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For TREATMENT-NAÏVE patients with wAMD

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Prescribing Information available overleaf

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Eylea® 40 mg/ml solution for injection in a vial (aflibercept)  

Prescribing Information. (Refer to full Summary of Product Characteristics (SmPC) before prescribing) Presentation: 1 ml solution for injection contains 40 mg aflibercept. Each vial contains 100 microfilters, equivalent to 4 mg aflibercept.  

Indication(s): Treatment of neovascular (wet) age-related macular degeneration (wAMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DMO) in adults and visual impairment due to myopic choroidal neovascularisation (myopic CNV). Posology & method of administration: For intravitreal injection only. Must be administered according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. Each vial should only be used for the treatment of a single eye. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequent infection. The vial contains more than the recommended dose of 2 mg. The extractable volume of the vial (100 microfilters) is not to be used in total. The excess volume should be expelled before injecting. Refer to SmPC for full details.  

Adults: The recommended dose is 1 mg aflibercept, equivalent to 50 microfilters. For wAMD treatment is initiated with 1 injection per month for 3 consecutive doses. The treatment interval is then extended to 2 months. Based on the physician’s judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly to a minimum of 2 months during the first 12 months of treatment. There is no requirement for monitoring between injections. Based on the physician’s judgement the schedule of monitoring visits may be more frequent than the injection visits. Treatment intervals greater than 4 months between injections have not been studied. For RVO (branch RVO or central RVO), after the initial injection, treatment is given monthly at intervals not shorter than 1 month. Discontinue if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. Treat monthly until maximum visual acuity and/or no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat-and-extend regimen with gradually increased injection intervals to maintain stable visual and/or anatomic outcomes, however there is insufficient data to conclude on the length of these intervals. Shorten treatment intervals if visual and/or anatomic outcomes deteriorate. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient’s response. For DMO, initiate treatment with 1 injection/month for 5 consecutive doses, followed by 1 injection every 2 months. No requirement for monitoring between injections. After the first 12 months of treatment, and based on visual and/or anatomic outcomes, the treatment interval may be extended such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however there is insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The schedule for monitoring should therefore be determined by the treating physician and may be more frequent than the schedule of injections. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, treatment should be discontinued. For myopic CNV, a single injection is to be administered. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease. The schedule for monitoring should be determined by the treating physician. The interval between 2 doses should not be shorter than 1 month. Hepatic and/or renal impairment: No specific studies have been conducted. Available data do not suggest a need for a dose adjustment. Elderly population: No special considerations are needed. Limited experience in those with DMO over 75 years old.  

Pregnancy & lactation:  

Not recommended during pregnancy unless potential benefit outweighs potential risk to the foetus. No data available in pregnant women. Studies in animals have shown embryo-fetal toxicity. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last injection. Not recommended during breastfeeding.  

Aqueous humor drainage pathway

Gel stent proves value in refractory OAG
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## Focal Points

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Platform links healthcare specialists from around the world
Season’s greetings! As 2019 comes to a close, it is only natural to reflect on the current advances in ophthalmology. Dr Michiel H. A. Luger starts us off, in cataract and refractive surgery, as he discusses his research performing PresbyMAX hybrid presbyopia laser correction, which is a micro-monovision technique plus an asymmetric extended-depth-of-focus approach, by induction of negative spherical aberration. This technique achieved stable extended depth of focus and micro-monovision. High patient satisfaction was achieved in overall visual quality and visual performance over the long term.

Data can be an invaluable tool, and Dr Mats H. Lundstrom discusses the European Registry of Quality Outcomes for Cataract and Refractive Surgery, which has amassed an enormous amount of data that identifies risk factors for cataract surgery patients. Drs Alexander James Silvester and Anil Pitalia tell us how topical antibiotics are unnecessary after routine cataract surgery, but intracameral antibiotics must be used to prevent endophthalmitis. We also hear from Dr Mark Packer, who outlines a theoretical retrospective study that found the percentage of eyes with ≤0.5 D residual refractive astigmatism after toric IOL implantation improved by 19% using a new vergence-based algorithm for power calculation versus the previous fixed-ratio algorithm.

Our glaucoma coverage this month looks at the LiGHT trial, which is examining ways to lower IOP and keep it low. Professor Gus Gazzard shares how repeat-selective laser trabeculoplasty lowered IOP in eyes in which IOP increased during the 1.5 years after the initial SLT application, and the decrease lasted longer than the initial lowering.

The specialty of glaucoma certainly hasn’t been sitting idle, as can be seen on the cover of this issue. Dr Davinder S. Grover describes the surgical technique, patient selection and outcomes for the subconjunctival gelatin stent, noting that it is a valuable addition to the glaucoma specialist’s surgical armamentarium.

In the retinal arena, medium-term perfluoro-n-octane (PFO) without a scleral buckle is the preferred treatment of Dr Steve Charles for inferior, nasal and temporal giant breaks as well as inferior retinal detachments. He uses the PFO after vitrectomy as a tamponade and leaves it in place in eyes completely filled with the substance for 14 days.

Dr Matthew Schlenker discusses how acute rises in IOP that may occur with anti-VEGF injections is a real phenomenon, but it is transient and may not necessarily warrant any intervention for many patients.

We then focus on cornea coverage with Dr Gairik Kundu, who discusses some of the keys to assessing true crosslinking outcomes. He notes that a novel method of noninvasively evaluating the outcomes after crosslinking is under development. Dr Friedrich E. Kruse tells us how the lack of consensus regarding limbal stem-cell deficiency has been addressed by a panel of experts that provided uniform guidelines for disease diagnosis and staging.

Being inclusive of younger patients, Dr Thomas Koch and Dr Christopher B. Oakley explain how reducing the economic and psychosocial cost of pediatric migraine requires correct classification and prompt treatment.

New techniques are offering surgeons improvements in the precision and safety of gene and cell therapy delivery to target tissue. Dr Allen C. Ho and Dr Ali Khan discuss research targeting precision dosing for gene and cell therapy. Dr Leslie Jones urges physicians to be prepared to manage patients who may receive misinformation when it comes to stem-cell therapies.

Finally, we round out this issue with a look at the Cybersight platform from ORBIS International, which links health personnel in developing countries to healthcare experts worldwide for consultations and training.

The significance of the year 2020 within the ophthalmology community is sure to bring even greater advances, which we look forward to sharing with you.

Happy holidays!
Technique puts focus on presbyopia laser correction: long-term results

Patient satisfaction of a hybrid approach examined after 6-year interval

By Steve Lenier; Reviewed by Dr Michiel H. A. Luger

In 2012, a research team led by Michiel H. A. Luger, MD, conducted a study performing PresbyMAX hybrid presbyopia laser correction, which is a micro-monovision technique plus an asymmetric extended-depth-of-focus approach, by induction of negative spherical aberration (SA).

In the distance eye, they targeted emmetropia and added a low negative SA. In the near eye, the team targeted a low myopia (−0.9 D), and added more negative SA, in order to achieve different depths of focus in the distance and near eyes.

In the study, the researchers employed the Near Activity Visual Quality Questionnaire (NAVQ) and the Quality of Vision (QoV) questionnaire both preop and postop. They also studied contrast sensitivity and glare, corneal aberrations, and ocular aberrations. Treatments were performed with Intralase iFS and AMARIS 750S.

Results after 6 years
The 1-year results were published in the American Journal of Ophthalmology,1 and were quite good. But in order to know whether the results were lasting long term, the group recently recalled the entire cohort to follow-up after a 6-year interval. Of the original 32 patients, 19 (60%) agreed to be included again, and these 38 presbyopic eyes were followed longitudinally.

UNCORRECTED DISTANCE VISUAL ACUITY
At 6 years postop, the uncorrected distance visual acuity appeared to be quite stable over time, especially binocularly, with a trend for slight improvement in the near eye.

QUALITY OF VISION
Surprisingly, quality of vision improved over time. Initially there were issues with hazy vision, blurred vision or double vision, which the authors believe had to do with adaptation and differences in depth of field, but over time it completely resolved and was even slightly improved (not significantly) over baseline.

REFRACTIVE ASTIGMATISM/KERATOMETRY/SPHERICAL EQUIVALENT
Refractive astigmatism and keratometry were stable, but there was some progress in spherical equivalent. This is due to lenticular changes and presbyopia progression of 0.12 D per year, which is in line with the literature.

DISTANCE VISUAL ACUITY
For distance visual acuity, the team achieved 20/20 binocular in 73% of patients, and quality of vision was comparable to before the operation. The initial effects of night vision symptoms decreased over time, and there was a good refractive outcome in that there was separation between the distance eye and near eye, and stability was achieved almost instantaneously.

There was some deterioration in uncorrected near vision due to presbyopia progression in the distance eye. Binocularly it stayed almost the same, with a slight decrease. Near activity visual quality also decreased slightly over time due to presbyopia progression.

IN SHORT
- This technique has achieved stable extended depth of focus and micro-monovision. High patient satisfaction has been achieved in overall visual quality and long-term visual performance.
progression but was still much better than it was preoperatively.

Looking again at the NAVQ, there were a few items that were not as good after 1 year as they were preoperatively, but all ten items resolved and became significantly better than they had been at baseline.

UNCORRECTED NEAR VISUAL ACUITY
Uncorrected near vision average was better than J2 binocularly, and J3 was achieved in over 75% of patients.

Answers on the NAVQ improved from little satisfaction to high satisfaction on all questions, although decreased from a 1-year follow-up.

