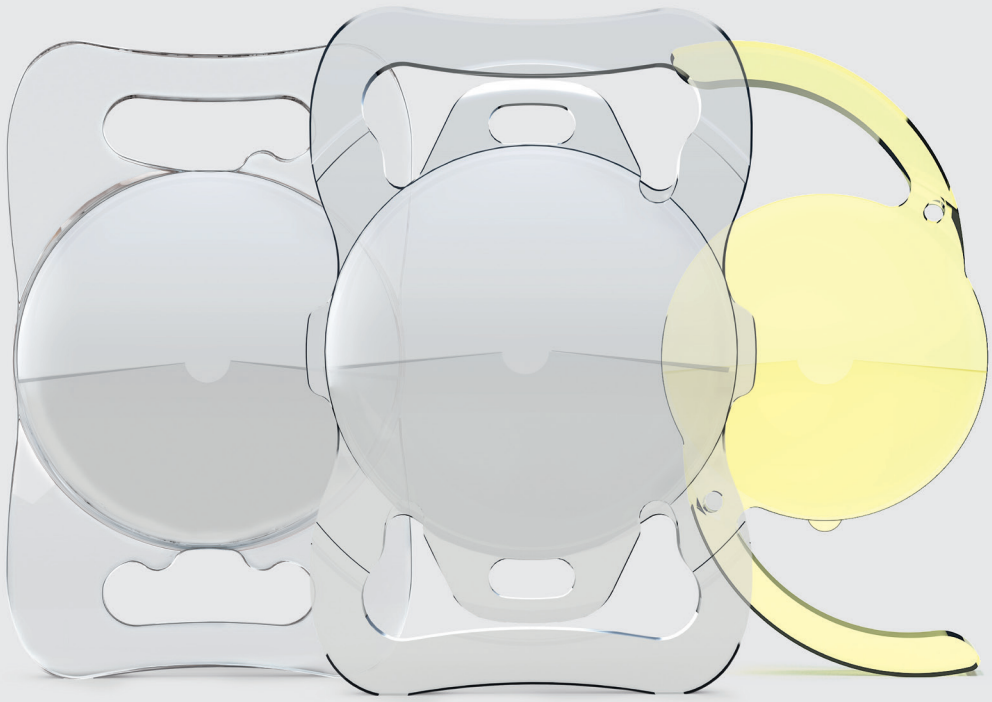

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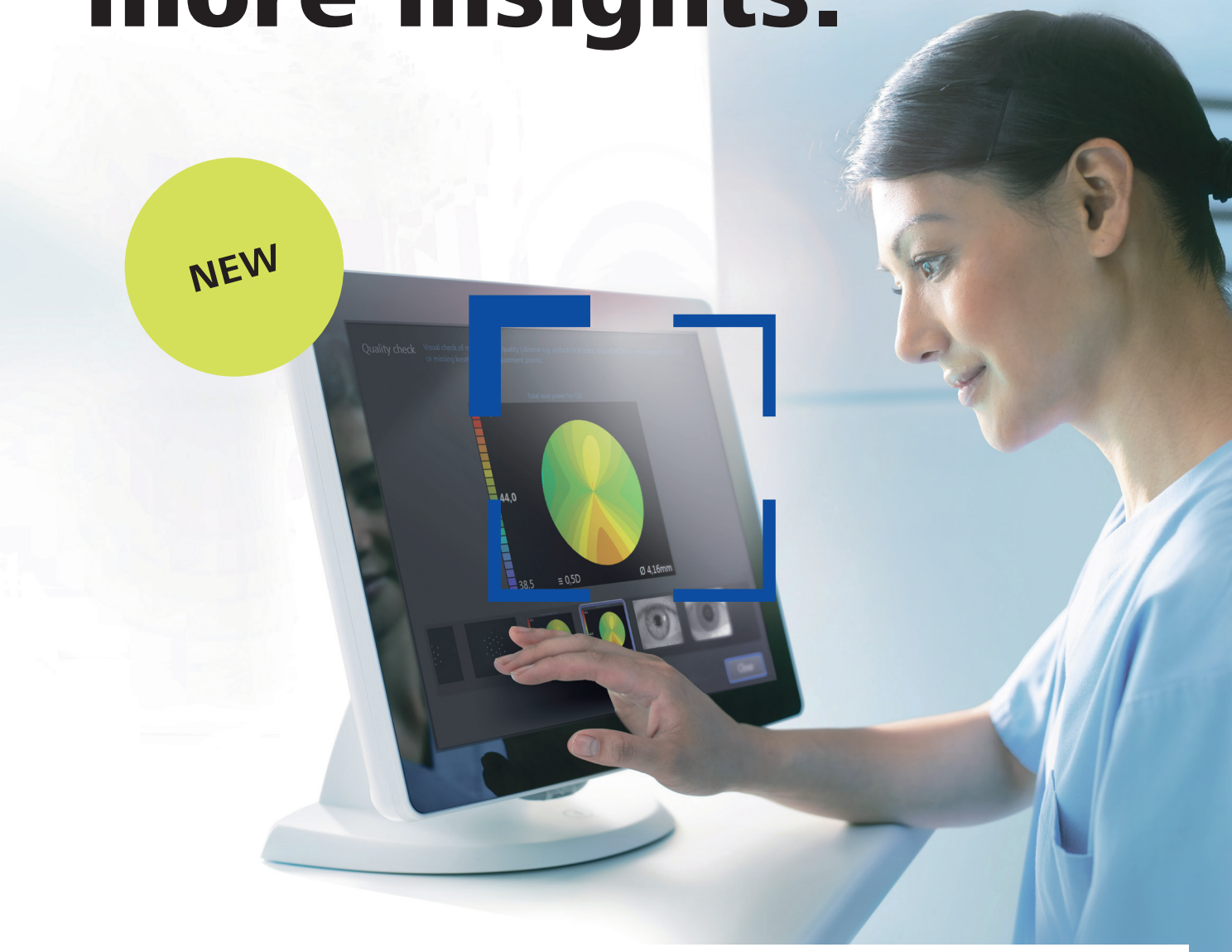

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