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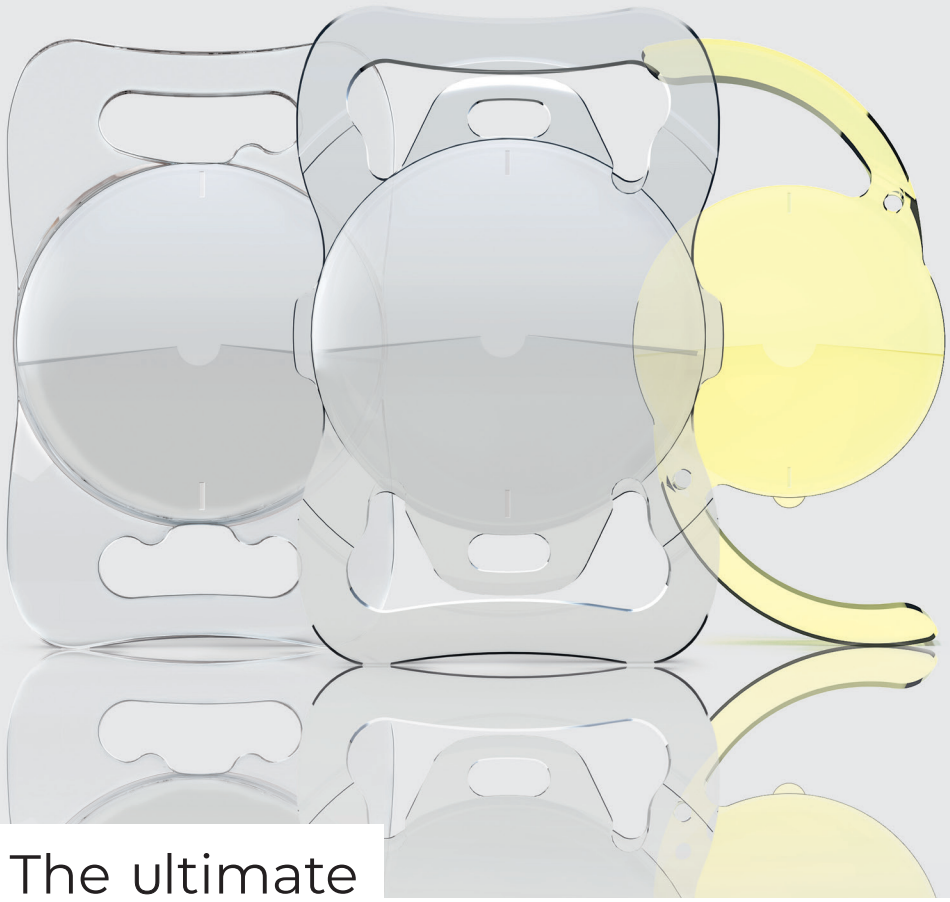

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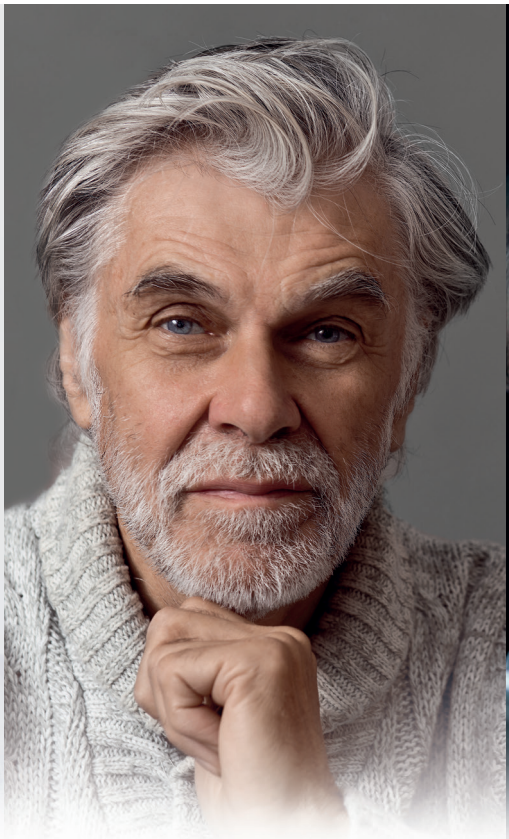

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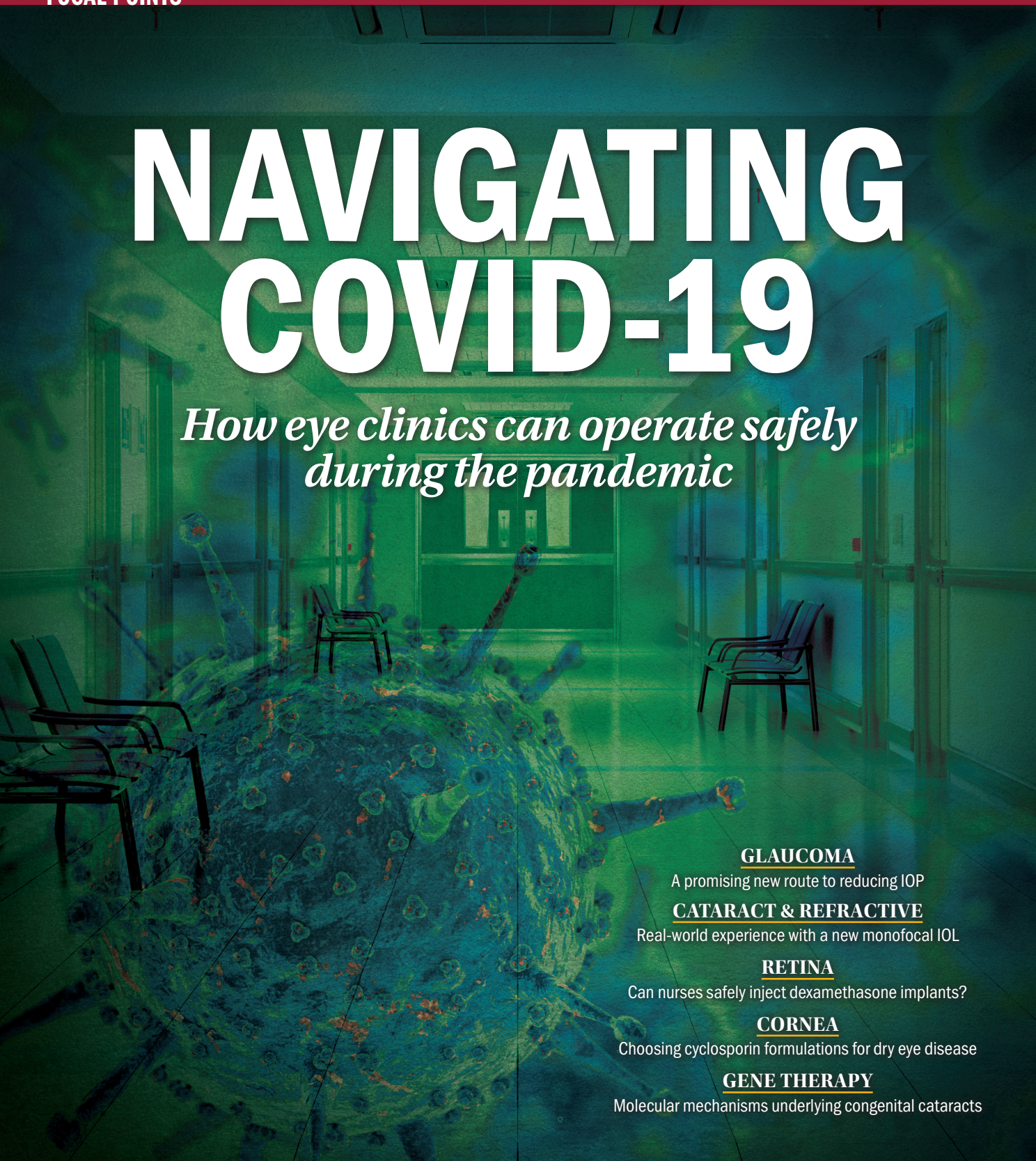

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A promising new route to reducing IOP

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DME, diabetic macular edema; IOP, intraocular pressure; VEGF, vascular endothelial growth factor.

1. Lo Giudice G *et al.* Eur J Ophthalmol 2018;28(1):74–79. **2.** Veritti D *et al.* Ophthalmologica 2017;238(1–2): 100–105. **3.** Escobar-Barranco JJ *et al.* Ophthalmologica 2015;233(3–4):176–185. **4.** Allergan. OZURDEX® Summary of Product Characteristics. **5.** Kodjikian L *et al.* Biomed Res Int 2018:8289253. **6.** Boyer DS *et al.* Ophthalmology 2014;121:(10):1904–1914.

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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

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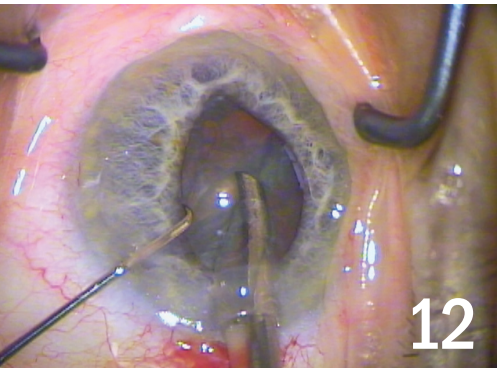

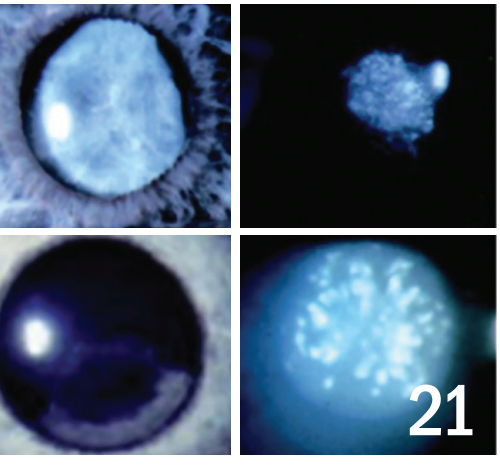

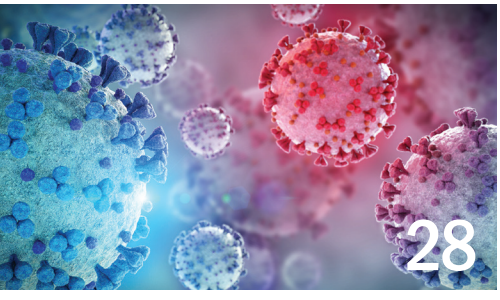

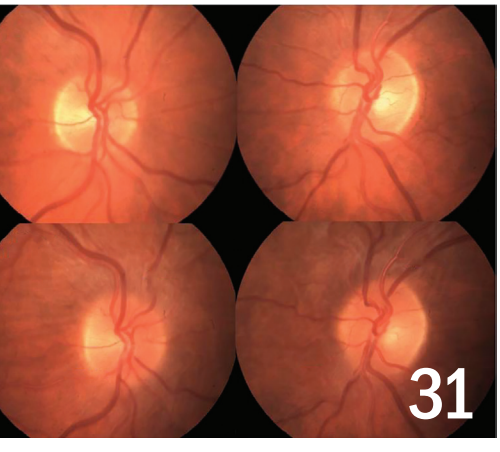

Issue Feature: Glaucoma Management Strategies

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Role of ophthalmic science aiming for new heights

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

March is the time of year when thoughts are uplifted by the promise of brighter days ahead. This year, it takes on even more significance amid the coronavirus disease 2019 (COVID-19) pandemic and safety protocols that have kept people indoors and at home. The continued development and early distribution of effective and safe vaccines are rays of hope as we move forward.

Consider the issue feature in this month's *Ophthalmology Times Europe*®, which focuses on glaucoma management strategies. To date, the suprachoroidal space has not been a feasible route to reduce intraocular pressure in glaucoma. Dr Antonio Fea explains how a new device promises to change that. Next, Dr Paul Healey shares considerations for the best surgical approach in angle-closure patients. The proximity of the iris to the trabecular meshwork makes angle surgery challenging. Intraocular drainage surgery in angle closure remains experimental and investigators are collecting data regarding its efficacy as well as adverse effects.

> "Several hundred genes have been found to be associated with congenital cataracts.

In cataract and refractive surgery, Dr Antonino Cuttitta examines the stability of a novel aspheric IOL in cataract patients. The monofocal lens was found to provide stability in the capsular bag 1 week and 1 month after implantation, with good refractive outcomes.

We also hear from Dr David F. Chang, who offers some practical pearls for success in cases of intraoperative floppy iris syndrome (IFIS). Strategies for the management and prevention of IFIS include intraoperative interventions and recommendations on alternatives to tamsulosin for medical therapy in men with cataracts.

Turning to cornea, Dr Lisa M. Nijm highlights cyclosporine therapies for dry eye relief. From a clinical standpoint, she notes it has been great to see options for long-term treatment. Whether clinicians prescribe an immunomodulator or, optimally, offer some combination of therapies, the possibilities allow ophthalmologists to tailor effective, economical and comfortable care, she says.

In retina, Dr Vasant Raman touches upon the rationale for enabling nurses to inject dexamethasone implants. Safety data on non-clinician-led services have shown a low complication rate. Nurses and other allied healthcare professionals can safely and effectively deliver intravitreal steroid implants in a clean room setting, which has reduced patient waiting times, he explains. Next, an overview provides clinician perspectives on the safety of brolucizumab for neovascular age-related macular degeneration; studies showed favourable retinal fluid outcomes, but a risk of vasculitis urges caution.

In gene therapy, Dr Vanita Berry, Prof. Roy A. Quinlan and Prof. Michel Michaelides look at improving our understanding of the molecular mechanisms underlying cataracts. Several hundred genes have been found to be associated with congenital forms. A greater knowledge of lens embryology and the phenotype/genotype correlation of cataracts should help guide future therapeutic approaches, the researchers believe.