DISTANCE CORRECTED NEAR VISUAL ACUITY
Distance corrected near visual acuity was found to be stable. There is some progression, due to presbyopia progression. Defocus curves also show some presbyopia progression, which is in line with the current literature.

MULTIFOCALITY
Distance corrected visual acuity is at the level of J6 in over 75% of patients. The defocus curves show no loss in best focus, no change for intermediate vergences, and a mean gain of one line for near vergences. This is a little worse than at 1-year follow-up.

ABERRATIONS
Aberrations are very important. The goal was to induce negative spherical aberrations and they were very stable over time, so the group achieved what they were looking for.

Conclusions
This technique achieved stable extended depth of focus and micro-monovision. High patient satisfaction was achieved in overall visual quality and visual performance over the long term. Overall, 100% of patients were corrected to 20/20 for distance and had J2 uncorrected near vision.

The study authors explained that they believe this is an excellent procedure to correct presbyopia and achieve long-term satisfactory results in the pre-cataract patient.

REFERENCE

Dr. Luger has no financial disclosures related to this content.

Table 1. Results from 6-year follow-up
N = 19 patients (38 eyes) out of original 32 patients (64 eyes) (60%)
Database identifies risk factors for iris damage and dropped nucleus

Rare cataract surgery complications focus of collaboration

By Lynda Charters; Reviewed by Dr Mats H. Lundstrom

The European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) is a collaboration established in 2008 between the European Union and the European Society of Cataract and Refractive Surgery. Data on both cataract and refractive surgeries can be entered through interface or manual input into the two registries contained in the EUREQUO, according to Mats H. Lundstrom, MD.

Data from almost 3-million surgeries have been entered into the database to date. The recorded data are comprehensive and reflect the entire range of the relevant information about the cataract surgeries from baseline, including demographics, preoperative visual acuity, and risk factors through follow-up, including the visual and refractive outcomes and any postoperative complications.

The surgical information reflects the type of surgery and the intraocular lens implanted as well as any surgical complications that might have occurred, such as posterior capsular rupture, vitreous loss, dropped nucleus, iris damage and any others.

Dr Lundstrom, who is adjunct professor emeritus in ophthalmology, Department of Clinical Sciences, Ophthalmology, Faculty of Medicine, Lund University, Kariskrona, Sweden, focused on the complications of dropped nucleus and iris damage.

Iris damage

In the study period, which ranged from January 1, 2008 to December 31, 2018, of the 1,715,348 reported procedures, iris damage during phacoemulsification occurred in 4,971 cases (0.3%).

Analysis of the registry data indicated that the rate of iris damage decreased from 0.41% in 2008 to 0.20% in 2018.

Logistic regression analysis of the surgical data showed that the independent variables related to iris damage were male gender, older age, small pupil, white cataract, poor preoperative visual acuity, and glaucoma ($p<0.001$ for all comparisons).

The mean postoperative logarithm of the minimum angle of resolution visual acuity in patients with iris damage was slightly worse than in patients without iris damage, i.e., $0.11 \pm 0.22$ versus $0.06 \pm 0.17$, a difference that reached significance ($p<0.001$), Dr Lundstrom reported.

The refractive outcome regarding the mean absolute biometric prediction error was also significantly ($p<0.001$) different between patients with and without iris damage, 0.58 D versus 0.43 D, respectively. Those with iris damage also had significantly ($p<0.001$) more postoperative complications compared with those who did not, 7.2% versus 2.0%.

Data from almost 3-million surgeries have been entered into the database to date.

Dropped nucleus

When considering this complication during the same time period and in the same number of recorded surgeries, a dropped nucleus occurred in 1,221 cases (0.07%).

This complication also decreased over time, from 0.093% in 2008 to 0.036% in 2018, according to Dr Lundstrom.

The independent variables that were found by logistic regression analysis to be related to a dropped nucleus included a white cataract, previous vitrectomy, poor preoperative visual acuity, small pupil, pseudoexfoliation, diabetic retinopathy and gender.

The visual outcomes associated with dropped

IN SHORT

- Comprehensive data from nearly 2-million cataract and refractive surgeries over 11 years used to identify the trends and risk factors for surgical complications.
The specific postoperative complications were corneal edema, high intraocular pressure, and endophthalmitis, among others, he noted.

The importance of the EUREQUO to provide such valuable data is underscored by the ability to identify risk factors in patients who are undergoing cataract surgery.

Dr Lundstrom concluded that iris damage and dropped nucleus have decreased over a decade. Several risk factors have been identified.

“Combinations of risk factors increase the risk,” he said. “The visual and refractive outcomes are worse compared with no complication. The poor outcomes are explained partly by the risk factors.”

The respective mean absolute biometric prediction errors were 1.02 D versus 0.45 D (p<0.01) and the respective rates of postoperative complications were 18.1% versus 2.0% (p<0.01).

Combinations of risk factors increase the risk. The visual and refractive outcomes are worse compared with no complication. The poor outcomes are explained partly by the risk factors.’

- Dr Mats H. Lundstrom

dr mats h. lundstrom

irish damage during phacoemulsification

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dropped nucleus

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Are topical antibiotics needed after cataract surgery? Maybe

Research finds therapy may not be required, easing burden on patients

By Lynda Charters;Reviewed by
Dr Alexander James Silvester and Dr Anil Pitalia

Let us be more specific, topical antibiotics after cataract surgery are not necessary, according to Alexander Silvester, MBCHB, as long as surgeons tick off all the boxes on the safety check list.

To lessen the postoperative burden on patients who underwent cataract surgery by eliminating the topical antibiotic regimen, Dr Silvester emphasised that the surgery must be uncomplicated and have no dropped nucleus or posterior capsular rupture. And, importantly, instillation of intracameral antibiotics is a must.

Surgeons in the UK have a licensed intracameral antibiotic to rely on, Aprokam (Cefuroxime), that is used in all cases.

While the endophthalmitis rate in the UK is only 0.03% after cataract surgery, the fear is that superbugs will surge ahead and dramatically increase that incidence rate.

“Overuse or inappropriate use of antibiotics is the largest cause of antibiotic resistance,” said Dr Silvester, an ophthalmologist and medical director of the SpaMedica group of eye hospitals, Bolton, UK.

Postop antibiotics

Studies over the past 8 years—a systematic review (Kessel et al. 2015), a retrospective study of 15,000 eyes (Raen et al. 2013) and review of the Swedish National Cataract Registry (Behndig et al. 2011)— supported the notion of eliminating antibiotic drops after cataract surgery.

“All found that topical postoperative antibiotics are not important in preventing endophthalmitis after cataract surgery when the patients have received intracameral antibiotics,” Dr Silvester said.

Published guidelines from the European Society of Cataract & Refractive Surgeons (ESCRS) in 2018 issued a statement that topical antibiotic drops confer no added benefit over intracameral cefuroxime.

The National Institute for Clinical Excellence in the United Kingdom echoed the ESCRs statement and called for more studies to assess the utility of postoperative antibiotics after cataract surgery.

Retrospective analysis

Dr Silvester pointed out that SpaMedica stopped using topical antibiotics following cataract surgery in September 2018.

Dr Silvester and co-investigator Anil Pitalia, MBCHB, retrospectively analysed the Medisoft database that contained almost 30,000 cataract surgeries performed by 28 surgeons in ten of SpaMedica’s UK hospitals between January 6, 2018, and March 3, 2019.

‘All [studies] found that topical postoperative antibiotics are not important in preventing endophthalmitis after cataract surgery when the patients have received intracameral antibiotics.’

– Dr Alexander Silvester

The primary outcome was the incidence rate of endophthalmitis. The secondary outcomes were the incidence of postoperative uveitis, cystoid macular edema, corneal edema, and visual loss of more than three lines of Snellen vision, Dr Silvester recounted.

A total of 13,873 patients were included who had been treated with a combination topical corticosteroid and antibiotic postoperatively and 16,124 patients who only received a topical corticosteroid. All patients had been treated with intracameral cefuroxime. All

IN SHORT

Retrospective analysis indicates that topical antibiotics are unnecessary after routine cataract surgery, with the caveat that intracameral antibiotics are necessary to reduce the risk of endophthalmitis.
patients were followed for up to 4 weeks postoperatively. “No cases of endophthalmitis developed in either group of patients,” he reported.

‘However, endophthalmitis is rare and perhaps our study was underpowered...a sample of 35,000 patients would be necessary to show that topical antibiotics are unnecessary.’

– Dr Alexander Silvester

Regarding the secondary outcomes, he reported that there were no clinical or statistical differences between the two groups. Anterior uveitis was the most frequent complication that occurred by 3.9% and 3.8%, respectively, in the two patient groups.

According to Dr Silvester, topical antibiotics are not necessary following routine cataract surgery.

“However, endophthalmitis is rare and perhaps our study was underpowered,” he said. “A power analysis suggested that a sample of 35,000 patients would be necessary to show that topical antibiotics are unnecessary.”

To add weight to his belief that topical antibiotics are superfluous, since September 2018, 36,661 cataract surgeries have been performed at SpaMedica without the use of postoperative topical antibiotics, and no cases of endophthalmitis have developed in that newer larger cohort. There also were no changes in the complications or visual outcomes.

Dr Silvester concluded by strongly suggesting that topical antibiotics are unnecessary after routine cataract surgery, with the caveat that intracameral antibiotics are necessary to reduce the risk of endophthalmitis.

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Dr Pitalia has no financial interest in any aspect of this report.