For paediatric patients, we learn from Dr Michael X. Repka how ophthalmologists are exploring the possibilities of myopia prevention and control in the United States. "The axial length progression is really the issue that we want to stop," he says. Investigators are reviewing options that include increased outdoor activity, bifocals and low-dose atropine drops.

In this issue's cover feature, Prof. Christina Grupcheva provides some helpful tips for navigating COVID-19 with ophthalmic patients in the hospital setting. Experience at one ophthalmic practice in Bulgaria demonstrates that new operating procedures, technologies and good management can enable clinics to remain open and operate safely during the COVID-19 pandemic. Ophthalmic training and education should continue to be a priority.

Last but not least, with NASA's sights set on Mars, continued research into further understanding and mitigating spaceflight-associated neuro-ocular syndrome is of the utmost importance for astronaut health and space exploration.

Rest assured that brighter days are ahead. Please continue to stay safe.

A new route to reducing intraocular pressure

Device could make suprachoroidal filtration a viable target for glaucoma surgery

By Dr Antonio Fea


Dr Fea

Minimally invasive surgeries (MIGS) have become popular in recent years. Nevertheless, current technologies have some drawbacks: Schlemm's-canal-based operations are limited by a modest intraocular pressure (IOP) reduction and the impossibility of predicting the level of IOP reduction in a particular patient, while subconjunctival MIGS share with trabeculectomy the need for bleb management and all its drawbacks.

The suprachoroidal space has significant potential, but all previous efforts to exploit this area for reducing IOP have been unsuccessful. Is there any hope for the future or should this pathway be abandoned?

Why suprachoroidal?

The uveoscleral outflow pathway, first described by Anders Bill in 1965,[1] is driven by the negative pressure gradient present in the suprachoroidal space. Traumatic disinsertion of the ciliary body results in IOP reduction.

The suprachoroidal space has been explored as a target for glaucoma surgery for over a century, from the initial simple creation of a cyclodialysis with a spatula to the use of different materials to keep the path from the anterior chamber to the suprachoroidal space open.

Suprachoroidal filtration has several potential advantages: unlike the trabecular outflow it does not depend on episcleral venous pressure; it can be easily accessed via an ab interno approach; it produces a significant IOP drop; and the surgical technique needed to access this space has a very short learning curve. Nevertheless, all efforts to use this route have proven unsuccessful.

Recent experience with the CyPass (Alcon) device led to its removal from the market because of endothelial cell damage.[2] A second problem is the potential sudden closure of the fluid channel due to fibrosis, which results in a marked increase in IOP.

New procedure

iSTAR Medical is pioneering a new product called Miniject that addresses some of the drawbacks of previous devices. The surgical procedure is ab interno, which allows for sparing of the conjunctiva and the sclera for further surgery if needed.

The material used is soft and flexible and protrudes only minimally into the anterior chamber; these characteristics are intended to minimise endothelial cell damage.[3] The material is made of hollow silicone spheres, providing a high degree of biocompatibility and bio-integration.

Studies of up to 26 weeks on rabbits[4] demonstrated that the material is colonised by host cells, a process which minimises fibrotic encapsulation around the device. These healthy cells do not prevent aqueous humour drainage but rather minimise the occurrence of long-term IOP spikes due to fibrosis.

All these observations are essential because a possible reason why previous attempts to utilise the suprachoroidal space as a viable surgical alternative in the treatment of glaucoma may have failed is that the devices were made of unsuitable materials.

Trial data

To date, approximately 130 patients have been implanted with the device in different stand-alone trials.[5] In pooled data from the STAR-I[6] and STAR-II[7] studies, mean postoperative pressure at 6 months was 14.5 mmHg on an average of 0.7 IOP-lowering medications with an IOP reduction of 40%, which is quite impressive compared with other technologies, especially considering that we are talking about stand-alone procedures.

Results at 24 months in the STAR-I trial showed a sustained IOP reduction of 41% to a mean of 13.8 mmHg on an average of one medication.[8] Furthermore, pooled data across all trials of the device show that secondary glaucoma surgery occurred at a low rate of 5%.[5]

Hypotony (<6 mmHg) was present in a low number of patients (1% in STAR-I, II, III trials), and transient. Transient hyphemia occurred in 11% of patients across all the trials, which may be linked to the first-generation dual-operator delivery injector

IN SHORT

- ***To date, the suprachoroidal space has not been a feasible route to reduce intraocular pressure in glaucoma. A new device promises to change that.***

that has since been replaced by a single-operator delivery tool. Rates of hyphema are particularly relevant in procedures that are combined with cataract surgery, due to the high visual expectations of patients.

Long-term reduction in mean visual acuity reduction (≥2 lines) was experienced by up to 11% of pooled patients and was mainly due to cataract progression. Little can be said at present regarding endothelial cell density (ECD) loss because longer follow-up is necessary. However, only a 5% mean corneal ECD loss has been reported with the device over 24 months, and no patient manifested a decrease ≥30%.

The delivery system has been improved over the years: it started as a two-operator procedure but now has a much more user-friendly inserter using a wheel for implantation and requiring only one operator. The width of the delivery device, nevertheless, requires some improvements in order to avoid unnecessarily wide clefts. A clinical study and further recent product development have evaluated the best sheath curvature and tip sharpness to enable effective penetration into the supra-choroidal space.

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Considering the best surgical approach in angle closure patients

Proximity of the iris to trabecular meshwork makes angle surgery challenging

By Lynda Charters;

Reviewed by Dr Paul Healey

Intraocular drainage surgery (IDS) may be relevant for patients with angle closure because the conventional outflow pathway can be blocked physically, first by the iris and then by secondary damage caused by the iris, inflammation and ischaemia in the trabecular meshwork (TM).

When considering the surgical approaches in these patients, removing the physical obstruction and enhancing the TM outflow by reducing the resistance with surgery to the TM may be the best options before considering enhancing or creating a nonconventional path of outflow, according to Dr Paul Healey. Dr Healey is clinical associate professor, based at the Centre for Vision Research, Westmead Institute for Medical Research; the Save Sight Institute, University of Sydney; and Westmead Hospital Eye Clinic and Sydney Eye Hospital, Sydney, Australia.

TM surgical options

In theory, TM or Schlemm's canal surgery for angle closure involves the same methods as established surgeries performed in open angles – remove, cut or dilate the TM or Schlemm's canal. Surgeons can choose from devices such as the Trabectome (NeoMedix), Kahook Dual Blade (New World Medical), Omni Glaucoma Treatment System (Sight Sciences) and iTrack (Nova Eye Medical) devices.

Trabecular microbypass stents include the Hydrus (Ivantis) or the iStent or iStent Inject (Glaukos Corporation). Dr Healey said any angle surgery is difficult in patients with angle closure because of the proximity of the iris to the TM.

"We know that the iris can cause further obstruction of the TM that can be hydrostatic or inflammatory. Therefore, in angle procedures that are inflammatory, we should consider what the risk of synechial closure in response to that inflammation might be," Dr Healey said. When using a stent in the TM to establish drainage in angle closure patients, the stent outlets need to clear the iris, both intraoperatively and postoperatively, he emphasised.

There are few published evaluations of internal drainage surgeries in angle closure. So far, the only available data were obtained from iStent implantations combined with cataract surgeries, he said. To further complicate the issues, no minimally invasive glaucoma surgery (MIGS) procedures or devices have been approved for this use. "The data we are discussing are purely experimental," Dr Healey said.

Experimental data

Dr Healey recounted a study by Chansangpetch et al that evaluated the efficacy of cataract surgery with trabecular microbypass stent implantation in patients with angle-closure glaucoma.[1] These patients had either open-angle or angle-closure glaucoma treated with iridotomy, but IOP remained elevated. The patients underwent either cataract extraction alone or accompanied by iStent implantation.

The highest success rate was achieved in patients with angle closure who underwent phacoemulsification and iStent implantation; patients with angle closure treated with cataract extraction also did well. The patients in both angle closure groups saw a substantial decrease in the number of required medications postoperatively.

Another study reported a case series of iStent implantations and phacoemulsification in primary angle-closure glaucoma.[2] The authors reported good decreases in IOP resulting from the combined procedure, but they also found that 27% of eyes had occlusion of the iStent by iris.

However, Dr Healey said the IOP was increased in only 2.7% of eyes. "While this may suggest some residual stent function, probably removal of the lens was the primary mechanism of preventing postoperative IOP increases in angle closure."

IN SHORT

Intraocular drainage surgery in angle closure remains experimental and investigators are collecting data regarding its efficacy as well as adverse effects.

The risk factor for occlusion of the stent in this study was a deeper anterior chamber. "This actually makes sense because a patient with angle closure with a deeper central anterior chamber is more likely to have a nonpupil block/nonlens vault aetiology and therefore less likely to have an angle that is more open after lens removal," he said.

Dr Healey handles these cases by first opening the closed angle, but iridotomy alone is usually inadequate. Lens extraction and sometimes goniosynechialysis are necessary to obtain close proximity to the TM.

He emphasised the importance of performing a procedure that is as minimally inflammatory as possible. Finally, surgeons also need to control the iris and the IOP during the postoperative period.

The current place for IDS

IDS in angle closure remains experimental. Investigators are collecting data regarding its efficacy as well as adverse effects.

Dr Healey said early case series often consist of two groups: those thought to have a higher probability of anatomic and physiologic success, and those for whom the choice of this procedure offered a lower risk of an adverse reaction compared with alternatives. "Evaluating outcomes from these and other studies will inform us of the value of these technologies in the management of angle closure and whether this is a procedure that is worth doing in the future," Dr Healey explained.

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Examining the stability of a new aspheric IOL in cataract patients

Bi-sign design compensates for abberations resulting from IOL misalignment

By Dr Antonino Cuttitta

Patients who wish to reduce their reliance on glasses have high expectations of their visual outcomes after cataract surgery. To meet their demands, lens technology has advanced significantly, particularly with the introduction of aspheric IOLs, which are designed to reproduce the natural shape of the crystalline lens to improve visual quality and contrast sensitivity.[1]

To achieve the best visual outcomes from advanced lens technology, lens stability in the capsular bag is essential. I recently studied the anterior chamber stability of the newly introduced CT Lucia 621 P (Carl Zeiss Meditec), a monofocal aspheric hydrophobic acrylic IOL with a heparin-coated surface (Figure 1).

It is important to know the patient's anterior chamber depth before surgery, so we can calculate the IOL power accurately. After surgery, it helps us determine the stability of the IOL in the capsular bag and assess the patient's refractive outcome.

Lens design

The bi-sign design of CT Lucia IOLs compensates for a number of aberrations resulting from IOL misalignment or the corneal contour, providing the benefits of neutral and correcting aspheric IOLs and improving retinal image quality.[2] The single-piece C-loop CT Lucia 621P follows the previously introduced monofocal spherical CT Lucia 211P and aspheric 611P(Y), in addition to other Zeiss monofocal IOLs.

It has a 6-mm-diameter optic and 13-mm total diameter and is available from +0.0 to +34.0 D in 0.5-D increments. The lens has step-vaulted haptics and a reinforced optic-haptic junction to promote stability in the capsular bag, for improved lens centration, refractive predictability and long-term visual outcomes.

Ease of use of the injector is an important consideration for surgeons and surgical staff. This lens comes fully preloaded in a redesigned injection system that makes injection easier, faster and safer than before.

As the injector is advanced to the intermediate position, there is an audible click. The ramp stop helps the surgeon apply the correct pressure to the thumb flange to release the IOL.

Assessing lens stability

Within a 1-month period, I implanted this monofocal lens in 60 eyes of 60 patients who ranged in age from 51 to 91 years. It was used in every patient having cataract surgery; there were no specific inclusion or exclusion criteria. Therefore, this protocol reflected our daily experience as cataract surgeons in performing routine cataract surgery with monofocal IOLs and demonstrated the typical clinical behaviour of the IOL in this setting.

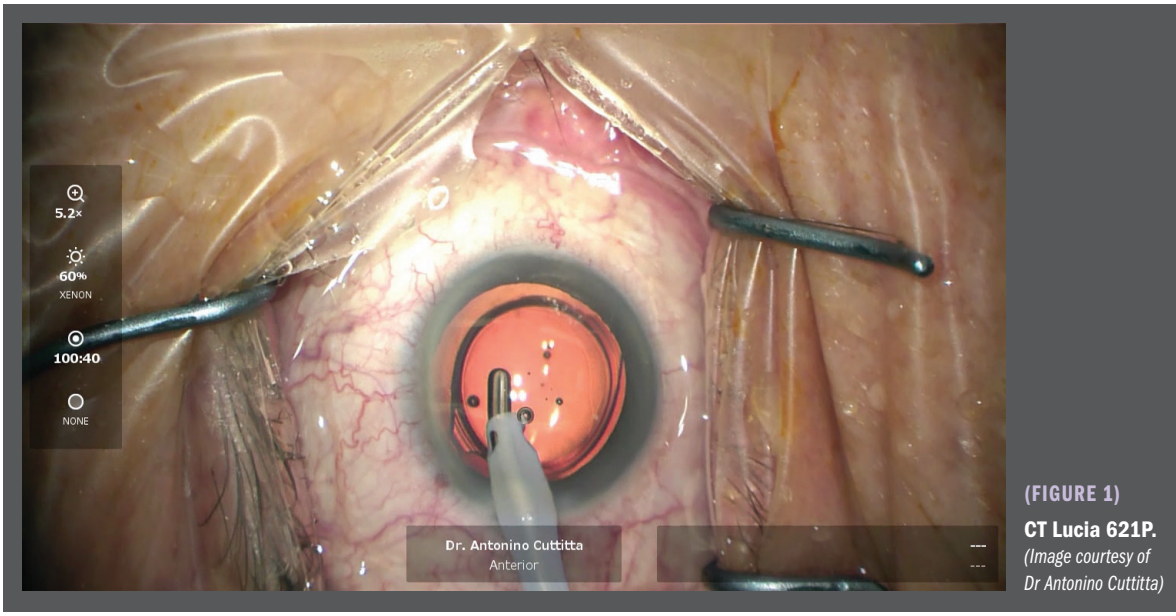
> To achieve the best visual outcomes from advanced lens technology, lens stability in the capsular bag is essential.

I examined the stability of the IOL by measuring anterior chamber depth with biometry (IOLMaster 700, Carl Zeiss Meditec). Preoperatively, the mean anterior chamber depth was 3.13 mm.

After surgery, the anterior chamber depth was measured twice: after 1 week and then 1 month later. Anterior chamber depth measurements indicated good stability within the capsular bag, without the IOL position changing significantly, whether patients were hyperopic or myopic. At 1 week, the mean anterior chamber depth was 5.36 mm and at 1 month it was 5.34 mm.

IN SHORT

- ***A new monofocal IOL was found to provide stability in the capsular bag 1 week and 1 month after implantation, with good refractive outcomes.***



(FIGURE 1)
CT Lucia 621P.
(Image courtesy of Dr Antonino Cuttitta)

No patients had complications, nor did they report glare or other light-related disturbances. They had very good refractive outcomes that were consistent with the expected calculations of the biometer, indicating that the lens was very stable in the bag from the first week after surgery. The mean corrected visual acuity was 10/10.

The injector system was very easy to use and performed well with the 60 lenses we implanted. One lens got stuck in the injector, but this was remedied and otherwise we had no issues. The learning curve was very easy; our experience was reproducible and we had a high level of reliability.

The IOL opens very quickly when injected and there were no problems with the optics. When the manufacturer questioned surgeons and nurses about the system, most reported that they preferred it over their reusable injector of choice.[3]

Surgical pearls

Based on my experience with the CT Lucia 621P, I would like to offer some advice for implanting it. It is very important to use the correct amount of viscoelastic during the procedure to help the IOL slide across the injector and unfold correctly in the capsular bag.

If too much viscoelastic is used, the lens will slide across the injector but open slowly in the capsular bag because the haptic will stick to the plate of the lens. In contrast, if there is not enough viscoelastic, the lens will not slide across the injector properly and a haptic may break.

It is also necessary in general to be especially careful with higher-power lenses because they are thicker and a bit more rigid. However, we did not have problems with higher-power versions of this lens.

Conclusion

In my experience, the CT Lucia 621P maintained stability in the capsular bag 1 week and 1 month after implantation and provided good refractive outcomes. The redesigned injector system was easy to use and provided smooth delivery of the IOL into the capsular bag.

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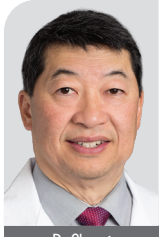
Expert on floppy iris syndrome offers practical pearls for success

Cataract surgeons must consider medication history in preoperative evaluation

By Cheryl Guttman Krader;

Reviewed by Dr David F. Chang



Dr Chang

The first report associating use of the α1A antagonist tamsulosin with intraoperative floppy iris syndrome (IFIS) appeared in the literature in 2005. Subsequently, studies have examined the underlying mechanism for the complication and determined that it occurs in women as well as in men, with other α1-antagonists, when α1-antagonist treatment has been stopped preoperatively, and in patients without a history of taking an α1-antagonist.

Furthermore, research shows that a significant proportion of physicians who prescribe α1-antagonists fail to consider or are even unaware of how these medications can cause complications during cataract surgery. With this background in mind, cataract surgeons need to carefully review medication history as part of the preoperative evaluation so that they can identify at-risk patients. They also need to be knowledgeable about the strategies for IFIS management.

In a clinical update on IFIS during the American Academy of Ophthalmology's 2020 virtual meeting, Dr David F. Chang reviewed the literature on these topics and provided some practical advice. Dr Chang works in private practice in Los Altos, California, United States, and is a clinical professor of ophthalmology at the University of California, San Francisco, US. He co-authored the 2005 paper linking tamsulosin use with IFIS and has since been involved in research and education about this complication.

Insights into IFIS risk

Dr Chang presented information on the pharmacology and pharmacokinetics of drugs that block α1-adrenergic receptors to explain why, within this medication class, tamsulosin is associated with the greatest risk of IFIS. In addition, he discussed evidence showing that tamsulosin not only blocks the α1A receptor in the iris dilator muscle but also causes atrophy of the dilator muscle, to explain why discontinuing treatment preoperatively does not eliminate IFIS risk.

There are potential factors to consider and investigators have looked at these issues. Dr Chang reviewed studies that identified other possible risk factors for IFIS, including hypertension and reports of IFIS in patients with no history of α1-antagonist use. Among the latter papers was a prospective study co-authored by Dr Chang that documented that in the absence of any epinephrine in the irrigating bottle, severe IFIS occurred during cataract surgery in almost 5% of patients who had no history of α1-antagonist use. He added that the study was also among the first to provide evidence supporting a benefit for routinely adding epinephrine in the irrigation bottle to prevent mild to moderate IFIS.

> Cataract surgeons need to carefully review medication history as part of the preoperative evaluation.

"The commercially available fixed combination of phenylephrine 1%/ketorolac 0.3% (Omidria, Omeros Corp.) is approved for maintaining pupil mydriasis, but off-label use of epinephrine in the bottle is also very effective," Dr Chang said.

Prevention and management

As an alternative to adding phenylephrine 1%/

IN SHORT

- ***Strategies for the management and prevention of floppy iris syndrome include intraoperative interventions and recommendations on alternatives to tamsulosin for medical therapy in men with cataracts.***

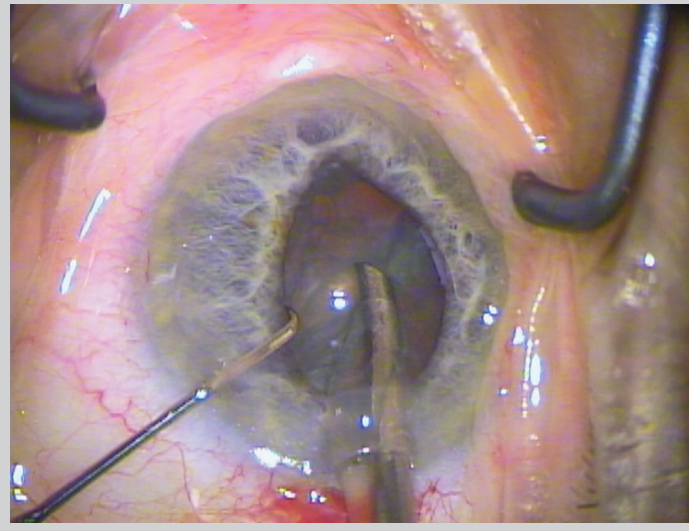
ketorolac or epinephrine in the irrigation bottle, Dr Chang recommends considering direct intracameral injection of an α-agonist, such as epinephrine or phenylephrine, for patients with a history of α1A-antagonist use. "Because of its low pH, epinephrine should be first diluted 1:4000 or 1:5000 with BSS [balanced salt solution] prior to off-label intracameral injection," Dr Chang said.

Epinephrine formulations containing chlorobutanol preservative or tartaric acid are not intended for intraocular use and should be avoided. Unpreserved epinephrine ampules may contain bisulfite 0.1% to slow oxidation, but corneal endothelial toxicity is avoided with the recommended dilution.

Intracameral injection of phenylephrine 1.5% offers an effective alternative to epinephrine for preventing IFIS, however, this must be obtained from a compounding pharmacy in the US. For any compounding of intraocular drugs, Dr Chang recommended using a 503B outsourcing facility that is authorised to ship products nationally and is subject to stringent Food and Drug Administration regulations and inspection.

Dr Chang cautioned against doing pupil stretching to manage IFIS or a small pupil in a patient at risk for IFIS but said iris retractors and mechanical pupil expansion rings are very effective for maintaining an enlarged pupil. "I use a pupil expander if there is any question about severe IFIS risk and also when there is a comorbidity, such as pseudoexfoliation, a dense lens or perhaps a shallow chamber, as well as when the pupil is not dilating well, even with intraocular phenylephrine," Dr Chang said.

Strategies for preventing IFIS also include efforts to educate physicians who prescribe α1-antagonists to treat benign prostatic hyperplasia (BPH) about the risk. These prescribers should be counselled to ask patients if they have cataracts, consider advising patients with symptomatic cataracts to undergo cataract surgery prior to initiating nonemergent treatment with an α1-antagonist, or treat BPH with a medication other than tamsulosin that carries a lower risk of IFIS or no risk.



(FIGURE 1) Prior to cataract surgery, ophthalmologists must consider the medication history of their patients. *(Photo courtesy of Dr David F. Chang)*

Conclusion

Dr Chang said he recommends that prescribing physicians consider tadalafil used alone or in combination with dutasteride as a first-line treatment for BPH in their patients with cataracts. While it is better known as a treatment for erectile dysfunction, tadalafil is a phosphodiesterase-5 inhibitor that is also able to offer some benefits for patients with lower urinary tract BPH symptoms by improving bladder emptying.

According to Dr Chang, dutasteride, a 5α-reductase inhibitor, decreases prostate size and offers an option for patients. It can prove to be a viable option for ophthalmologists.

When an α-antagonist is needed, Dr Chang noted that alfuzosin carries a low risk of postural hypotension in patients and is less likely to cause severe IFIS than tamsulosin, according to a masked comparison study he and his colleagues published.

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This article is based on Dr Chang's presentation at the American Academy of Ophthalmology's virtual 2020 annual meeting. He has no financial interest in any product mentioned.

Cyclosporine options for dry eye relief

Hydrophobic, lipophilic molecule is effective but can cause burning or stinging

By Dr Lisa M. Nijm;

Special to
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Dr Nijm

My clinic is very busy managing dry eye, as our already-strong demand for services has swelled in response to patients' COVID-19-era increased screen time, work-from-home arrangements and elevated stress. During this past year, I have implanted more punctal plugs, prescribed more dry eye medications and scheduled more dry eye procedures than ever before.

Cyclosporine is a well-established stalwart of long-term management for dry eye disease (DED). Ophthalmologists have trusted it for years as an effective immunomodulator that alleviates dry eye symptoms without major negative side effects.

We have several options for cyclosporine: Cequa (0.09%, Sun Ophthalmics), Restasis (0.05%, Allergan) and the compounded Klarity-C Drops (0.1%, Imprimis). Several more are in the pipeline, including generic Restasis, CyclASol (0.1%, Novaliq), Ikervis (0.1%, Santen Pharmaceutical) and OTX-CSI ophthalmic insert (0.36 mg, Ocular Therapeutix).

Although the concentrations range from 0.05% to 0.1%, I have found cyclosporine to be efficacious at all levels, with some subtle differences. The choice usually comes down to tolerability and affordability.

As a topical ophthalmic agent, cyclosporine poses several challenges. Firstly, it is a hydrophobic, lipophilic molecule, so does not easily penetrate the aqueous layer and reach the eye. Secondly, it can cause burning or stinging on instillation.

As a result, manufacturers need to formulate a vehicle that achieves the penetration required for efficacy, produces minimal side effects and feels comfortable for chronic use – a notoriously difficult feat. The tolerability of different cyclosporine formulations hinges primarily on the vehicle, which varies among different products.

Although I tend to favour products with an established track record of comfort, some patients might tolerate one better than another.

Because I have used Restasis—which has an anionic castor oil-in-water emulsion vehicle[1]—for many years, I know to expect patients to be comfortable with its long-term use. As it has been around a long time, Restasis is also covered by most insurance plans.

My patients have also tolerated Cequa well, which has a nanomicelle-based solution. Commercial patients can obtain Cequa at its lowest price through a specialty pharmacy, so we check with patients in advance to see if that is a convenient arrangement.

The third current option, Klarity-C Drops, has a chondroitin sulfate, glycerin and dextran-based solution.[2] This can be the most cost-effective choice. However, in my limited experience, it also seems to be less well tolerated.

I use both cyclosporine and lifitegrast (Xiidra, Novartis) as part of long-term management plans. With cyclosporine, my best candidates have chronic dry eye and possibly wear contact lenses, so they need long-term relief from inflammation.

It can take up to 3 months for cyclosporine to build up the concentration required for full efficacy, so I tend to choose it for patients who can patiently await some improvement. For more severe cases, I also utilise a steroid during the cyclosporine induction period, such as loteprednol etabonate ophthalmic suspension 0.25% (Eyesuvis, Kala Pharmaceuticals) which can be used on-label for short term treatment of dry eye.

In addition, my patients who have dry eye secondary to autoimmune conditions such as Sjogren's syndrome or rheumatoid arthritis tend to respond very well to cyclosporine.

From a clinical standpoint, it has been great to see more options for long-term DED treatment. Whether we prescribe an immunomodulator or, optimally, offer some combination of therapies, the options allow ophthalmologists to tailor effective, economical and comfortable care.

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The rationale for enabling nurses to inject dexamethasone implants

Safety data on non-clinician-led services have shown a low complication rate

By Dr Vasant Raman


Dr Raman

Intravitreal pharmacotherapy has emerged as the most effective means of delivering drugs for retinal diseases. From a mere few thousand injections delivered worldwide in the early part of this century, it has now become one of the most commonly performed procedures in ophthalmology.

However, with an ageing population in the western world requiring treatment for wet age-related macular degeneration, and with diabetes mellitus and its associated diabetic maculopathy projected to rise in the coming years, delivery of intravitreal injections remains a challenge. In a publicly funded health service, as with the UK's National Health Service, resource constraints do not permit clinicians to deliver the injections themselves, as this would lead to a shortfall in clinical and surgical activity.