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Contact Sheryl Stevenson, Group Editorial Director, with questions at SStevenson@mmhgroup.com
Advanced toric IOL calculator improves refractive outcomes

A new vergence-based algorithm used for power calculation

By Cheryl Guttman Krader
Reviewed by Dr Mark Packer

The use of an advanced vergence-based algorithm to calculate power for the MX60T neutral aspheric monofocal toric intraocular lens (IOL) (enVista, Bausch + Lomb) significantly improved refractive outcomes when compared with a previous fixed-ratio algorithm, according to Mark Packer, MD.

Dr Packer, president, Mark Packer, MD Consulting, Boulder, CO, USA, described the new algorithm and presented findings from a theoretical study using historical data to compare predicted residual refractive error and astigmatism using the vergence-based algorithm versus the previous formula.

Fixed-ratio versus vergence-based algorithm

According to Dr Packer, unlike a fixed-ratio algorithm that assumes the toric power is always in the same place, the new formula takes into account the distance between the corneal plane and the IOL plane.

The new formula incorporates platform-specific inputs for surgically induced astigmatism (SIA) and posterior corneal astigmatism (PCA).

Dr Packer reported that the outcomes analysis showed that the percentage of eyes predicted to have <1 D residual refractive error improved from 55% using the fixed-ratio algorithm to 74% with the vergence-based formula.

Looking at astigmatism alone, the percentage of eyes with residual refractive astigmatism ≤0.5 D also improved from 55% with the fixed-ratio algorithm to 74% using the vergence-based formula.

“The percentage of eyes predicted to be left with 0.5 D or less residual refractive astigmatism with the vergence-based formula approaches the value of 80% that has been reported using other toric IOL formulas that are vergence-based and take into account posterior corneal astigmatism,” said Dr Packer.

“While the new formula seems to achieve its goal in reducing residual astigmatism, it is important to continue this project because I think the results can be further improved.”

Developing algorithm

Data for the theoretical comparative study and some values for the new algorithm were derived from patients who were implanted with the MX60T or the monofocal nontoric MX60 (enVista, Bausch + Lomb) IOLs in their respective US FDA investigational device exemption clinical trials.

A value of 0.46 D at 84.60° was used for SIA and represented the average of SIA values from patients implanted with the MX60 and MX60T IOLs in the clinical trials.

The value of PCA was set at 0.3 D at 90°. It was taken from published population studies and is similar to the postoperative manifest refraction cylinder of eyes implanted with the MX60T IOL, Dr Packer said.

IN SHORT

Refraction outcomes significantly improved with the use of an advanced vergence-based algorithm to calculate power.
To limit influence of biometric errors, the vergence-based portion of the algorithm was developed using values for anterior chamber depth and effective lens position that were derived from optical modelling averaged over the full range of dioptric powers of the toric lens.

A regression analysis was then performed in order to uncover a scaling factor needed to predict the power relationship between the corneal and IOL planes over the implant’s spherical power range.

‘Although SIA is also an important factor to include in toric IOL calculations, the value used has to be based on historical data because patient-specific values are not known until after the operation.’

– Dr Mark Packer

A regression analysis was then performed in order to uncover a scaling factor needed to predict the power relationship between the corneal and IOL planes over the implant’s spherical power range.

**Future refinements**

Dr Packer suggested that the predictability of IOL calculation using the vergence-based formula could be improved in the future by using individual measurements for PCA rather than a population average.

“Although SIA is also an important factor to include in toric IOL calculations, the value used has to be based on historical data because patient-specific values are not known until after the operation,” he concluded.

“The SIA for each case is multifactorial and depends on incision size, the injector used, incision location, the physical dimensions of the IOL and corneal healing.”

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**OUTCOMES ANALYSIS**

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**Fixed-ratio algorithm:**

- **55%**
- **74%**

**Vergence-based formula:**

- **55%**
- **74%**

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**BY THE NUMBERS**

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**PERCENTAGE EYES</1 D RESIDUAL REFRACTIVE ERROR:**

**Fixed-ratio algorithm: 55%**

**Vergence-based formula: 74%**

**PERCENTAGE EYES WITH RESIDUAL REFRACTIVE ASTIGMATISM ≤0.5 D:**

**Fixed-ratio algorithm: 55%**

**Vergence-based formula: 74%**

---

**Future refinements**

Dr Packer suggested that the predictability of IOL calculation using the vergence-based formula could be improved in the future by using individual measurements for PCA rather than a population average.

“Although SIA is also an important factor to include in toric IOL calculations, the value used has to be based on historical data because patient-specific values are not known until after the operation,” he concluded.

“The SIA for each case is multifactorial and depends on incision size, the injector used, incision location, the physical dimensions of the IOL and corneal healing.”

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**Weigh in on SIA as a factor to include in toric IOL calculations**

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The article is adapted from Dr Packer’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr Packer is a consultant to Bausch + Lomb.

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Repeat-selective laser trabeculoplasty (SLT), a protocol explored in a subset of patients in the SLT Laser in Glaucoma and Ocular Hypertension (LIGHT) trial, successfully lowered the IOP in eyes in which the IOP increased after 1.5 years after the initial SLT application. The IOP decrease resulting from repeat-SLT lasted longer than the first round of IOP lowering.

The 3-year trial evaluated initial treatments using SLT laser or medications in 718 treatment-naïve patients with newly diagnosed primary open-angle glaucoma (POAG) or ocular hypertension in one or both eyes; treatments were increased as required, according to Gus Gazzard, FRCOphthMA, MBBCHIR, MD, professor of ophthalmology at UCL-University College and consultant ophthalmic surgeon, Moorfields Eye Hospital, London.

The initial standardised SLT protocol included 360º of treatment in which 100 laser shots were applied using a Latina SLT contact lens. The clinical endpoint was that at least 50% of the shots had visible bubble formation without free streams of bubbles. The SLT could be repeated once, Prof. Gazzard explained.

**Repeat-SLT**

The criteria for undergoing repeat-SLT were failure within 18 months after the initial SLT and eyes in which retreatment was triggered at a pre-defined criteria using eye-specific, severity-dependent target IOP, and/or disease progression based on a custom-designed clinical decision-support algorithm.

The investigators also considered the degree of IOP lowering at 2 months, which is strongly predictive of the 3-year outcome. The 2-month time point was the first at which treatment increases were allowed.

Duration of the effect after the initial and repeated applications determined how long the target IOP remained controlled, Prof. Gazzard explained.

In the initial LIGHT trial, 611 eyes underwent SLT. Of those, 158 eyes failed during the first 18 months, of which 115 eyes (90 patients) underwent repeat-SLT.

The initial SLT power was 89.1 mJ versus 100.5 mJ for repeat-SLT, a significant increase ($p<0.001$).

**Study results**

Prof. Gazzard reported that the mean IOP was higher before the initial SLT compared with the repeat-SLT (24.5 versus 21.0 mm Hg, $p<0.001$).

“We did not allow the patients to return to the baseline IOPs before we re-intervened, to mirror normal clinical practice,” he pointed out.

At that important 2-month time point, the absolute IOP reduction was greater after the initial SLT (5.3 versus 4.6 mm Hg, $p=0.02$).

Prof. Gazzard also explained that, if the 2-month IOP adjusted for the starting IOP immediately before laser treatment was used, there was a greater adjusted effect after the repeat-SLT. The results also showed that the targeted IOP after repeat-SLT was maintained better than the IOP after the initial SLT.

Comparison of the early failures (34 eyes that were retreated at 2 months) with later failures who were not included in the repeated-SLT subgroup (81 eyes that failed after 2 months) was made to determine a bias. There was no difference in effect in the early versus later failures; the mean difference in the IOP reduction was 0.3 mmHg.

“The early failures tended to more often have moderate to more severe POAG, and, therefore, the IOP target was more stringent,” said Prof. Gazzard.

Prof. Gazzard concluded that repeat-SLT successfully reduced IOP in eyes that failed within 1.5 years of the start of the LIGHT trial.
Gel stent proves valuable in refractory open-angle glaucoma

Procedure could prove to be alternative to trabeculectomy

By Cheryl Guttman Krader;
Reviewed by Dr Davinder S. Grover

The subconjunctival gelatin stent (Xen45 Gel Stent, Allergan) is a valuable addition to the glaucoma specialist’s surgical armamentarium because it provides a safe, effective and predictable means of creating a new pathway for aqueous humor drainage in eyes with an atrophic collector system, Davinder S. Grover, MD, MPH, said during the 2019 American Academy of Ophthalmology annual meeting.

“Trabeculectomy is not dead, but with the availability of this minimally invasive glaucoma surgery device that creates a new outflow system, I have significantly decreased the number of cases where I need to lean on trabeculectomy and expose patients to the risks associated with a conventional filtering procedure,” said Dr Grover, attending surgeon and clinician, Glaucoma Associates of Texas, Dallas, TX, USA.

“With proper training and postoperative care as well as scar tissue modulation, the gel stent can safely and successfully help control IOP in a large number of refractory surgical glaucoma cases.”

The stent is made of porcine gel crosslinked with glutaraldehyde. It measures 6 mm in length, has an outer diameter of 210 µm and an inner lumen diameter of 45 µm. In the United States, it is indicated for treatment of refractory open-angle glaucoma. The stent can be used regardless of glaucoma stage, and does not have to be combined with cataract surgery.

Traditionally, the stent has been placed in an ab interno procedure with delivery through a 1.8 mm clear corneal incision, but an ab externo approach performed through the conjunctiva or a small peritomy is possible, and the technique appears to be moving in that direction, Dr Grover said.