An approach that has been widely accepted and implemented across the UK is to allow nurses and other allied healthcare professionals (AHP), including optometrists and orthoptists, to deliver anti-vascular endothelial growth factor (VEGF). In fact, the UK is now at the forefront of adopting the nurse injector as a model for service delivery.

Initiated in 2009, the safety of this service[1] has been amply demonstrated in many studies wordwide.[2] However, the role of nurses and other AHPs has not yet been extended to the delivery of steroid implants for patients with macular oedema due to diabetic maculopathy, retinal vein occlusion and uveitis.

Barriers to nurse-led steroid injections

Despite the demonstrated safety, there is still some apprehension about nurse-led delivery of steroid implants, one reason purportedly being the bulkier injection system used: the dexamethasone (Ozurdex, Allergan) implant delivery system uses a larger needle (19 G) than the fine-bore needle (30 G) used for anti-VEGF injections. This could potentially lead to a higher rate of complications.

There may also be concerns about a lack of demand. The number of steroid implants being injected is a small fraction of the number of anti-VEGF injections given – 1:15 in our unit. However, this ratio, while small, is significant in terms of logistics in service delivery and has been steadily increasing.

Historically, clinicians have been averse to the idea of sharing their work with AHPs. In ophthalmology, it was seen as a novelty when nurses started injecting anti-VEGF drugs, although ophthalmic nurses had been doing minor invasive procedures such as meibomian cyst excision or subtenon injections of anaesthesia for cataract surgery[3] from the early part of this century.

In addition, AHP and nurses have been delivering complex invasive screening and diagnostic services in gastrointestinal medicine, urology, respiratory and haematology since the late 1980s. Randomised studies have shown comparable success and complication rates between clinicians and nurses.[4]

Our experience

Our impetus for encouraging nurses to deliver a dexamethasone implant service arose from the protracted waiting time for patients after the clinical decision was made. This sometimes exceeded 30 days. Audit analysis of the delay revealed two reasons for this: firstly, dexamethasone injections were delivered in the operating theatre by doctors and secondly, the injections were being scheduled as the last procedure on the theatre list, meaning they were prone to cancellation if an emergency operation was added.

We restructured our setup by moving the dexamethasone injection service from the theatre to the clean room setting alongside the anti-VEGF service. This was considered the only way to reduce the waiting time for injecting the implant and sustaining the service in the long term.

IN SHORT

- ***Nurses and other allied healthcare professionals can safely and effectively deliver intravitreal steroid implants in a clean room setting, which has reduced patient waiting times.***

Two senior nurses, experienced in intravitreal injection, were selected to undergo training for injecting the dexamethasone implant. After initially practising using porcine eyes in a wet lab, they were then trained on patients by a retina specialist. They were certified to undertake the procedures after undergoing competency assessment by a second independent physician.

The first significant outcome of this nurse-led service was a halving of the waiting time for patients, from 30 to 15 days. In addition, the safety of the service delivered was audited after the nurses had given 1,000 injections and there were no visually significant complications such as endophthalmitis, iatrogenic cataract, vitreous haemorrhage or retinal detachment. There was only one case of incomplete penetration of the implant[5] but this resolved following conservative treatment with no sequelae.

We believe the following may be some of the reasons for our low complication rate:

- **We recruited nurses who were already experienced in intravitreal injections;**
- **Their self-audited personal safety profile and complication rate was very low;**
- **We have adopted a standard anatomical landmark (4 mm behind the limbus) for injection in patients irrespective of their phakic status; and**
- **The framework of training and supervision is robust and the service is closely supported by clinicians.**

Published safety data about nurse-led injection services have been encouraging, with a very low, acceptable level of complications in a clinical care environment.[1,2] A patient satisfaction questionnaire conducted 3 months after introducing this service showed overwhelming patient satisfaction, with most expressing a desire for the continuation of the nurse-led service. They also felt the experience was less stressful in the outpatient clean room setting as opposed to an operating theatre environment.

Cost savings

It is relatively easy to train experienced nurse practitioners as the principle of injection remains essentially the same for all intravitreal injections. The time and resources needed are minimal and costs are reduced by allowing the clinicians time for other activities. Furthermore, since intravitreal dexamethasone injection is not an operation, it can be safely performed in a clean room as with anti-VEGF injections.

It is worth noting that the Royal College of Ophthalmologists, the professional body for ophthalmologists in the UK, supports AHPs delivering intravitreal injections within a robust clinical governance framework. However, the pharmaceutical industry does not advocate injection by non-clinicians in their summary of product characteristics either for anti-VEGF or steroid implants. With more safety data being published and with the widespread adoption of nurses and AHPs delivering intravitreal injection of different delivery systems, this will probably change.

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Brolucizumab for neovascular AMD: Clinician perspectives on safety

Studies showed favourable retinal fluid outcomes but vasculitis risk urges caution

By Rod McNeil;

Reviewed by Dr David S. Boyer, Prof. Ramin Tadayoni, Dr Jeffrey S. Heier and Dr Paul Hahn

Two Phase 3 clinical trials, HAWK and HARRIER, demonstrated that brolucizumab (Beovu, Novartis) is an effective treatment for neovascular age-related macular degeneration (nAMD), demonstrating non-inferiority to aflibercept (Eylea, Bayer/Regeneron) in visual function at week 48 and more favourable retinal fluid outcomes than those seen with aflibercept (see Table 1)[1,2] However, although the safety profiles of the two drugs were found to be similar, intraocular inflammation and ocular occlusive events were more frequently reported with bolucizumab.[3,4]

In 2020, Novartis carried out a post-marketing safety review of the drug and, along with an independent external safety review committee, concluded that it can cause retinal vasculitis and/or retinal vascular occlusion, which may result in severe vision loss. Typically, these adverse events occur in the presence of intraocular inflammation.

The unmasked post hoc assessment of brolucizumab-treated patients in HAWK and HARRIER showed that the overall rate of intraocular inflammation, retinal vasculitis and concomitant retinal vasculitis and retinal vascular occlusion was 4.6%, 3.3% and 2.1%, respectively.[5] The overall rate of developing intraocular inflammation of any form and losing 15 or more letters was 0.74%.[5] This compares with an incidence of intraocular inflammation of 1.1% in aflibercept-treated eyes, with at least a moderate visual acuity loss seen in 0.14%.[5]

Safety-related product label updates for brolucizumab have now been approved by several health authorities in Europe, the United States, Canada, Australia and Japan, incorporating the additional information that retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with its use.[6] The product's summary of product characteristics states that in patients developing these conditions, treatment should be discontinued and the events promptly managed. Physicians are also advised to ensure provision of clear information to patients, establish an appropriate control plan and confirm absence of inflammation prior to re-injection.

The true incidence of post-brolucizumab vaso-occlusive events remains unknown. Post-marketing data for cases reported through to 18 December 2020 indicate a total incidence of 15.73 of the three adverse events of interest for every 10,000 (distributed) injections, with combined retinal vasculitis and retinal vascular occlusion being the most prevalent at 7.46 per 10,000 injections.[6]

Expert perspectives

Despite the risk of potentially serious adverse events seen with brolucizumab, events that are not commonly associated with intravitreal anti-vascular endothelial growth factor (VEGF) agents,[5,7] rates of moderate and severe vision loss were similar for brolucizumab and aflibercept in the HAWK and HARRIER registration trials (Table 2).[1,2] Asked under what circumstances physicians consider using brolucizumab for nAMD, Dr David S. Boyer, Retina-Vitreous Associates Medical Group, Los Angeles, California, US, said: "The HAWK and HARRIER trials confirmed the outstanding drying effects of brolucizumab compared with aflibercept."

He added: "Unfortunately, the safety of brolucizumab will limit use as a first line therapy, delegating its use to patients who do not respond at all, or are very poor responders to the currently available anti-VEGF treatments. I am hoping that the uveitis and vaso-occlusive retinal issues can be mitigated by Novartis to allow a safer drug safety profile, thereby allowing more widespread use of brolucizumab."

Speaking at the 20th EURETINA virtual congress, Prof. Ramin Tadayoni, Universite de Paris, France,

IN SHORT

- ***Although most nAMD patients benefit from brolucizumab treatment without severe adverse events, the risks need to be balanced with potential benefits.***

Table 1. ***Fluid resolution and central subfield thickness data in HAWK and HARRIER.[1,2*]***

		HAWK		HARRIER	
Secondary Endpoint	Week	Brolucizumab 6 mg (q12w/q8w)	Aflibercept 2 mg (q8w)	Brolucizumab 6 mg (q12w/q8w)	Aflibercept 2 mg (q8w)
Proportion of patients with IRF and/or SRF (%)	48	31	45	26	44
	96	24	37	24	39
Proportion of patients with sub-RPE fluid (%)	48	14	22	13	22
	96	11	15	17	22
Decrease in CST from baseline (in microns)	48	-173	-144	-194	-144
	96	-175	-149	-198	-155

**All dosing regimens following initial monthly loading. CST: central subfield thickness; IRF: intraretinal fluid; SRF: subretinal fluid; sub-RPE: subretinal pigment epithelium.*

(Adapted from: Dugel PU, Koh A, Ogura Y, et al; HAWK and HARRIER Study Investigators. Ophthalmology. *2020;127:72-84 and Dugel PU, Singh RP, Koh A, et al.* Ophthalmology. *2021;128:89-99)*

said that brolucizumab represents an important treatment option for nAMD, with an overall favourable benefit/risk profile, in particular in patients uncontrolled with other intraocular anti-VEGF therapies.[8] He added that the product addresses key unmet needs by providing robust vision gains and favourable anatomic outcomes with the potential to extend treatment intervals.

He added: "Brolucizumab is of particular interest when the physician thinks he can better control the disease with this molecule than with other anti-VEGFs. Once patients are carefully selected, the prerequisite is to obtain appropriate informed consent and provide clear education about which signs should lead to a rapid consultation, especially any inflammation following brolucizumab. The more we learn about how to control and treat rare but potentially serious ocular adverse events after brolucizumab injection, the more real-life use would extend."

Through the Novartis-lead Brolucizumab Coalition partnership, which incorporates a multidisciplinary internal team and external global experts, key questions are being raised to try to better characterise adverse events of interest associated with brolucizumab and mitigate the risk of patients developing retinal vasculitis and/or retinal vascular occlusion. Preliminary investigations by the Coalition suggest that treatment-emergent anti-drug antibodies (boosted and induced) may be associated with an increased incidence of retinal vasculitis and/or retinal vascular occlusion.[9]

Initial descriptive findings, presented by Dr Jeffrey S. Heier, Ophthalmic Consultants of Boston, US, at the American Academy of Ophthalmology (AAO) 2020 Virtual Retina Subspecialty Day meeting, showed that 86% of patients with at least one retinal vasculitis and/or retinal vascular occlusion event in HAWK and HARRIER were neutralising antibody-positive at baseline (29%) and/or post-baseline (57%).[9] Additional analyses from ongoing brolucizumab trials will help further assess these findings.

Meanwhile, analyses of real-world brolucizumab data (n=10,654 patient eyes from the AAO IRIS Registry) suggest that the observed risk for retinal vasculitis and/or retinal vascular occlusion is increased in patients with prior intraocular inflammation and/or prior vascular occlusion.[10] In this large real-life cohort, the majority of patients (91%) who started receiving brolucizumab were switched from a prior anti-VEGF agent.

Retinal vasculitis

Post-approval analysis demonstrates that brolucizumab can be associated with intraocular inflammation with or without associated retinal vasculitis and some cases are associated with vision loss, noted Dr Paul Hahn, NJRetina, New Jersey, US and Chair of the ASRS Research & Safety in Therapeutics (ReST) Committee, presenting an update on brolucizumab-related inflammation at the AAO 2020 Virtual Retina Subspecialty Day.[11]

Intraocular inflammation alone may often be managed with topical steroids but the optimal treatment strategy for vasculitis remains unknown, Dr Hahn said. Treatment likely involves steroids, with route of delivery titrated according to severity.

The ASRS ReST Committee recommends that informed consent should discuss the benefit vs risk profile based on available information and patient selection should consider the altered risk profile.[11] Physicians should carefully check for inflammation prior to every brolucizumab injection, discuss appropriate warning signs with a

Table 2. ***Ocular safety profile, HAWK and HARRIER Phase 3 trials up to 96 weeks.***[1,2]

Data from Phase III clinical trials	HAWK			HARRIER			
	Brolucizumab 3 mg (n=358)	Brolucizumab 6 mg (n=360)	Aflibercept 2 mg (n=360)	Brolucizumab 6 mg (n=370)	Aflibercept 2 mg (n=369)		
Patients with ≥1 ocular AE, n (%)	218 (60.9)	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)		
Patients with ≥ 1 ocular serious AE, n (%)	7 (2.0)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)	**After rounding by the FDA, the rates on the US label are[a]:**	
Ocular AEs of potential relevance to intravitreal anti-VEGF in HAWK and HARRIER						Brolucizumab 6 mg	Aflibercept 2 mg
Intraocular inflammation, n (%)	17 (4.7)	21 (5.8)	2 (0.6)	11 (3.0)	4 (1.1)	4%	1%
Retinal artery occlusion, n (%)	4 (1.1)	4 (1.1)	0 (0.0)	2 (0.5)	1 (0.3)	1%	<1%
Endophthalmitis, n (%)	4 (1.1)	4 (1.1)	0 (0.0)	1 (0.3)	1 (0.3)	1%	<1%
Visual outcomes							
Patients with ≥15 letter loss from baseline at week 96, %	8.6	8.1	7.4	7.1	7.5		
Patients with ≥30 letter loss from baseline at week 96, %	2.6	2.0	3.0	2.3	3.3		

[a] *Beovu [US prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; Oct 2019.*

(Adapted from: Dugel PU, Koh A, Ogura Y, Jaffe GJ, et al; HAWK and HARRIER Study Investigators. Ophthalmology. *2020;127:72-84 and Dugel PU, Singh RP, Koh A, et al.* Ophthalmology. *2021;128:89-99)*

low threshold for clinic visit and ensure close follow-up with any issues. Caution is advised when considering brolucizumab treatment in monocular patients or when bilateral injections are indicated, due to the potentially severe nature of the consequences of retinal vasculitis.[12]

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Understanding the molecular mechanisms underlying cataracts

Several hundred genes have been found to be associated with congenital forms

By Dr Vanita Berry, Prof. Roy A. Quinlan and Prof. Michel Michaelides


Dr Berry


Prof. Quinlan


Prof. Michaelides

Cataract is the most common cause of blindness worldwide[1] and a very significant cause of visual impairment in infants and children. Congenital cataracts are seen in 10–60/100,000 births in the UK and 50–150/100,000 births in developing countries.[2]

Improving our understanding of the underlying molecular mechanisms behind cataracts will positively impact clinical care, triggering the development of non-surgical treatment strategies. For example, the identification of genetic variants causing congenital cataract has not only improved our understanding of the pathogenesis of infantile cataract, the most frequent treatable cause of blindness in childhood, but also its more common counterpart, adult-onset cataract.

This may lead to new strategies for preventing cataracts or mitigating the progression of early lens opacity, thus reducing the significant global demand for surgery.

Lens development

The ocular lens provides a unique model for understanding the inductive interaction of various embryonic tissues, as well as cell differentiation, signalling, proliferation, physiology, biochemistry, longevity and organelle degradation. The structure is surrounded by a thick capsule and filled with elongated lens epithelial cells (LECs) that have differentiated into lens fibre cells.

The lens is the only organ that continually evolves and increases in size without replacing any cell in its system. Regardless, it performs its role to refract light onto the retina until mutation or the effects of ageing, the environment or intrauterine infections compromise its transparency and optical function. Such insults cause changes to the biomolecules and trigger homeostatic imbalance in the lens, leading to protein aggregation and cataracts, and thus increasing light scatter to affect refraction and cause loss of vision.

Lens development is a result of a series of inductive events during eye morphogenesis. The eye begins to develop during gastrulation at the beginning of week 4 (day 22, Carnegie stage 9). A single eye field (eye primordium) arises in the middle of the anterior neural plate (diencephalon region of the developing brain), which separates into two optic vesicles and induces the overlying surface ectoderm to form the lens placode (lens primordium) by day 28 (Carnegie stages 12–13).

During this stage, a series of inductive interactions begin to shape the eye, driven by signalling molecules such as bone morphogenetic proteins and fibroblastic growth factor 2, as well as by eye field transcription factors including PAX6, RAX, SIX3 and LHX2.[3–5] The lens placode invaginates to form the cup-shaped lens pit, which makes a complete circle of cells and separates from the surface ectoderm to develop into the lens vesicle. By the end of week 4 (Carnegie stages 10–13), the cells from the posterior vesicle start to elongate towards the anterior epithelial cell layer to become the primary lens fibres that fill the lens vesicle and later become the embryonic nucleus of the mature lens.

The portion of the optic vesicle that faced the lens placode gives rise to the retina. The retina, in turn, provides oxygen and inductive signals that regulate the growth and apical-posterior axis of the lens, and this tissue integration continues to enable the functional optimisation of eye function with the establishment of emmetropia.

In the early optic cup stage, the lens vesicle releases signals that induce the overlying surface ectoderm to differentiate into the corneal epithelium. After the lens vesicle has closed (weeks 4–5; Carnegie stage 15), secondary fibre cells add to the growing lens as the

IN SHORT

- ***A greater understanding of lens embryology and the phenotype/genotype correlation of cataracts should help guide future therapeutic approaches.***

Figure 1A: ***Cataract Phenotypes***

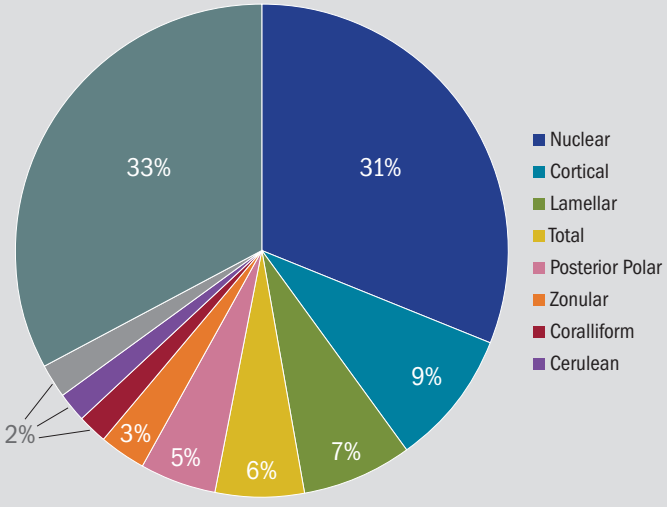
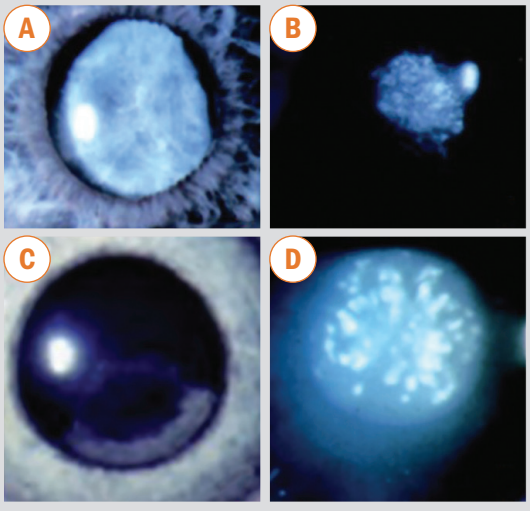


Figure 1B: ***Inherited Cataract Phenotypes***



(FIGURE 1A) Frequency of cataract phenotypes seen in families.[12] (1B) Slit-lamp presentation of examples of inherited cataract phenotypes: (A) nuclear cataract, (B) posterior polar cataract, (C) cortical cataract and (D) pulverulent cataract.
(Figures courtesy of Dr Vanita Berry, Prof. Roy A. Quinlan and Prof. Michel Michaelides)

foetal nucleus starts to form in weeks 6–7 (Carnegie stages 16-19), derived from the epithelial cells located at the equator of the developing lens.

Around week 8 (Carnegie stage 20), the Y-shaped suture appears at the anterior and posterior poles of the embryonic nucleus of the lens, as the terminal ends of the secondary lens fibres abut each other. During this process of terminal differentiation, fibre cells degenerate their nuclei and other cell organelles such as ribosomes and mitochondria, the Golgi apparatus and the endoplasmic reticulum to minimise light scattering and optimise the optical function of the tissue.

Congenital cataracts

Childhood cataract may occur in isolation associated with other ocular abnormalities, such as anterior segment mesenchymal dysgenesis due to variants in transcription/development factors, or be part of multisystem genetic disorders. Nearly half of congenital cataracts are characterised as inherited and they are a clinical feature of almost 200 syndromic genetic diseases.[6] Cataract was the first autosomal disease to be genetically mapped in humans following its identification at the start of the 20th century.[7,8] Since then, congenital cataract has been shown to be associated with considerable genetic and phenotypic heterogeneity.[9–11]

> Cataract was the first autosomal disease to be genetically mapped in humans following its identification at the start of the 20th century.

Most (57.5%) inherited cataracts are autosomal dominant (AD) with complete penetrance but variable expression; autosomal recessive (AR; 21.4%) and X-linked (XL; 6.2%) inheritance are less frequent.[12] There are several distinct phenotypes of congenital cataract (Figure 1A), defined mainly by the timing, position (embryonic, foetal or cortical) and appearance (nuclear, cortical, complete, blue-dot, anterior polar, posterior polar, pulverulent, lamellar, coralliform, posterior nuclear or polymorphic) of the opacification during lens development (Figure 1B).[13,14]

To date, 1,460 novel and recurrent disease-causing sequence variants have been identified,[12] with a well-defined distinct phenotype observed in 823. Nevertheless, it is important to remember that phenotypic variability is seen within families with the same mutation;[10] conversely, different variants in different genes can present with the same phenotype.[10,15] This emphasises the multifactorial nature of cataract formation and the contribution of non-genetic environmental and lifestyle factors.[15]

Molecular genetics of inherited cataract

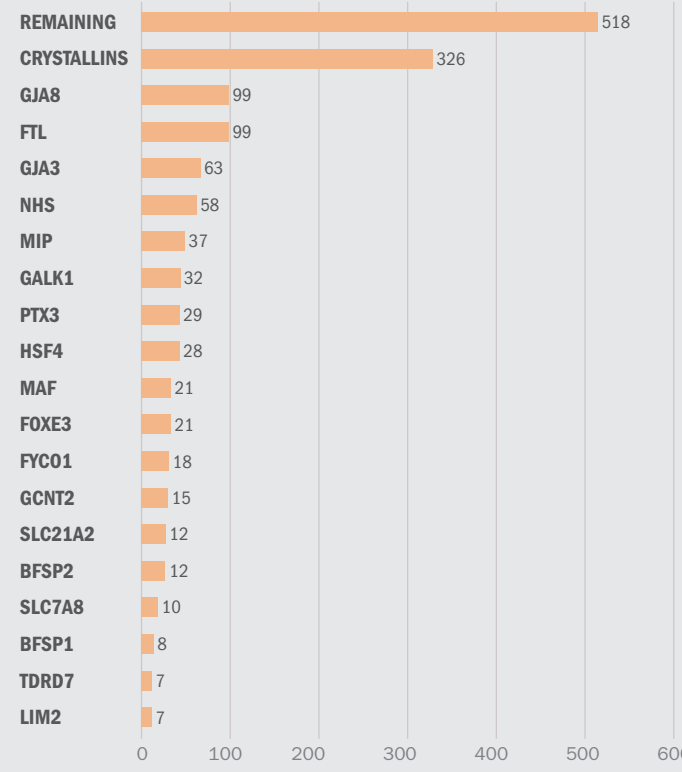
To date, 356 genes have been found to be associated with syndromic and non-syndromic cataract and nearly 50 disease-causing genes have been identified to be associated with isolated cataract (Figure 2). Disease-causing variants have been identified in genes encoding many different proteins and can be categorised into

different groups according to their biological role in the lens, as follows:

- **Intracellular lens proteins (the crystallins);**
- **Membrane proteins, which are the water channel proteins (aquaporins) that regulate water transport, gap junction proteins (connexins) and lens integral membrane protein (LIM2);**
- **Transcription factors including PAX6, SOX, PITX3, FOXE3 and MAFA;**
- **Cytoskeletal proteins including BFSP1 (filensin), BFSP2 (CP49; phakinin) and VIM (vimentin), which stabilise the plasma membrane and the fibre cells themselves; and**
- **Gene products with special roles in the lens, including EPHA2, FYCO1 and TDRD7, and for lipid metabolism (LSS)[12] (Figure 2).**

Recent advances in molecular genetics, particularly next-generation sequencing, has improved molecular diagnosis in the clinic.[16]

Figure 2: ***Variants in highly expressed genes in the lens***



(FIGURE 2) Cataract-causing variants by gene. A total of 1,460 disease-causing variants (novel and recurrent) to date are shown in various highly expressed genes,[12] including crystallins, gap junction proteins, membrane proteins and developmental and cytoskeletal proteins in the lens; the remaining 518 variants are found in genes important for the normal function of the crystalline lens. *(Chart courtesy of Dr Vanita Berry, Prof. Roy A. Quinlan and Prof. Michel Michaelides)*

Intracellular lens proteins

CRYSTALLINS

Crystallins (α, β and γ) account for nearly 90% of all lens proteins and are essential for the lens' optical properties and function and for its remarkable resilience, sustaining optical function over centuries in some animals[17] and maintaining transparency.[18,19] Nearly 23% of congenital cataracts are due to mutations in crystallin genes.

Alpha-crystallins (αA-crystallin and αB-crystallin) are members of the small heat shock protein family, which are molecular chaperones protecting lens proteins and enzymes from aggregation, which could otherwise lead to lens opacification, and assisting in protein assembly.[20] CRYAA is primarily expressed in the lens, while CRYAB is expressed in the lens epithelial cells and also in the retina, skeletal muscle, heart, kidney and brain.[21,22]

The βγ-crystallins comprise four homologous Greek key motifs organised into two domains.[23] The β-crystallin family comprises three acidic (A) and three basic (B) forms.

γ-Crystallins are encoded by the γ-gene cluster, which encompasses genes *CRYGA* to *CRYGB*.[24,25] Fewer sequence variants have been identified in γA and γB than γC and γD, although, interestingly, most of the variants in the *CRYGC* and *CRYGD* genes cause AD nuclear and coralliform cataract phenotypes. There is a single γS-crystallin gene (*CRYGS*) whose variants are linked to AD cataract but have a broad phenotypic spectrum.

Membrane proteins

CONNEXINS

The lens is an avascular, ever-growing organ; to maintain its life-long transparency and nourishment, especially in the mature fibre cells of the lens core, it has developed a sophisticated cell-to-cell communication network via gap junction proteins called connexins. These 20 transmembrane proteins, expressed in various tissues,[26,27] allow the flow of ions, second messengers

and metabolites between lens fibre cells and are made up of three connexin isoforms: GJA1 (Cx43), GJA3 (Cx46) and GJA8 (Cx50).