Presenting an intraoperative video, he provided this caution, “The surgery is not as easy as it looks, but with experience and proper training, it can be done well and provide a very safe and effective surgical treatment for glaucoma.”

“One of the greatest technical challenges is becoming familiar with the ergonomics of the slider and injector used for the procedure.”

Describing his personal ab interno approach, Dr Grover said the implantation is done under topical anaesthesia. He creates a 1 mm paracentesis in the superior temporal cornea, roughly 90° away from the planned main corneal incision through which he injects a high-molecular-weight cohesive viscoelastic (Healon GV, Johnson & Johnson Vision). Then he makes the clear corneal incision, and

(FIGURE 1) Using an ab interno approach, the injector needle is slightly tenting up the conjunctiva, which allows for more predictable subconjunctival placement of the gel stent. (Image courtesy of Dr Grover)
after rotating the globe inferiorly and drying the superior conjunctiva, places a mark 2 mm posterior to the limbus, as a guide to proper subconjunctival and intrascleral positioning of the stent.

“The device is 6 mm long, and in my experience, it ideally should lie 1 mm in the anterior chamber, 2 mm in the scleral wall, and 3 mm in the subconjunctival space,” he explained. Passing the needle tip of the injector system through the corneal wound can be a little difficult but a slight “shimmy” is helpful.

Positioning and seating the needle in the superior angle is done under gonioscopic guidance. Dr Grover noted that placing viscoelastic on the goniopism is useful for maintaining good visibility.

According to Dr Grover, his goal is to seat the needle tip of the injector just slightly anterior to the trabecular meshwork. A key manoeuvre involves stabilising the injector while delivering the stent to avoid a flick as the needle from the injector disengages from the scleral wall and retracts into the injector. “This was an initial hurdle for me,” he said.

Once the injector has been fully inserted and the needle tip is tenting up the conjunctiva, Dr Grover slowly advances the blue slider halfway to insert the gel stent in the subconjunctival space.

“I want to exit right where the 2-mm mark is, and I want to be certain that it is in the subconjunctival space,” he said. “Perforation is possible, but it would be hard to do and is extremely rare.”

If perforation occurs, the surgeon should simply bring the injector back into the anterior chamber, move the needle tip 1 to 2 clock hours to either side, and re-implant.

“The small conjunctival perforation is usually small and does not leak, but make sure it is Seidel negative at the end of the case,” Dr Grover said.

After implantation, inspection with gonioscopy should confirm that the implant is positioned away from the iris with proper proportions in the anterior chamber and subconjunctival space.

“Using a blunt instrument or the back side of a cannula, the surgeon can roll away the chemosis, starting from the limbus towards to fornix, to flatten the conjunctiva and visualise the implant in the subconjunctival space,” Dr Grover said. “You want to see that the stent is mobile and able to flap freely to the left and right, which is a sign that it is free of any obstruction and not imbedded in Tenon’s capsule.”

Undiluted mitomycin-C (40–80 μg) is then injected subconjunctivally in the target quadrant away from the limbus, but first Dr Grover said he injects a small bolus of 2% lidocaine to improve patient comfort.

“Because the procedure is done under topical anaesthesia, patients will feel the burn of the mitomycin-C,” he explained. “A small lidocaine bolus has made a big difference for my patients and for me.”

A low bleb forms with the gelatin stent. Dr Grover said that postoperative needling with mitomycin-C is needed in about 20% to 30% of cases.

“Knowing how to needle and manipulate the bleb postoperatively is an essential component to success,” he said. “If the idea of a bleb or the need for postoperative manipulation scares you, my advice would be to ask yourself if this is a procedure that you want to learn.”

**Outcomes**

Data from the 510(k) pivotal trial that included 65 eyes of 65 patients showed that at 12 months, 75.4% of eyes had achieved IOP lowering from baseline of at least 20% while being on the same number or fewer medications. Mean baseline IOP was 25 mm Hg and it was reduced by an average of 9.1 mm Hg in the 52 patients who completed the 12-month follow-up. Mean number of medications was reduced by 50% from 3.5 to 1.7. There were no significant or unexpected complications.


“In general, success rates over time in glaucoma surgery are in the 70–80% range, and so this is a very good result considering that the eyes in the study were very refractory cases with advanced disease,” he said.

**Patient selection**

Dr Grover said he uses the gel stent when angle surgery cannot be used, has failed, or is not expected to be effective. It can be effective if follow-up is difficult, for example because the patient has a long commute, is expected to be non-compliant, or needs to get back to work quickly; if a patient is on a blood thinner that cannot be discontinued for a few weeks; and when it is important to have a predictable refractive outcome.

Dr Grover added that he will not use it if there is active inflammation; extensive superior peripheral anterior synechiae; angle closure (unless the procedure is combined with phacoemulsification), neovascular glaucoma; an anterior chamber, unstable posterior chamber, or sutured IOL; or if the patient has iridocorneal endothelial syndrome or is expected to need penetrating keratoplasty.

Dr Grover provided a caution to consider facial anatomy because the presence of a prominent cheekbone and sunken eye may make surgery more challenging.

“In this situation, try to go as far nasal as possible,” he concluded.
Surgeon provides pearls for handling retinal tears with perfluoro-n-octane

Approach eliminates need for postoperative prone positioning

Medium-term perfluoro-N-octane (PFO) without a scleral buckle is the preferred treatment of Steve Charles, MD, for inferior, nasal and temporal giant breaks as well as inferior retinal detachments. He uses the PFO after vitrectomy as a tamponade and leaves it in place in eyes completely filled with the substance for 14 days.

According to Dr Charles, clinical professor ophthalmology, University of Tennessee, Memphis, TN, USA, this approach, which he has used in excess of 1,000 cases over almost 20 years, eliminates the need for postoperative prone or face-down positioning and does not limit the patients’ activities or positioning such as is associated with the use of gas bubbles as a tamponade.

“I use this for inferior detachments and not for detachments above the horizontal meridian,” he said.

“Without the use of scleral buckles, no myopia or strabismus is induced, and there is no pain, ocular surface disorder such as poor conjunctival closure, or corneal damage. This treatment is ideal in phakic and pseudophakic eyes.”

**IN SHORT**

Surgeon uses medium-term perfluoro-n-octane without a scleral buckle for inferior, nasal and temporal giant breaks as well as inferior retinal detachments.

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**FIGURE 1** Perfluoro-n-octane can be injected into the eye, and subretinal fluid can be drained if it persists after injection. (Image courtesy of Dr Charles)
in those with intraocular lenses.”

He also discounted the notion that this tamponade is associated with toxicity.

“In my series of eyes, I have seen no evidence of toxicity associated with the Alcon product which is used off-label,” he stated.

**Surgical pearls**

When performing peripheral vitrectomy to repair inferior detachments, Dr Charles emphasised the importance of removing residual vitreous at the top of the bubble.

“Surgeons must be meticulous about removing vitreous at the point at which the top of the bubble interacts with the superior retina,” he explained. “Don’t be casual about scleral depression and wide-angle visualisation to remove superior vitreous.”

Dr Charles injects PFO, which was developed by Stanley Chang, MD, to treat giant breaks, using a dual-bore cannula (MedOne Surgical Inc.). He advises using the following procedure. Keep the tip of the cannula in contact with the initial bubble made over the optic nerve head, carefully focus and follow that bubble upwards as it expands.

“If method is used, a single bubble will result,” he said. “If multiple small bubbles are created, the chances are higher of one of them going through the break and into the subfoveal space.”

Regarding treating retinal breaks with laser, Dr Charles has always used confluent laser around the breaks.

“You should never apply multiple rows of spots because of the potential for creation of under lapping, over lapping and larger peripheral field defects,” he said.

Dr Charles also advises draining subretinal fluid if it persists after PFO is injected.

“If the break is carefully cannulated, the subretinal fluid drainage can be initiated,” he said. “Internal drainage techniques can still be used even in the presence of PFO.”

Dr Charles noted that if this is done carefully, usually going anteriorly can be avoided as the fluid is forced anteriorly. He uses medium term PFO for all inferior, nasal, and temporal giant breaks as well as all inferior retinal detachments.

If the breaks are nasal and temporal, the patients lies on his or her side postoperatively. Dr Charles emphasised that the cavity is filled with PFO, using less is not as effective. A full fill results in less formation of small bubbles and the advantage, he noted, is that there is no exchange and, therefore, no slippage when managing giant breaks.

“The retina is put back where it belongs,” he said, adding that he has used this technique in pediatric patients with inferotemporal breaks, in whom the PFO was left in the eye for two weeks. In these patients, the lenses remained clear after 15–20 years.

An associated point is that vitrectomy does not cause cataracts, vitrectomy causes nuclear sclerotic cataract progression.

“The idea that medium-term PFO should not be used in phakic patients is nonsense,” Dr Charles stressed.

Removing the PFO in 14 days is mandatory, because of development of a foreign-body reaction in some patients. He uses topical difluprednate twice daily in these cases unless the patient is a steroid responder.

Dr Charles pointed out that he always excises the anterior flap in giant break cases to avoid its moving forward and causing epipodial tissue and hypotony.

He again reemphasised the importance of completely filling the eye with PFO.

“To do this carefully in a phakic eye, the contact lens must be removed,” he said. “Go to the highest magnification right behind the lens, and very carefully remove the last layer of subretinal fluid, infusion fluid, and liquid vitreous that floats up to the top of the PFO to achieve a full fill.”