So far, 162 pathogenic variants have been found in connexin genes: 63 in *GJA3*, with various associated lens phenotypes including pulverulent, nuclear, lamellar, coralliform and total, and 99 in *GJA8*, associated not only with inherited cataract but also age-related cataract and other eye anomalies including microcornea, microphthalmia and corneal opacification.[28] GJA1 is expressed only in the lens epithelial cells during early stages of lens development and is not associated with lens pathology.[29,30]

MIP26 (AQP0)

This is a member of the ubiquitous family of water channel proteins called aquaporins that allow rapid movements of water across cell membranes. MIP is highly expressed in terminally differentiated lens fibre, comprising nearly half of the total lens fibre cell membrane proteins.[31]

We identified two AD variants (G134E and T138R) leading to polymorphic and lamellar cataract.[32,33] So far, 37 heterozygous variants have been found in *MIP*, all causing AD cataract.

LIM2 (MP19)

This is another lens-specific integral membrane protein, found at the junctions of lens fibre cells, where it may contribute to cell junction organisation. It acts as a receptor for calmodulin and may play an important role in both lens development and cataractogenesis. Mutations in LIM2 have been associated with AR cataracts and age-related cataracts.[34,35]

Transcription factors

PAX6, FOXE3, HSF4, MAF and PITX3 are examples of transcription factors (TFs) that play an important role in lens development. PAX6, the paired-box protein, is a key player in vertebrate eye development and plays a role regulating lens-specific crystallins.[36]

FOXE3 is a forkhead-box TF required for morphogenesis and differentiation of the anterior segment of the eye. Disease-causing variants in this gene cause anterior segment mesenchymal dysgenesis and congenital cataracts. Nearly 21 homozygous and heterozygous variants have been reported, displaying severe developmental eye anomalies including cataract.

Another important gene is *PITX3*, a member of the *REIG/PITX* family of homeobox TFs.[37] To date, 29 variants in *PITX3* have been identified (including a hot spot in exon 4, c.640_656dup17bp) to cause mainly posterior cataracts and anterior segment dysgenesis in different ethnicities.[38]

Cytoskeletal proteins

The cytoskeleton of a cell comprises microfilaments, microtubules and intermediate filaments. In the lens, beaded filaments, a type of intermediate filament that is comprised of the proteins BFSP1 (filensin) and BFSP2 (CP49; phakinin), are expressed.[39] Several variants in *BFSP2* lead to sutural opacities and nuclear cataract in association with *BFSP1* variants.

Nance-Horan syndrome (NHS) is also associated with abnormalities in the lens cytoskeleton and epithelial cell junctions. A total of 58 sequence variants in the gene underlying the XL-dominant NHS have been identified. Affected men have dense nuclear cataracts and frequently microcornea, whereas heterozygous women show sutural cataracts with microcornea, craniofacial dysmorphism, nystagmus, strabismus and dental anomalies.[40,41]

Cataract therapy and future direction

The timing of the appearance of cataract, either during infancy or at other life stages, depends on whether it is due to a harmful sequence variant or primarily due to accumulated biomolecular damage.[15] Both can be described as accumulated cataractogenic load.

Effective therapeutic approaches have yet to be established for preventing or mitigating the cataract process. However, a therapeutic approach to treat cataracts by stabilising alpha-crystallin has been suggested[42] and several studies have identified compounds that can reverse light scattering caused by protein aggregates, including the small molecule 'compound 29' (25 hydroxy-cholesterol), which binds to alpha-crystallin.

Lanosterol treatment has been shown to reverse crystallin aggregation *in vitro*[43,44] although recent studies have cast doubt on the efficacy of the identified oxysterols lanosterol and 25 hydroxy-cholesterol to treat cataract.[45] Genetic evidence clearly shows that deficiencies in cholesterol and lipid metabolism are linked to cataract, so the debate concerning statin use and cataract continues.[46,47]

Lens regeneration from endogenous stem cells has been developed to treat cataract: cataract lenses have been removed from mammals and human infants while preserving the lens capsule and LECs.[42] In cases of inherited cataract, this method deploys further gene-editing using CRISPR/Cas9 technology in order to rectify the genetic variant in the regenerated lens.

Small-molecule therapy, using eye drops for example, seems to remain the most pragmatic solution in developing parts of the world, where immediacy and cost effectiveness is key. The search for small-molecule inhibitors has been ongoing with promising effects obtained with molecules such as pantethine, rosmarinic acid, polyherbal preparations and multi-functional antioxidants. Those that have shown the most promise have met the challenge of reducing cataractogenic load and this is therefore an important mechanistic focus for future work.[48,49]

The more invasive and time-consuming stem cell therapy approaches are apt in cases where gene editing is the only option to correct the mutant gene, for example, inherited cataracts. Identification of genetic variants causing congenital cataract and elucidation of their impact on the lens is of vital importance to develop new therapies for cataracts.[47]

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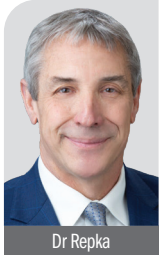
Exploring possibilities of myopia prevention and control in the US

Investigators are reviewing options that include bifocals, low-dose atropine drops

By Lynda Charters;

Reviewed by by Dr Michael X. Repka



Dr Repka

Among ophthalmologists, interest in preventing and controlling myopia has increased markedly in the United States. Combination therapies under study include bifocals and low-dose atropine drops.

No one doubts that myopia is progressing in the nation; this has been a concern since 1989, when the CLEERE study[1] including more than 4,500 schoolchildren followed over time reported that 9.2% were myopic, 12.8% hyperopic and 28.4% astigmatic. A total of 605 children who were emmetropic at baseline ultimately became myopic by a minimum of –0.75 D; this finding was common to all racial and ethnic groups and a 0.5-D increase was seen annually.

This annual review change, according to Dr Michael X. Repka, is the basic rate to which myopia control treatments could be compared. Dr Repka is a professor of ophthalmology and paediatrics at Johns Hopkins University in Baltimore, Maryland, US.

In the early 2000s, the Food and Drug Administration (FDA)'s focus was on determining the value of pharmacologic therapy for myopia. In 2016, the FDA Center for Devices and Radiological Health considered contact lenses (CLs) and other medical devices for their potential role in controlling myopia. The goal was to develop guidelines for what constituted a suitable level of control.

Drug therapy

Although not approved by the FDA, atropine 1% had long been considered a therapy for myopia and seemed to work well, Dr Repka noted, when it was evaluated in nonrandomised trials as well as in the ATOM study[2] of myopia progression; however, the adverse effects (AEs) associated with the drug have reduced its popularity.

In a randomised controlled trial, pirenzepine (Gastrozepin, Darnista Pharmaceuticals), another candidate for myopia therapy, showed a mean 0.58-D increase in myopia in the active treatment group compared with a 0.99-D increase in the placebo group at the 2-year time point. Both the lack of a significant effect and loss of 26% of study patients due to AEs were concerns. The drug was never approved in the US for this indication.

The 5-year results of the ATOM study[2] had a profound impact on the way low-dose atropine 0.01% eyedrops were viewed in the US. The study showed that the treatment dose that was considered the placebo group was more effective than the higher drug concentrations.

This finding was bolstered by the LAMP study[3] that tested three doses of the drug and a placebo; the 1-year results showed that the 0.05% dose was superior to the 0.025% and 0.01% doses. Not only were the rates of progression positively affected but the axial lengths were impacted as well.

"The axial length progression is really the issue that we want to stop, because it is what is associated with retinal damage," Dr Repka emphasised. The 2-year LAMP data also showed that the 0.05% dose continued to have a better effect than the others tested. Because the LAMP study found the 0.01% treatment to be less effective than in the ATOM1 study, this finding has led to debate about the most effective atropine dose.

Current approaches

Five behavioural and optical approaches are now considered acceptable in the US for controlling myopia. The first, avoidance of extensive and prolonged near work, gets mixed scientific reviews, but patients can resort to this without AEs. Removing glasses for near work is another easy method for older patients, although adherence is an issue for children.

Use of bifocals, both near segments and progressive lenses, is associated with some supportive clinical

IN SHORT

- ***Investigators have indicated that combination therapies of outdoor activity, bifocals and low-dose atropine are being studied.***

trials data in that they reduce accommodation and positively affect any changes caused in the eye. The COMET study[4] compared progressive-add lenses with single-vision lenses over 3 years. Myopia progressed in both groups, by 1.25 D and 1.48 D, respectively.

The progressive-add lenses significantly slowed progression, but not enough to be felt clinically relevant. The COMET2 study[5] looked at a subset of patients identified in the previous COMET study who had accommodative lag and seemed to benefit most in the previous study. The analysis showed that the change in myopia over 3 years—that is, –1.15 D in the single-vision group and –0.87 D in the progressive-add lens group—was nearly the same as in the first COMET study, demonstrating no clinically significant benefit, Dr Repka commented.

> Combination therapies of outdoor activity, bifocals and low-dose atropine are being evaluated.

CLs to control myopia are increasingly being used. Little data support the use of monofocal soft CLs. In contrast, orthokeratology may have a meaningful role in controlling myopia progression (studies are underway) and carefully choosing patients as candidates for the treatment is important.

Dual-focus CLs (centre focus and peripheral defocus) have been found to slow myopia progression, possibly by inducing myopic peripheral defocus while providing clear foveal vision, Dr Repka said. "The concept in this technology is that myopic defocus caused by a typical lens causes ocular elongation, and this lens design eliminates that by pulling the image into the vitreous, which stops that process," he explained.

MiSight CLs (CooperVision), the only approved daily-wear, single-use, single-vision lenses that use this concept, are prescribed for children aged 8–12 years with myopia ranging from –0.75 D to –4.0 D of spherical equivalent with low astigmatism. The BLINK study[6] evaluated three FDA-approved disposable month lenses (Biofinity) worn during the day, spherical lenses (control) and two bifocal CLs with different reading powers of +1.5 and +2.5 to attempt to slow myopia.

The children, aged 7 to 11 years, were followed for 3 years. The results showed –0.6 D for the high add power, –0.89 D for the medium add power and –1.05 D for the spherical lenses, indicating that the progression rate was slowed by about 0.5 D at 3 years.

"This result is comparable to that achieved with low-dose atropine and more powerful than observed with bifocals," Dr Repka commented.

Low-dose atropine continues to be studied in the US, but the optimal dose has not been pinpointed. Currently, there is great interest about clinical care that can be offered to prevent myopia and myopic progression.

Increased outdoor activities have also been of interest because studies have shown some positive impact. Combination therapies of outdoor activity, bifocals and low-dose atropine are being evaluated. At this point, a big concern when considering future studies is parental support for use of a control group of children for 2 or 3 years or longer.

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Navigating COVID-19 with ophthalmic patients in the hospital setting

New operating procedures ensure eye clinics can operate safely during pandemic

By Prof. Christina Grupcheva

Prof. Grupcheva

Although SARS-CoV-2 has been detected in tears, it is important to note that there is currently no proof that it affects the ocular surface. However, clinics and ophthalmic practices have implemented new operating procedures to ensure they can remain open and operate safely during the COVID-19 pandemic, and it is more important than ever for surgeons to protect themselves and their patients.

Ophthalmologists and patients need to follow the rules and regulations mandated by the state or country where their practice or hospital is located. Unfortunately, the rules can differ between countries and sometimes between states in the same country. A large part of navigating this virus has been determining ways in which we can individually implement safe practices.

Battling emotional strain

The COVID-19 pandemic has placed an emotional strain on our patients. They are extremely afraid of contracting the virus, which has kept many from entering hospitals where there are potentially other sick people and where the virus is concentrated.

In ophthalmology, less than 5% of our cases are urgent, wherein a patient has endured trauma to the eye. Most of our patients need to be seen on a regular basis, so are now presented with a dilemma: is it more important to preserve their general eye health, increasing their chances of coming into contact with COVID-19, or better to defer their checkups and lessen their chances of contracting the virus?

Unfortunately, many patients have chosen to postpone their visits. Some have been doing so for months and even up to a year at this point, depending on when the COVID-19 outbreak occurred in their place of residence.

Additionally, our staff—not only physicians but also technicians, nurses, support staff and administrators—are at high risk of being exposed to the virus due to the number of people they come into contact with daily. Although staff may not express their worry outright, they know they are in a difficult position as their chosen profession does not allow them the privilege of working safely from home.

From a manager's point of view, the COVID-19 pandemic has created a constant need to navigate the doubts of all parties involved as well as find a way to prevent sickness and preserve the health and safety of everyone while continuing to function. In this unfortunate situation, we learned that spending more time with each member of staff and sharing common assignments between staff members calms the atmosphere and provides a feeling of collective safety and security.

The approach to patients, however, is different. Their greatest need is to receive information in advance and to manoeuvre quickly and securely through the diagnostic pathways. In the past, several members of staff undertook specific procedures for many patients: today, we try to reduce each patient's contact to no more than one staff member and care is dictated more by the patient than the procedure.

Distancing in the operating room

When the pandemic first started, the first thing we did as a practice was to make special shields to prevent very close contact with patients during an examination. Even though we and the patients wear protective gear, the patient is not fully covered, especially if they are claustrophobic, and we need to make adjustments.

In the operating room, the patient lies flat on his or her back, and we use a microscope that hovers over

IN SHORT

- ***Experience at one ophthalmic practice in Bulgaria demonstrates that new operating procedures, technologies and good management can enable clinics to remain open and operate safely during the COVID-19 pandemic. Ophthalmic training and education should continue to be a priority.***

them, meaning that we are in line with their breath at all times. Equally, when we are over the operating field, what comes out of our airways goes down to the patient's exposed eyes. It is technically impossible to wear a shield when operating a traditional microscope during surgery.

To combat this concern, we use a digital microscope, which offers greater opportunities to protect both patients and surgeons from infection during operations than a traditional kind. The three-dimensional heads-up microscope allows more distance from the patient. Moreover, because oculars are not used for 3D surgery, the protection shield above the 3D glasses is very easy to adjust.