Dr Charles also advises a PFO/gas exchange or a PFO/silicone oil exchange for a superior giant retinal tear; he uses silicone oil in eyes with proliferative vitreoretinopathy.

“The technique for the exchange is extremely important,” he said.

Under chandelier illumination, the silicone oil injection VFC is held in one hand and the extrusion cannula without a soft tip in the other hand to remove the PFO. Dr Charles advises not using the soft-tipped cannula on the optic nerve head to avoid slippage; the cannula should be positioned at the top surface of the outer margin of the PFO.

This position at the periphery facilitates skimming off of any aqueous liquid and not PFO at the top surface. In a phakic eye, care must be taken to not touch the lens with the cannula. The surgeon must remain focused on the cannula tip during the exchange posteriorly to get the best view of the interface. This technique allows all the residual fluids to be removed before the PFO.

**A novel tamponade**

When performing an autologous macular patch graft, Dr Charles uses a procedure developed by Tamer Mahmoud, MD, PhD, to address a macular hole that is under medium-term PFO. The PFO is removed after seven days. The PFO provides better oxygenation than silicone oil and enables the oxygenation from the anterior surface, not just the choriocapillaris.
Anti-VEGF injections and glaucoma: Surgeons must watch IOP elevation

Physicians finding they have to pay close attention to IOP levels in patients

By Louise Gagnon; Reviewed by Dr Matthew Schlenker

Anti-VEGF injections are associated with acute IOP spikes and chronic IOP rise in patients, and these increases in IOP need to be acknowledged and managed, according to Matthew Schlenker MD, MSc, FRCP.

Dr Schlenker is assistant professor and a University of Toronto, glaucoma, cataract, and anterior segment surgeon, Trillium Health Partners, Kensington Eye Institute, and Toronto Western Hospital, Toronto, Canada. Speaking at the annual Sally Letson Symposium, Dr Schlenker discussed whether anti-VEGF injections are treating or causing glaucoma, Dr Schlenker described instances where VEGF inhibitors have a role and where IOP elevations may be a concern that need to be addressed.

“When you see neovascularisation of the iris, these eyes need anti-VEGF (injections) as soon as possible,” said Dr Schlenker. “This is an opportunity to prevent peripheral anterior synechiae (PAS), and we all know the outcomes are guarded once we have 360° of PAS.”

With respect to wound modulation in filtering surgery, it is complicated to decide whether to use subconjunctival anti-VEGF injections, according to Dr Schlenker.

“There are plausible mechanisms of action,” he said. “There are some in vitro studies that are promising, and there have been animal studies that are promising. However, the clinical studies have yielded mixed results.”

Dr Schlenker pointed to some promising data from a prospective, randomised, controlled trial involving 138 patients which found that intracameral injection of bevacizumab improved the outcome of trabeculectomy (Br J Ophthalmol. 2014; 98:73-8).

“The data suggested that bevacizumab, administered intracameral during surgery, was a useful adjunct to mitomycin C,” said Dr Schlenker. “However, several other studies have been unable to show a benefit.”

**Tackling IOP spikes**

Acute rises in IOP that occur with anti-VEGF injections is a real phenomenon, but it is transient and may not necessarily warrant any intervention for many patients, he noted.

“This rise (in IOP) does not last very long for the average patient,” Dr Schlenker said. “For patients with healthy optic nerves, it may be reasonable to do nothing. However, they should be educated that it is happening.” If a physician opts to treat this elevation in IOP, they can consider various modalities to manage the IOP rise.

One study has shown the most effective medical treatment to blunt fluctuations is apraclonidine, the same medication used to blunt IOP spikes post-glaucoma laser treatments.

A physician also can try to allow for subconjunctival reflux, said Dr Schlenker. “In the past, the main medication injected intravitreally was triamcinolone, and a 27-gauge needle was used which likely allowed for more reflux,” he said. “Studies show that if you allow for (subconjunctival) reflux when you do your anti VEGF-injection, there is a much lower risk of having a spike (in IOP).”

Still another intervention that can be in the armamentarium to manage acute rises in IOP resulting from injections of anti-VEGF agents is anterior chamber paracentesis, he noted, though the long-term effects of repeat paracenteses is unknown.

**Chronic IOP spikes**

Chronic rises in IOP can occur as a result of numerous mechanisms, such as silicone microdroplets from syringes associated with anti-VEGF injections, protein aggregates of the anti-VEGF therapies themselves, particularly if they have been stored for some time.

**IN SHORT**

> Anti-VEGF injections can be linked to IOP spikes and chronic IOP increases in patients. These issues must be recognised and managed by physicians as a concern to be addressed.
time, direct toxic effects on the trabecular meshwork, inflammation and a decrease in nitrous oxide production.

“It is thought that there are certain people at risk for chronic IOP rises, such as people who already have ocular hypertension,” he said, noting such patients have their outflow facility impaired after anti-VEGF injections.

**Landmark trials**

The clinical trials MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) showed the benefit of injections of VEGF inhibitors and also measured safety of IOP levels, said Dr Schlenker.

These trials originally reported mean IOPs but did not look specifically at the number of patients with a clinically significant IOP rise over time. In post-hoc analysis, there was a statistically significant difference in patients who had a chronic IOP rise between those receiving injections and those receiving sham injections.

IOP rise can also be a concern in patients with diabetic macular edema receiving injections of VEGF inhibitors. Dr Schlenker noted data from a trial that compared ranibizumab and laser versus laser alone, where the investigators concluded repeated intravitreous injections of ranibizumab may increase the risk of sustained IOP elevation, suggesting a possible need for ocular hypotensive therapy (JAMA Ophthalmol. 2015; 133:589-97).

The investigators concluded that the data indicate IOP be monitored periodically in eyes receiving repeated injections of anti-VEGF therapy, said Dr Schlenker. “There was not a large number of patients with a problem in these studies; however, these studies mainly included patients who did not have a glaucoma, so may not be generalisable to other patient populations,” he said.

**POAG increase**

There has been talk anecdotally of a spate of cases of primary open-angle glaucoma (POAG) requiring surgery in patients who had undergone anti-VEGF injections in British Columbia (BC), noted Dr Schlenker.

“We have learned that there are some differences in the preparation (of the anti-VEGF injections) compared to Ontario,” he said.

Dr Schlenker noted the differences in preparation are of unknown significance. “We do not really know the answers,” he concluded. “It is something where big data can hopefully elucidate what is going on.”
Assessing crosslinking outcomes
Virtual Bowman’s topography software clears path to hidden steepening

By Lynda Charters;
Reviewed by Dr Gairik Kundu

A novel method of noninvasively evaluating the outcomes after crosslinking is under development. The software will become commercially available in the near future.

“A decade after crosslinking was developed, the question remains about what actually determines the true outcomes of crosslinking; is it flattening or the demarcation line?” asked Gairik Kundu, MBBS, MS, a fellow, Department of Cornea and Refractive Surgery, Narayana Nethralaya, Bangalore, Karnataka, India.

It is important to consider the accuracy of the technology and limitations of topographers. Placido devices can image the anterior but not posterior corneal surface; however, the technology is affected by changes in corneal irregularities and alterations of the ocular surface. The Scheimplug camera does not have sufficient resolution to delink the epithelium from the surface of Bowman’s layer, according to Dr Kundu.

Another consideration after crosslinking is that the epithelium might be a “masquerader”. “Is the epithelium the confounder? Is this the factor that we are not actually looking at?” Dr Kundu asked, adding that the epithelium can change after crosslinking. The curvature at the air/epithelium interface will differ from that at the epithelium/Bowman’s interface.

Not all outcomes after crosslinking are necessarily the desired ones. This can happen as the result of progression. Surgeons must question what is being measured and what should be measured. “Are we looking at the air/epithelial interface? In most cases, this is the masquerader that actually masks the changes that are taking place beneath.”

Dr Kundu and colleagues assessed the true outcomes after crosslinking by using a virtual de-epithelialisation technique that they developed: a noninvasive way of delinking the epithelium from the surface of Bowman’s layer, according to Dr Kundu.

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Dr Kundu and colleagues assessed the true outcomes after crosslinking by using a virtual de-epithelialisation technique that they developed: a noninvasive way of delinking the epithelium from the surface of Bowman’s layer. They analysed 40 eyes of 40 patients with keratoconus who had undergone crosslinking. The Pentacam and anterior-segment OCT data were collected pre- and postoperatively.

They used the Optovue spectral-domain OCT and obtained eight radial 2D frames using MATLAB software, which facilitated viewing of the air/epithelium and the epithelium/Bowman’s interface.

The results showed that the Bowman’s surface was actually more than 1 D steeper than the air/epithelium surface, a significant difference ($p<0.05$).

The air/epithelium interface determined by OCT was similar to the Pentacam anterior surface data. “However, when we went deeper and looked at the Bowman’s surface, it was much steeper,” Dr Kundu noted. Evaluating the aberration profiles showed that the Bowman’s surface higher- and lower-order aberrations were significantly higher than those determined from the air/epithelial surface. The investigators questioned if this could help them in evaluating crosslinking outcomes postop.

When they determined the degree of flattening from pre- to postop of the anterior surface followed by the stromal surface, the group found that the Bowman’s surface had 55% more flattening compared to the air/epithelial interface. Dr Kundu recounted a case in which the anterior surface topography after crosslinking flattened by about 1.05 D. “When we applied our algorithm and used the virtual de-epithelialisation technique, flattening was found to be actually more than 2 D 6 months postop,” he said.

In a second case, the anterior surface flattening was about 3.5 D after crosslinking, but Bowman’s surface had flattened by almost 1 D.

The future
Dr Kundu pointed out two known factors: the curvature is steeper on the stromal surface compared with the anterior surface, and that stromal changes are masked by the epithelial thickness and haze that hide that crosslinking outcomes. “This method provides a non-invasive way to quantify tomographic features at the Bowman’s surface and early detection of diseases and progression,” Dr Kundu concluded. “Bowman’s surface actually shows the real crosslinking outcomes. This method facilitates customised treatments and prevention of unnecessary retreatments in patients with keratoconus.”

**IN SHORT**
Software provides a noninvasive way to look at crosslinking outcomes.

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This article is adapted from Dr Kundu’s presentation at the American Academy of Ophthalmology’s 2019 annual meeting. Dr Kundu has no financial interest in this technology.

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The importance of the limbal stem cells was never in dispute, and they are fundamental to regeneration of the corneal epithelium. However, the general good health of the cells must be maintained to ensure such regeneration, and uniform guidelines were absent regarding what exactly constituted limbal stem cell disease.

“Stem cells are the source of the regeneration and maintain a healthy phenotype of the corneal epithelium,” Friedrich E. Kruse, MD, explained, underscoring their importance.

In an unhealthy state when the stem cells are not functioning well, the result is conjunctivalisation, in which normal corneal epithelium is replaced by conjunctival epithelium.

“When this happens, the characteristic picture of limbal stem cell deficiency arises,” said Dr. Kruse, professor of ophthalmology, Department of Ophthalmology, University of Erlangen-Nuremberg, Erlangen, Germany.

**Treatments**

The potential treatments for the scenario detailed are limbal stem cell transplantation or *ex vivo* expanded grafts.

Numerous studies have reported the results of limbal stem cell transplantation, with great variations in the diagnostic criteria, staging systems and outcome criteria, resulting in marked heterogeneity of the clinical picture of stem cell deficiency and potential confusion with other ocular surface diseases, Dr. Kruse explained.

“We think it is important to look for signs of conjunctivalisation on the ocular surface and to prove the existence of goblet cells when invasive therapy is performed.”

– Dr. Friedrich E. Kruse

**IN SHORT**

The lack of consensus regarding limbal stem cell deficiency has been resolved by a panel of experts that provided uniform guidelines for disease diagnosis and staging.

Recognition of the lack of uniformity in the definition and diagnostic criteria resulted in a consensus conference in which corneal experts ultimately produced two reports, the first of which focuses on definition, classification, diagnosis, and staging of limbal stem cell deficiency.

The committee published a global consensus in *Cornea* earlier this year (Deng et al. 2019; 38:364-375). The second report on treatment guidelines is currently under review.

**New definition**

The new definition of limbal stem cell deficiency is that it is “an ocular surface disease caused by a decrease in the population and/or function of corneal epithelial stem/progenitor cells that leads to the inability to sustain normal homeostasis of the corneal epithelium.”

This scenario leads to the clinical picture of conjunctivalisation (goblet cells on the ocular surface), signs of epithelial dysfunction or both that include epithelial abnormalities, superficial neovascularisation, ocular surface inflammation and scarring.

However, decreased vision, pain and negatively impacted quality of life are the frequent results for patients.

**Indirect evidence**

When goblet cells are present on the corneal surface, changes of the epithelial phenotype provide indirect evidence for the diagnosis of limbal stem cell deficiency: irregularity and haziness, vascularisation, absence of the limbal palisades, persistent and
recurrent epithelial defects, and subepithelial fibrosis, according to Dr Kruse.

The symptoms include pain, foreign-body sensation, photophobia, resulting in decreased vision and quality of life.

The most important diagnostic test is surface late staining with fluorescein; the dye diffuses into the paracellular space of the conjunctivalised surface, and the abnormal delayed staining is seen 10 minutes or longer after fluorescein is instilled on the ocular surface, Dr Kruse explained.

Other histological and immunohistochemistry tests, that is, impression cytology and biopsy, also can be performed to diagnosis the presence of limbal stem cell disease. *In vivo* imaging also has emerged as a noninvasive diagnostic tool that is equivalent to cytology, he noted.

An alternative imaging method is anterior-segment optical coherence tomography, which is also noninvasive and provides a larger field of view.

**Staging**

The expert panel also established a new staging system to guide therapy and surgery.

“Stage I is characterised by healthy corneal epithelium in the centre and various degrees of conjunctivalisation in the periphery,” Dr Kruse explained. “In stage II, the corneal centre shows signs of disease with various changes in the periphery. Stage III shows complete vascularisation of the corneal surface.”

**Limbal stem cell deficiency**

Acquired limbal stem cell deficiency can result primarily from nonimmune causes: chemical, thermal, or radiation injury; contact lens-induced changes; surgery; trachoma and lid disease; and drugs. The immune causes include Stevens-Johnson syndrome, mucous membrane pemphigoid, allergic ocular surface disease, vernal and atopic keratoconjunctivitis, graft-versus-host disease, severe dry eye, and idiopathic problems.

Hereditary limbal stem cell deficiency results from congenital aniridia, dyskeratosis congenita, autoimmune polyglandular syndrome, ectodermal dysplasia, multiple endocrine deficiency and xeroderma pigmentosum.

**Conclusion**

Dr Kruse noted that the panel has established a new definition of limbal stem cell disease.

‘Stem cells are the source of the regeneration and maintain a healthy phenotype of the corneal epithelium.’

– Dr Friedrich E. Kruse

“We think it is important to look for signs of conjunctivalisation on the ocular surface and to prove the existence of goblet cells when invasive therapy is performed,” he concluded. “We have provided a list of diseases causing limbal stem cell deficiency that is based on the current literature.”

**Dr Friedrich E. Kruse, MD**

E: Friedrich.kruse@uk-erlangen.de

Dr Kruse has no financial interest in any aspect of this report.
A common complaint among children and adolescents, headaches including migraines remain the top reason for referrals to paediatric neurology.² The worldwide prevalence of migraine in children and adolescents is 7.7%.³ Reported prevalence increases with age, from 3% (age 3–7 years) to 8–23% (age 11–15+ years).⁴ Approximately 10% of school-aged children suffer from migraine, with boys being more frequently affected before puberty, and girls more frequently thereafter.⁵ A comprehensive 2010 survey estimated that migraine has a global prevalence of 14.7%, making it the third-most-common disease in the world in men and women.⁶

The migraine burden cannot be measured with dollars alone. Researchers have likened the impact of migraines on children’s quality of life to that of arthritis, diabetes and cancer.

All these headaches carry costs beyond their physical toll. On average, children with migraine miss 8 school days yearly, versus 4 for children without migraines.⁷ Among adults globally, migraine ranks seventh among specific causes of disability, and among the top ten causes of disability in 14 of 21 world regions.⁸ One analysis reveals that, between 2008 and 2013, patients with migraine had significantly higher direct and indirect healthcare costs ($10,363 and $11,294, respectively) than did patients without migraines ($4,619 and $8,945, respectively).⁹

Additionally, the migraine burden cannot be measured with dollars alone. Researchers have likened the impact of migraines on children’s quality of life to that of arthritis, diabetes and cancer.¹⁰,¹¹

Yet the seriousness of migraine remains under-appreciated by parents, teachers, primary care providers,¹² and often migraine sufferers themselves, most of whom are never diagnosed or treated.⁵ The psychosocial and economic burden of paediatric migraine, coupled with the relief offered by newer treatments, including triptans, lends urgency to accurately identifying and promptly treating migraine.²,¹²

**Migraine classification**

The considerable variability of migraine within and among patients stems from dysfunction of an ion channel in brainstem nuclei that normally modulates sensory input and regulates the meningeal blood vessels.¹³ Pathophysiologically, neural abnormalities drive dilation of cranial blood vessels, resulting in further nerve activation and pain.¹⁴

The *International Classification of Headache Disorders*, 3rd edition (ICHD-3), classifies headaches into primary, secondary, and those caused by cranial neuropathies and other headaches.¹⁵

**PRIMARY HEADACHES**

This category includes diagnostic criteria for migraine and its variants, along with tension-type headache (TTH) and other trigeminal autonomic cephalalgias (TACs).

Migraines can occur with or without aura; specifically, at least two attacks that include one or more reversible visual, sensory or other symptoms that meet specific temporal criteria.

Patients who have migraine without aura may experience prodromal symptoms up to 48 hours before other migraine symptoms. These symptoms may include:

- **Fatigue**
- **Nausea**
- **Difficulty concentrating**

IN SHORT

- Reducing the economic and psychosocial cost of paediatric migraine requires correct classification and prompt treatment.
Stiffness
Photophobia/phonophobia
Blurred vision
Yawning
Pallor.

Additional types of primary headaches include TTH and TAC.

All forms of TTH typically involve a mild-to-moderate bilateral headache, pressing or tightening in quality. Increased pericranial tenderness is the most significant abnormal finding in patients with any type of TTH. Pain does not worsen with routine physical activity and may or may not be associated with nausea; phonophobia or photophobia may occur.

Finally, TACs are unilateral headaches, usually accompanied by prominent cranial parasympathetic autonomic features (such as conjunctival injection and/or lacrimation, nasal congestion, and facial sweating), which are lateralisled and ipsilateral to the headache.