This technology also benefits nurses, who need to have close contact with patients in all steps related to preparation, the surgery itself and immediate postoperative care. The microscope allows the nurse to be on the other side of the room and still view the procedure in real time using 3D glasses, which provides additional safety and allows for social distancing from the patient. Although the surgeon, nurse and assistant need to be in the operating room, we can distribute ourselves evenly, maintaining safer separation.

Treating COVID-19-positive patients

It seems that it would be easy for a surgeon to choose not to operate on patients who test positive for COVID-19. However, in Bulgaria at least, whether patients should be requested to take a COVID 19 test has been a controversial topic for ethical and legal reasons and hospitals have varying policies in this country.

Although my hospital does not ask patients to be tested for COVID-19 prior to surgery, we do screen them for fever and 'flu symptoms as well as taking their temperature. If a patient is displaying symptoms, we ask them to see their general practitioner who decides whether a COVID-19 test is appropriate.

I experienced the delicacy of treating patients with suspected COVID-19 in a case that presented to me at the beginning of the pandemic. In Bulgaria, we initially had a very small number of cases. As most people experienced, we were not allowed to leave the city or even go outside for walks.

During this time, I received a call from my associate at the hospital to say that there was a 12-year-old girl traveling from Pleven, the hottest region for COVID-19 in Bulgaria, with a perforated eye. The reason for the perforation was unknown and the child was also experiencing a fever and a cough. At that time, I was most worried that the child was coughing, since in cases of perforation the tissues might prolapse.

The anaesthesiologist was unable to give the child general anaesthesia because of her temperature and other factors. I agreed

> A large part of navigating this virus has been determining ways in which we can individually implement safe practices.

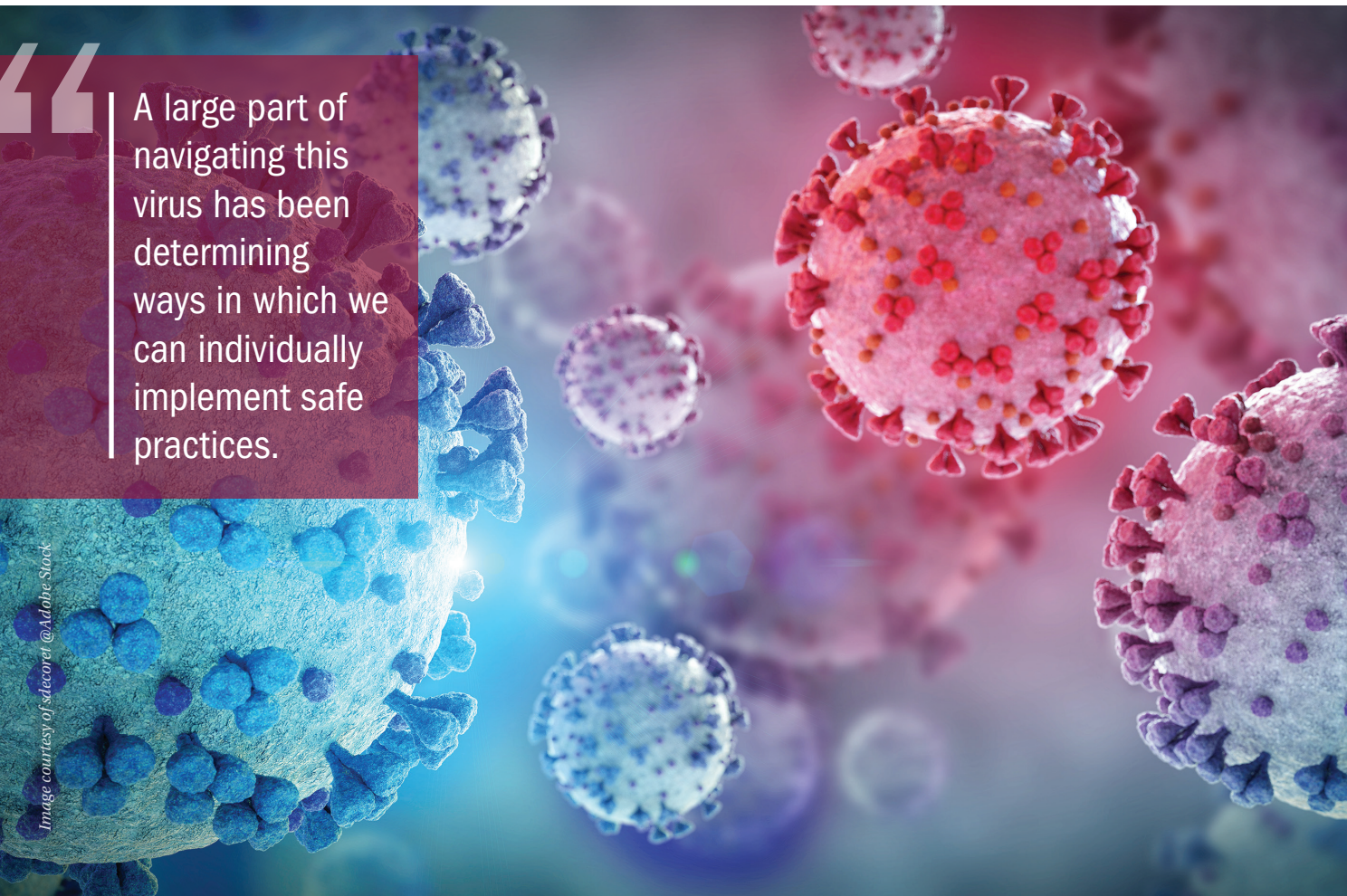

Image courtesy of sdecoret @Adobe Stock

to see the child, and when I arrived at the hospital almost everyone was staying almost 3 meters away from the family. The family was frightened because they did not understand what was happening.

It turned out that the child was a contact-lens wearer; because of the lockdown she had been unable to buy contact lenses. As a result, she was wearing old lenses that were 2 weeks overdue. She had anisometropia with plano refraction on one eye and −7.0 D on the other.

> In the age of COVID-19 we must be flexible and consider the circumstances of each case individually.

From the documentation, I discovered that she had developed bacterial keratitis very quickly and her eye was almost perforated. In normal times she would undergo a lot of tests but instead of moving her around the hospital for evaluations, I decided to examine her in the operating room and be prepared to take material for microbiological evaluation if necessary.

I explained to the patient that she needed to be very cooperative because I could not give her general anaesthesia due to her coughing. Fortunately, she calmly agreed, especially when I explained that it would be painless.

Using the digital microscope and optical coherence tomography (OCT) imaging, I managed to evaluate her entire cornea while protecting myself from what I thought was a potential COVID-19-positive patient. I found that she, in fact, did not have any perforation. Instead, she had a zone of thinning surrounded by cornea with massive infiltration.

Thus, I performed a noninvasive procedure that is painless to the patient, called PAX crosslinking, which uses ultraviolet light to kill microorganisms and also makes the cornea stronger. I combined the procedure with transplantation of amniotic membrane as a cover. The 3D technology and the OCT control, which often is called 'the third hand', allowed me to be very precise as I performed these steps. As a result, the child now sees 20/50 with correction, which is a big accomplishment considering that she was about to lose her eyesight.

To complicate the case further, the child and her parents tested negative for COVID-19. In fact, she had ordinary 'flu. However, if I had decided to wait for 48 hours for COVID-19 test results before operating, she would definitely have lost her vision, which would have been devastating for a girl of such a young age.

Thus, in the age of COVID-19 we must be flexible and consider the circumstances of each case individually. In medicine, we still need to take some risks, but it should be well understood and well planned. I was able to go confidently into the operating room with this patient because I felt assured that I would be able to protect her and the staff and provide an option that was less traumatic for her.

Continuing education

Even though we are in the midst of a pandemic, we should not forget the importance of education in medicine. Unfortunately, the first thing that happens during a lockdown in a hospital is that, while the permanent staff stays, all people who are on educational duties are sent home for distance learning. In the long term, we need to think that if we postpone education for 6 months and then postpone it for another 6 months, a year will go by very quickly, which will create gaps in the system for qualified eye specialists.

3D microscopy offers a great educational tool because students can stay 10 meters away from patients, wear 3D glasses and be able to look at a big screen and view the surgery as if they are participating. They see so much more detail than if they were looking over the patient with a conventional microscope. I do believe that we need to continue with practical education, perhaps on a smaller scale, but it is necessary for education and training to continue in whatever way is possible.

Conclusion

We do not really know how to react to the stress of a global pandemic, and we have surely made—and will make—a lot of mistakes that will be revealed in time. However, we need to focus first on being good doctors, good managers and good teachers. Regardless of the situation, we should continue to treat and work in teams.

Safety is the priority, of course, and new technology is facilitating novel and sometimes very complicated procedures for disinfection and social distancing. Integration and shared information when using equipment is of great help when reducing patient movement is necessary in the clinical setting. The circumstances are not easy, but we will survive this and learn more and, I hope, will end up with better solutions for the future that are beneficial for ophthalmic care not only during a pandemic but also when we return to normal life.

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Investigators research astronauts' ocular health following space flights

Spaceflight-associated neuro-ocular syndrome can be a challenge with long missions

By Mr Joshua Ong; Dr Peter Mortensen; Dr Tyson Brunstetter; Dr William J. Tarver; and Dr Andrew G. Lee

Ophthalmology continues to play a major role in the characterisation and mitigation of one of the highest-priority risks for astronauts during extended spaceflights: spaceflight-associated neuro-ocular syndrome (SANS). SANS represents the collective neuro-ophthalmic changes found in astronauts who have been exposed to extended periods of microgravity during long-duration spaceflights (LDSFs).

Previously known as visual impairment intracranial pressure (VIIP) syndrome, SANS has a high "likelihood and consequence" rating from the National Aeronautics and Space Administration (NASA), which requires a mitigation plan for missions that range from 1 to 3 years (planetary and deep space habitation).[1] VIIP became known as SANS because of the emerging hypothesis that the condition's aetiology may not stem primarily from intracranial hypertension alone and may, although being possibly multifactorial, require further investigation.[1]

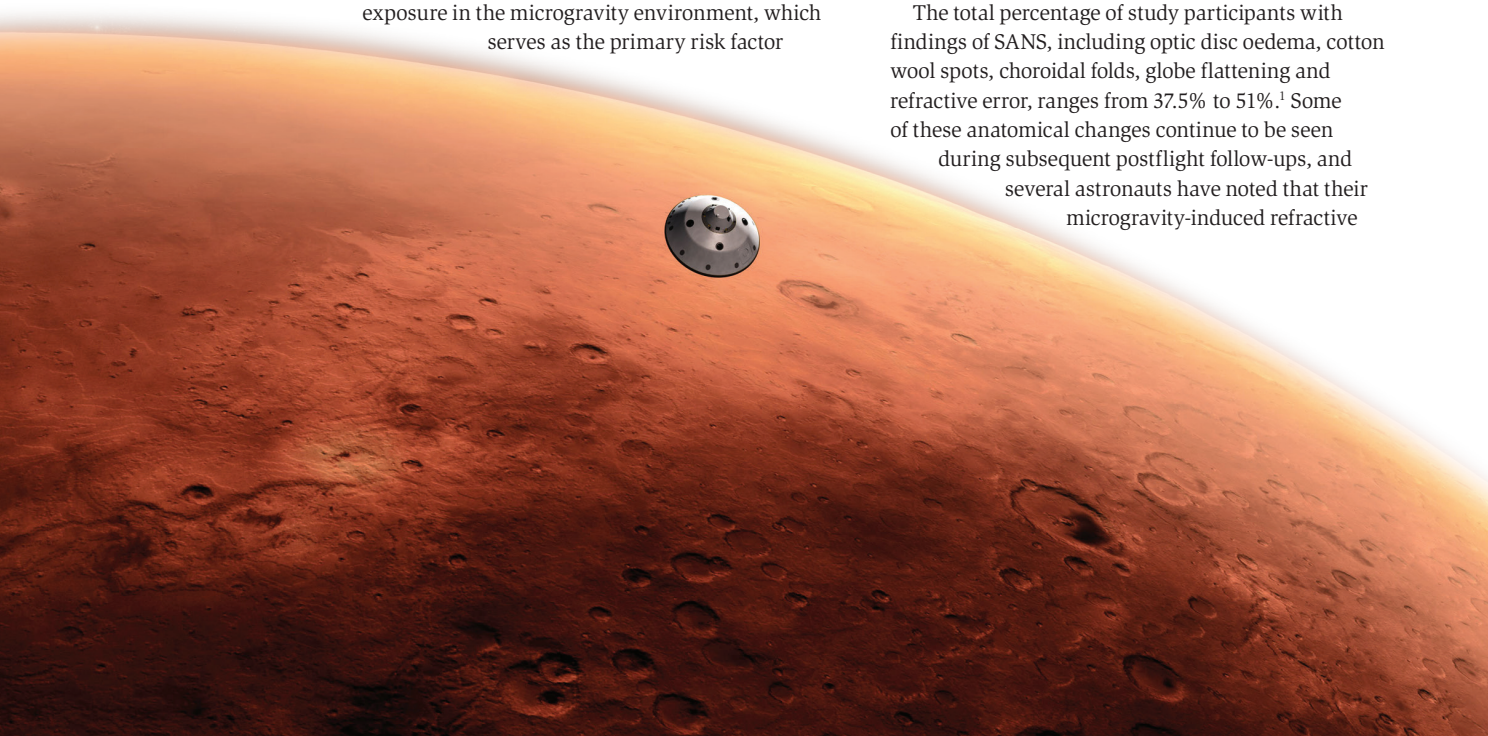
During LDSF, astronauts are subjected to extended exposure in the microgravity environment, which serves as the primary risk factor for SANS. Approximately 60% of astronauts who underwent LDSF reported a decrease in distance and near visual acuity.[1-3]