OTHER PRIMARY HEADACHES

SECONDARY HEADACHES
Secondary headaches include new headaches and preexisting or significantly worsening preexisting headaches caused by primary disorders such as trauma and systemic diseases. Other causes include:

- Trauma or injury to head and/or neck
- Cranial and/or cervical vascular disorder
- Nonvascular intracranial disorder
- Increased intracranial pressure
- Substance or its withdrawal
- Infection
- Disorder of homeostasis
- Psychiatric disorder
- Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial/cranial structure.

Cranial neuropathies, centrofacial pain and other headaches include painful cranial-nerve lesions and other facial pains deriving from a complex catalogue of causes such as trigeminal, glossopharyngeal, occipital and other neuralgias; optic neuritis; ischaemic oculomotor nerve palsy; and various facial neuropathies and syndromes.

Evaluating paediatric migraine requires a systematic approach involving the following steps:

### Table 1. Medical history questions

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>NOTES/RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the pattern of your headaches, and at what time of day do they occur?</td>
<td>• Acute onset of first episode, without prior history. • Recurring headache with symptom-free intervals. • Chronic pattern of progressively increasing headache. • Nonprogressive daily or near-daily headache. • Mixed pattern of daily headache with more intense attacks superimposed.</td>
</tr>
<tr>
<td>How and when did your headaches begin?</td>
<td>Establish origin/history of attacks.</td>
</tr>
<tr>
<td>How often do they occur, and how long do they last?</td>
<td>Identify characteristic patterns. A weekly 4-h attack suggests migraine or TTH; brief attacks occurring multiple times daily suggest TACs.</td>
</tr>
<tr>
<td>Where is the pain located?</td>
<td>• Holocephalic • Bilateral • Unilateral • Posterior</td>
</tr>
<tr>
<td>What is the quality of the pain?</td>
<td>• Throbbing/pounding • Squeezing/pressure • Stabbing • Other</td>
</tr>
<tr>
<td>What other symptoms accompany your headaches?</td>
<td>• Nausea, vomiting, abdominal pain • Visual aura, diplopia • Photophobia/phonophobia • Vertigo/dizziness • Motion sickness, nocturnal leg cramps • Numbness/weakness</td>
</tr>
<tr>
<td>Does anyone in your family suffer from headaches?</td>
<td>Use the open-ended term “headache,” not “migraine”; parents’ migraines may have been misdiagnosed as other headache types.</td>
</tr>
<tr>
<td>What do you think might be causing your headaches?</td>
<td>Possibly the most important question—children and parents’ main fear is usually a brain tumour. Normal physical and neurological examinations can provide reassurance.</td>
</tr>
</tbody>
</table>

Abbreviations: TAC, trigeminal autonomic cephalalgias; TTH, tension-type headache. Adapted from Rothner AD.

 europe.ophthalmologytimes.com
1. MEDICAL HISTORY: Usually, a thorough headache history provides enough clues for accurate diagnosis. Questions (Table 1) are structured to identify more concerning headache patterns early in the process.

Keep in mind that there are red flags that should trigger consideration of neuroimaging for suspicion of intracranial pathology.

2. PHYSICAL EXAMINATION: This portion of the evaluation should include the following measurements/investigations:

3. NEUROLOGICAL EXAMINATION: More than 98% of children with brain tumours who present with headache have objective neurological findings. Look for abnormalities in these areas during the basic neurological exam:

Routine neuroimaging is not indicated in children with recurrent headaches and normal examination. However, physicians should consider neuroimaging if certain warning signs appear:

4. ANCILLARY TESTING AS INDICATED: No evidence supports the use of routine laboratory studies, lumbar puncture or electroencephalogram (EEG) in headache-afflicted children with normal physical and neurological findings. However, if findings in steps 1 to 3 warrant further exploration, consider appropriate modalities.

5. IMAGING AS INDICATED: Similarly, no evidence supports the use of routine neuroimaging in children with a history of recurring headaches who have a normal neurological exam. Neuroimaging in children with headaches should be considered when findings in steps 1 to 3 warrant further investigation. More specifically, when the neurological exam is abnormal, when other simultaneous neurologic concerns such as seizures are present, or when headache historical factors such as first, worst, or marked change in headache

### Table 2. Tiered-treatment approach to migraine

<table>
<thead>
<tr>
<th>1st tier</th>
<th>Lifestyle modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td>Hydration</td>
</tr>
<tr>
<td>– Good sleep hygiene and habits</td>
<td>– Exercise (hot, sweaty, out-of-breath: 3 min, 3-4 times/wk)</td>
</tr>
<tr>
<td>– Age-appropriate duration</td>
<td>– Stress avoidance</td>
</tr>
<tr>
<td>Diet</td>
<td>Herbal/supplements: vitamin B2 and magnesium¹³</td>
</tr>
<tr>
<td>– Consistent, well-balanced meals</td>
<td>Physical therapies and other complementary treatments</td>
</tr>
<tr>
<td>– Avoidance of caffeine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd tier</th>
<th>Integrative therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural therapies: cognitive behavioural therapy (CBT), biofeedback, and stress management techniques</td>
<td></td>
</tr>
<tr>
<td>Preventive/prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Antihypertensives:</td>
<td></td>
</tr>
<tr>
<td>– Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>– Angiotensin II receptor blockers (ARBs)</td>
<td></td>
</tr>
<tr>
<td>– Beta blockers</td>
<td></td>
</tr>
<tr>
<td>– Flunarizine (not available in United States)</td>
<td></td>
</tr>
<tr>
<td>Antiepileptics</td>
<td></td>
</tr>
<tr>
<td>Antihistamines</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3rd tier</th>
<th>Pharmacologic treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute/abortive treatment (in emergency department, hospital, or home)</td>
<td></td>
</tr>
<tr>
<td>Analgesics</td>
<td>Devices (such as nerve stimulators, transcranial magnetic stimulation devices)</td>
</tr>
<tr>
<td>Antiemetics (to facilitate absorption of primary drugs)</td>
<td>Surgery (although not typically offered)</td>
</tr>
<tr>
<td>Serotonin agonists/triptans</td>
<td></td>
</tr>
<tr>
<td>Dihydroergotamine (DHE)</td>
<td></td>
</tr>
<tr>
<td>Valproate sodium</td>
<td></td>
</tr>
<tr>
<td>Dopamine antagonists</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4th tier</th>
<th>Other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onabotulinum toxin A</td>
<td></td>
</tr>
<tr>
<td>Nerve blocks</td>
<td></td>
</tr>
</tbody>
</table>

¹³Kacperski J, et al.¹²
From Lewis D, et al.²²
Let Us Be Your Eyes and Ears

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pattern are reported, neuroimaging should be considered. When considering neuroimaging, magnetic resonance imaging (MRI) would be the preferred imaging modality unless there is a concern for an acute or life-threatening etiology that warrants quick imaging such as computed tomography (CT).

**Treatment**

Treatment of pediatric migraines requires a multi-tiered approach (Table 2), which tailors an individualized treatment plan to each patient’s headache pattern and lifestyle and that can accommodate changes if needed.22 Headache frequency may spontaneously increase, for example, and patients may require higher or lower doses than for previous headaches, or, for more difficult headaches, combination therapy. Each child’s degree of headache burden should determine how aggressively one treats and manages his or her headaches, considering the following factors:

1. Headache frequency, duration and intensity;
2. Patient’s functional disability and pain tolerance;
3. Patient’s comorbidities; and
4. Patient’s quality of life.

Many patients with moderate-to-severe migraine respond well to oral treatment with analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) administered at the time of an attack (acute/abortive treatment; Table 3). Patients must be educated and able to use their medication as early during the headache as possible. This requires ready access to medications in school, home and social situations.2,12,23 Patients also must avoid medication overuse, a known cause of headaches, by limiting analgesic and NSAID use to 2 to 3 days or less weekly. Keeping a headache diary can track drug use patterns. Additional agents require caution. For example, aspirin-butalbital-caffeine is frequently prescribed for adult headaches, although, like other aspirin-containing products, it should be avoided in children aged younger than 16 years due to the risk of Reye syndrome.24 Always avoid opiates and other narcotics in children.

### Table 3. Nonspecific treatments for pediatric migraine

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>10 mg/kg every 6 h</td>
<td>The most widely studied analgesic for pediatric headaches.</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>10–15 mg/kg</td>
<td>Considered second-line, reserved for children with hypersensitivity or other contraindications to NSAIDs: • Upper gastrointestinal disease • Renal impairment • Bleeding disorders • Oral anticoagulant use</td>
</tr>
<tr>
<td>Naproxen</td>
<td>10-20 mg/kg/d</td>
<td>Tends not to cause rebound headache.</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.5 mg/kg IV, 15 mg max</td>
<td>Works best in combination with prochlorperazine.4</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.