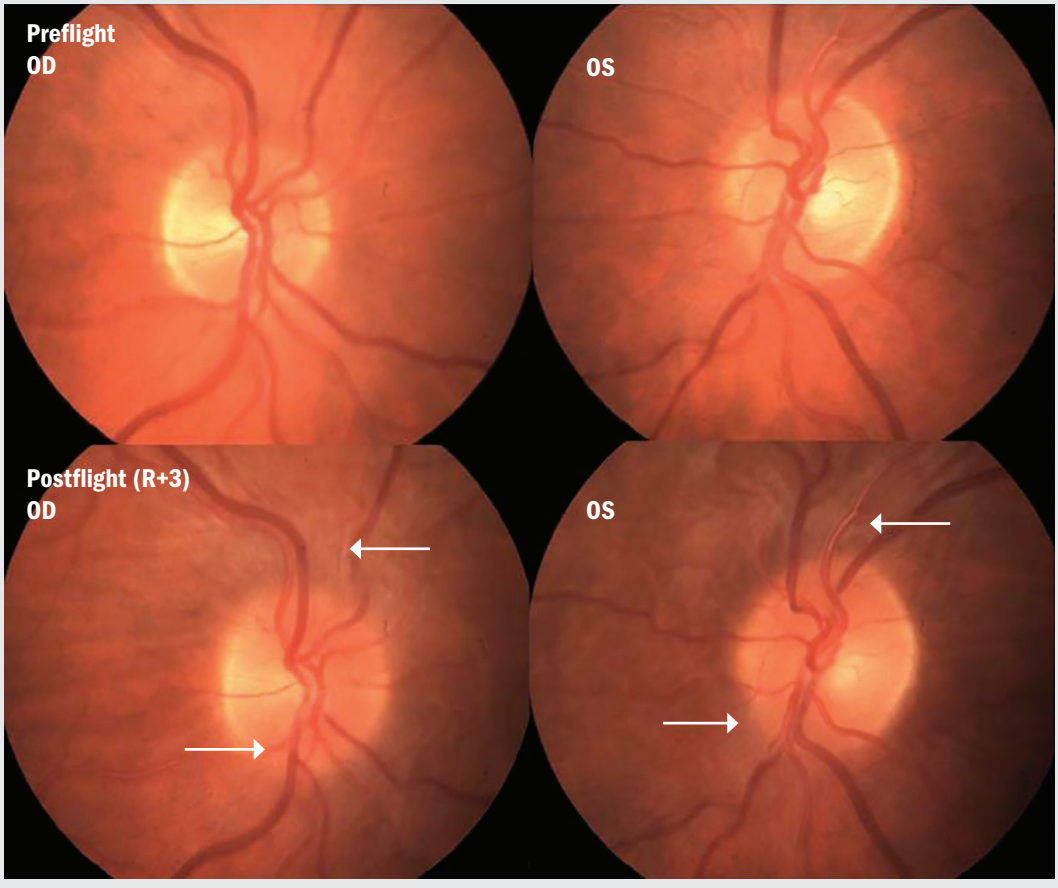
Furthermore, findings from case studies have shown that some astronauts flying on missions longer than 30 days had baseline ocular anatomic changes, which clinicians observed in fundoscopy, orbital ultrasonography, optical coherence tomography scans or brain MRI scans.[1-3] These neuro-ocular anatomical changes included optic disc oedema, hyperopic shift, cotton wool spots, globe flattening and choroidal folds (Figure 1).[2,3,5]

The total percentage of study participants with findings of SANS, including optic disc oedema, cotton wool spots, choroidal folds, globe flattening and refractive error, ranges from 37.5% to 51%.[1] Some of these anatomical changes continue to be seen during subsequent postflight follow-ups, and several astronauts have noted that their microgravity-induced refractive

IN SHORT

With NASA's sights set on Mars, continued research into further understanding and mitigating spaceflight-associated neuro-ocular syndrome is of the utmost importance for astronaut health and space exploration.





(FIGURE 1) Pre- and postflight images from an astronaut after a 6-month mission. Postflight images show optic disc oedema and choroidal folds. *(Photo courtesy of NASA Risk of Spaceflight Associated Neuro-ocular Syndrome Evidence Report)*

errors persist years after their LDSF mission.[4]

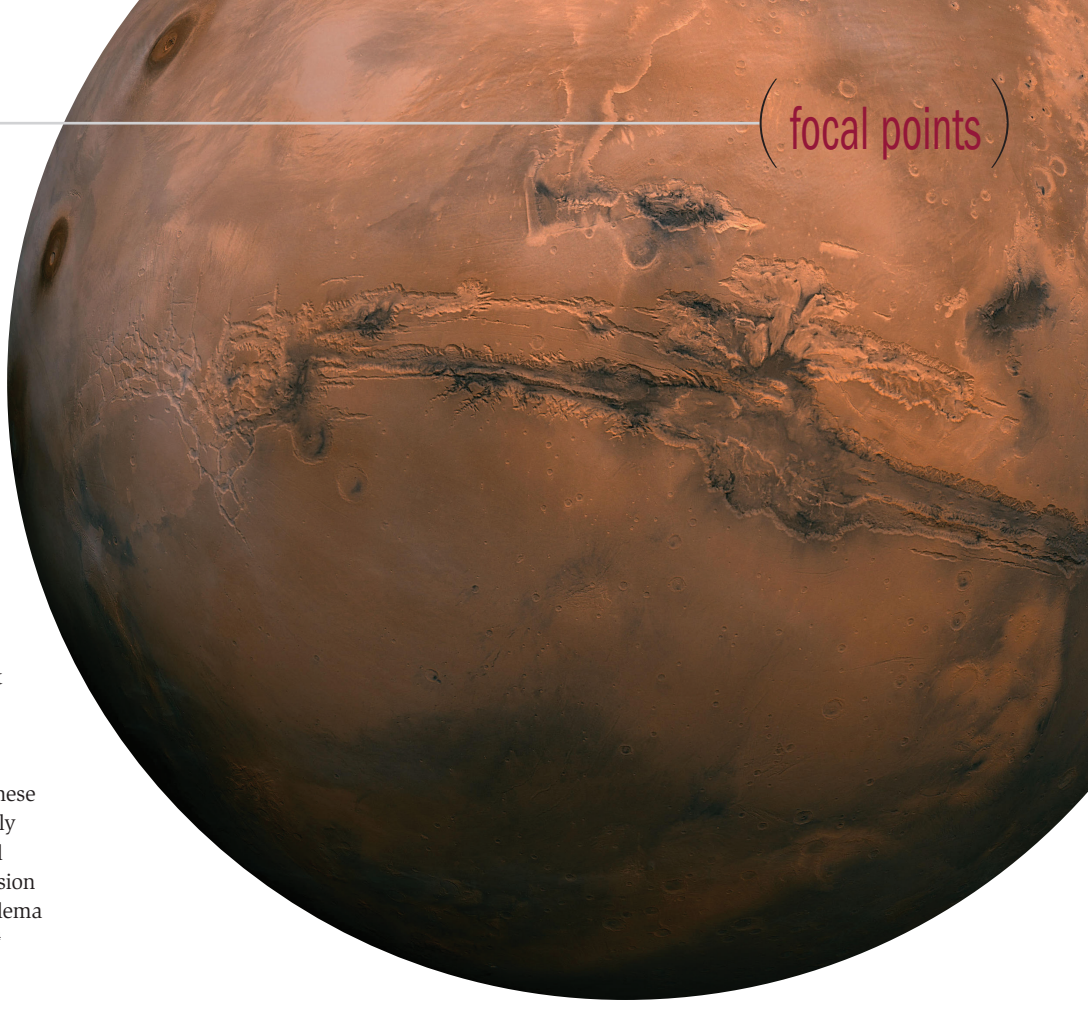
> Approximately 60% of astronauts who underwent LDSF reported a decrease in distance and near visual acuity.

Two theories

Our understanding of the specific pathophysiology behind SANS has evolved over time and two current theories behind this unique manifestation of neuro-ocular symptoms have emerged. The first theory stems from the changes in intracranial pressure that arise from cephalad fluid shifts in astronauts.[2]

Results of studies in transient microgravity have shown a physiological jugular venous distension (JVD), which alludes to possible cerebral and internal jugular venous congestion leading to the intracranial hypertension and subsequent optic disc oedema seen in SANS.[1] However, the persistence of optic disc oedema after astronauts return to Earth, asymmetric disc swelling and absence of additional clinical findings in intracranial hypertension, such as severe headaches and tinnitus, suggest that increased intracranial pressure may not be the sole underlying cause of the syndrome.

In addition, although intracranial pressure readings in astronauts post-LDSF have been elevated, they fall nearly within normal limits and do not reach the expected elevation of pressure that is seen in typical patients with intracranial hypertension. These findings ultimately suggested that intracranial pressure may not be the sole explanation for SANS and



sparked further discussion for the second theory of the condition's pathophysiology.

The second leading theory hypothesises that the cerebrospinal fluid (CSF) becomes compartmentalised or 'accumulates' inside the optic nerve sheath due to a one-way valve-like system during microgravity. This CSF compartmentalisation results in a heterogenous pressure gradient between the CSF pressure in the optic nerve sheath and the CSF surrounding the brain. The difference in pressure between these two areas could explain the nearly normal intracranial pressure and absence of intracranial hypertension symptoms but extensive disc oedema that clinicians see in astronauts.[4]

More research

The pathogenesis behind SANS continues to be a subject of investigation and investigators are conducting further studies with astronauts to understand more about SANS' etiology. Currently, astronauts are using different powers of reading glasses (formerly 'space anticipation glasses') that have an increased dioptre strength to help mitigate the visual acuity changes when their normal prescription glasses are no longer strong enough to carry out tasks on board the International Space Station (ISS).[1]

The overall prognosis in astronauts with SANS findings has been variable, but no permanent vision loss has been reported due to LDSF on the ISS. However, there are reports of persisting choroidal folds years after a mission, as well as hyperopic visual changes that have yet to resolve.[2,5] With NASA's sights set on Mars, continued research into further understanding and mitigating SANS is of the utmost importance for astronaut health and space exploration.

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Post-cataract surgery combination eyedrop launched in Europe

Santen has launched a fixed-dose combination of levofloxacin and dexamethasone (Ducressa) for the prevention of infection associated with cataract surgery in adults, making it the first eyedrop to combine a quinolone antibiotic with an anti-inflammatory steroid to become available in Europe.

Currently, cataract surgery patients are usually prescribed a topical antibiotic/corticosteroid combination for 14 days. Ducressa can be taken for just 7 days and is designed to help reduce potential antibiotic resistance by cutting antibiotic exposure by a half, according to the company.

In the multicentre, randomised, masked-assessor, non-inferiority study LEADER7, 95.2% of patients who received levofloxacin/dexamethasone for 1 week followed by 1 week of dexamethasone alone had no signs of inflammation in the anterior chamber, versus 94.9% of control patients who received the standard 2-week tobramycin/dexamethasone (Tobradex, Alcon). The study thus met its primary endpoint. In addition, both arms of the study were well tolerated. The product has been launched in Denmark, Finland, Italy, Norway, Spain and Sweden. The company plans to roll it out to further countries in Europe in the coming months.

Monofocal IOLs technology breakthrough boosts US market

The United States Food and Drug Administration has approved the monofocal IOLs Tecnis Eyhance and Tecnis Eyhance Toric II for the treatment of cataract patients with or without astigmatism, Johnson & Johnson Vision has announced.

The lenses' refractive surfaces and specific shape are designed to slightly extend the depth of focus, making them the first monofocals to achieve this, according to the company. They are also designed to deliver better image contrast in low light (Tecnic Eyhance IOLs deliver 30% improvement in image contrast compared with AcrySof IQ SN60WF at 5mm). In addition, the new Tecnis Simplicity system has been designed to streamline lens delivery and protect against contamination, the company said.

The Tecnis Eyhance Toric II lens is engineered with a squared and frosted haptic design for added friction inside the capsular bag to treat cataract patients with astigmatism. Tecnis Eyhance first launched in Europe in February 2019. The firm plans to launch Toric II in Europe and Canada later this year.

Moorfields installs new diagnostic hubs

Moorfields Eye Hospital has started opening new diagnostic centres designed to enable more patients to be seen in a socially distanced environment during the COVID-19 pandemic, including in glaucoma and medical retina specialties. One such facility recently opened Hoxton, London, using space that was previously occupied by commercial offices.

Instead of waiting to see a consultant on the same day that diagnostic eye tests take place, the diagnostic hubs take people through a series of rapid tests which are all completed within a 45-minute visit, according to Moorfields. Each patient's results are then individually reviewed online by the consultants and their teams.

Patients then receive a letter informing them of the outcome of their tests, while some are offered a virtual video or telephone appointment to discuss particular results. Patients are only asked to attend a subsequent hospital visit if the consultant sees something requiring urgent or personal attention.

This format is designed to reduce the time each patient spends in clinic and the number of overall face-to-face attendances, making the patient journey more efficient. The diagnostic hubs are also intended to free up more time for consultants to spend with those patients who need more in-depth specialist care in-person.

IOLs manufacturing to benefit from track and trace technology

Ophtec has announced that it has started imprinting unique identification codes on its IOLs to enable them to be quickly and securely tracked from the beginning to end of the production process.

A laser is used to impart a "micro ID matrix code" in the IOLs' loop junctions, which can then be identified by special scanners. The technology assists in the speedy production of 2,000 different optical characteristics in the IOLs, according to the company.

Because the code is imprinted outside the optical zone on the IOL, there is no interference with the optic or the patient's vision. The code is visible through a surgical microscope preoperatively but cannot be seen after the lens is implanted.

"For now, we use it for fast production and traceability; the next step is to have fully customised IOLs," commented Tiago Guerreiro, global marketing director at the firm.

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