4 O’Brien HL, et al.2

### Table 4. Triptans approved for pediatric migraine

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
<th>AGE RANGE (Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan/naproxen® (Treximet)</td>
<td>10/60 mg Daily max: 85/500 mg</td>
<td>12–17</td>
</tr>
<tr>
<td>Sumatriptan nasal spray® (Approved in Europe, Asia, and other countries; intranasal sumatriptan also has support from a strong RCT performed in the United States)</td>
<td>5 or 20 mg</td>
<td>12–17</td>
</tr>
<tr>
<td>Rizatriptan®</td>
<td>Weight &lt;40 kg: 5 mg Weight &gt;40 kg: 10 mg</td>
<td>6–17</td>
</tr>
<tr>
<td>Almotriptan®</td>
<td>6.25 or 12.5 mg Daily max: 25 mg</td>
<td>12–17</td>
</tr>
<tr>
<td>Zolmitriptan nasal spray®</td>
<td>2.5 mg or 5 mg Daily max: 10 mg</td>
<td>12–17</td>
</tr>
</tbody>
</table>

5 Pernix Ireland Limited.26 6Lewis D, et al.27 7Winner P, et al.27 8Merck and Co. Inc.28 9Elanssen Pharmaceuticals.

24 Impax/AstraZeneca.29

Abbreviation: RCT, randomised controlled trial.
established dosing regimens, safety and tolerability. Sumatriptan, almotriptan, zolmitriptan, and rizatriptan have earned US Food and Drug Administration (FDA) approval for acute paediatric migraine. All triptans activate the atypical 5-HT\textsubscript{1B/1D} receptor that has been implicated in the pathophysiology of migraine, and, to a lesser degree, other 5-HT receptors. They do this through three main mechanisms of action:

1. Cranial vasoconstriction;
2. Peripheral trigeminal inhibition; and
3. Inhibition of transmission through second-order neurons of the trigeminal cervical complex.

In 2006, the FDA warned consumers that taking triptans with selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) could raise users’ risk of life-threatening serotonin syndrome. However, careful review of the available evidence has shown that this is not the case.

Experts have suggested guidelines for triptan use in paediatric migraine. Adverse effects of triptan generally last less than 30 minutes.

### ADDITIONAL TREATMENT OPTIONS

With few medications approved for paediatric migraine, physicians frequently prescribe drugs used for migraine in adults (Table 5).

#### Migraine prevention

Whereas no consensus exists for when and how to implement preventive therapy for migraine in children, various authors suggest considering prophylaxis in patients who experience at least three or four migraines monthly, and in those for whom acute treatments prove insufficient and/or poorly tolerated. Children who experience significant pain and/or disability also may warrant prophylaxis.

Authors of the American Migraine Prevalence and Prevention (AMPP) trial recommend considering and offering prophylaxis to patients aged 12 years and older. The only agent the FDA has approved for preventive use in children is topiramate.

Inadequate and often conflicting evidence notwithstanding, additional drugs commonly used for this purpose in children include antidepressives, antihypertensives, antiepileptics, antihistamines and nutraceuticals.

### On the horizon: CGRP antagonists

A promising strategy for acute and preventive migraine treatment involves blocking calcitonin gene-related peptide (CGRP), a potent vasodilator whose concentration in the external jugular vein rises during migraine attacks and decreases in the serum after triptan administration and symptomatic relief.

Developers of the following monoclonal antibodies targeting CGRP have filed for FDA review, with decisions expected in 2018:

1. Erenumab
2. Fremanezumab

Additional treatments under study specifically for paediatric headaches including migraine are propofol, prochlorperazine, dexamethasone, diclofenac, fentanyl, and several behavioural and nutraceutical approaches. As the array of interventions for preventing and treating paediatric migraine grows, timely and appropriate application of such agents will continue to reduce its burden.

---

**Table 5. Other medications used for paediatric migraine**

<table>
<thead>
<tr>
<th>Triptans</th>
<th>E: E0.1–1.0 mg, depending on age, tolerability; 20 doses maximum.</th>
<th>Effective for status migrainosus in children and adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydroergotamine (DHE)</td>
<td>Zolmitriptan (adult dose: 2.5 or 5 mg; daily max: 10 mg)</td>
<td>An option for status migrainosus if DHE is contraindicated or not tolerated</td>
</tr>
<tr>
<td>Valproate sodium injection</td>
<td>Sumatriptan (adult dose: 25–100 mg; daily max: 200 mg)</td>
<td>Adult dosage: 15 mg/kg every 8 h until headache resolves, or total of 10 doses.</td>
</tr>
<tr>
<td>Dopamine antagonists</td>
<td>Naratriptan (adult dose: 1 or 2.5 mg every 4 h; daily max: 5 mg)</td>
<td>Useful for acute migraine including nausea and vomiting symptoms, particularly in combination with IV DHE:</td>
</tr>
<tr>
<td>Nutraceuticals</td>
<td>Frovatriptan (adult dose: 2.5 mg; daily max: 7.5 mg)</td>
<td>Magnesium, Vitamin B2 (riboflavin)</td>
</tr>
</tbody>
</table>

Abbreviation: IV, intravenous.

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**For article references, go to**

ContemporaryPediatrics.com/pediatric-migraine
Gene therapy is happening today and cell therapy may soon follow, according to Allen C. Ho, MD. Dr Ho, professor of ophthalmology, Thomas Jefferson University, and director of retina research, Mid Atlantic Retina and Wills Eye Hospital, Philadelphia, PA, USA, and his colleagues have been focusing on improving the consistency and precision of therapeutic delivery to target tissues.

“Subretinal delivery provides direct surgical access to target retinal pigment epithelial cells and retinal photoreceptors,” he said. “This direct access may be important for gene and cell therapies for treating retinal diseases.”

The first FDA-approved gene therapy is voretigene (Luxturna, Spark Therapeutics) for biallelic RPE65 mutation-associated retinal dystrophy. In addition to restoring vision to patients, the studies evaluating the efficacy of voretigene (among other gene therapy studies) have established the safety and feasibility of subretinal delivery of gene therapy.

The use of gene therapy for other retinal diseases, such as neovascular age-related macular degeneration (AMD), are currently in clinical trials. According to Dr Ho, translational scientists are working on improving viral capsids and transgene selections to improve efficacy. In this aim, Dr Ho and colleagues are hoping to improve the consistency and precision of delivery systems for gene and cell therapy.

**Methods of drug delivery**

Subretinal delivery is achieved in a few ways, the most familiar of these is “transretinal” via pars plana vitrectomy (PPV) and retinotomy using a microcatheter.

Another approach is subretinal delivery via the suprachoroidal space. In this method, Dr Ho explained, a flexible microcatheter follows the curvature of the sclera and a microneedle, which is under the visual control of the surgeon, enters the subretinal space without the need for a PPV and retinotomy.

“A new intriguing way of transfecting target tissue is suprachoroidal injection therapy,” he said. A major advantage of such a treatment would be the potential ability to perform the procedure in the office setting.

**Gene therapy clinical trials**

A Phase I/IIa gene therapy clinical trial by RegenexBio for neovascular AMD is currently under way. Enrolled subjects have been treated for neovascular AMD previously and needed frequent anti-VEGF injections over years; he described one subject who needed 21 monthly injections of ranibizumab (Lucentis, Genentech). In the study, a high-affinity AAV8 viral vector that encodes for an anti-vascular endothelial growth factor protein that is similar to ranibizumab is injected into the subretinal space, Dr Ho explained.

The surgery is performed as follows. A core vitrectomy is performed. A 41-gauge internal diameter microcatheter is then used to deliver the vector into the subretinal space.

This manoeuvre is performed outside of the macula about two disc areas away from the neovascular lesion. An air-fluid exchange is performed. The traditional eye drops are instilled; no systemic steroids are used in the subretinal injection procedures.

“We have seen very good safety data for this surgical procedure,” Dr Ho reported.

Improvement in the precision and control of subretinal delivery has been achieved using a new tool, the MicroDose injection kit (MedOne Surgical Inc.) that includes a 1-cc microcalibrated syringe that is hooked up to the viscous fluid injection system.

“The surgeon has foot pedal control of precise volumes of fluid injected into the subretinal space.”

**IN SHORT**

- Novel surgical techniques can improve the precision and safety of gene and cell therapy delivery to target tissue.
Dr Ho noted, “To control any surgeon variability, all procedures, i.e., vitrectomy and subretinal injection, are standardised and automated, and the surgical videos of all surgeons are reviewed in order to improve the techniques and standardise them.”

Suprachoroidal delivery
Cell therapies to replace retinal pigment epithelium cells for the treatment of advanced geographic atrophy in dry AMD are under investigation. Replacement RPE cells may be delivered on a synthetic sheet or in suspension delivered into the subretinal space via a surgical procedure involving PPV and retinotomy formation, according to Dr Ho.

Potentially complicating these cell therapies is the possibility of scar tissue formation, including epiretinal membrane formation or proliferative vitreoretinopathy-related tractional retinal detachment.

“Complications from proliferative vitreoretinopathy will be a topic of interest for treating retinal specialists. The retina community will be watching this as new cell therapy-related trials are initiated,” said M. Ali Khan, MD, assistant professor of ophthalmology, Thomas Jefferson University and Wills Eye Hospital.

The investigators hypothesised that these complications are the result of egress of delivered cells through the retinotomy on to the surface of the retina.

“That failure stimulated development of multiple approaches to reach the subretinal space. A suprachoroidal microcatheter was developed with a flexible microneedle; this needle emanates into the subretinal space to create a detachment and deliver cells.

The advantages are that no vitrectomy and retinotomy are needed, there is no efflux, and as a result the dosing might be more precise and consistent,” Dr Ho commented.

The procedure begins with insertion of a chandelier light source. A sclerotomy is fashioned 6 mm posterior to the surgical limbus after conjunctival peritomy is performed.

A microcatheter is then inserted via the sclerotomy into the suprachoroidal space after being held in place with scleral sutures (microloops) to stabilise the path of the microcatheter and to reduce the amount of internal catheter movement to avoid damage, Dr Khan described.

When the microcatheter is visualised to be in the desired location, a microneedle is advanced into the subretinal space. A saline bleb confirms the location. Cells are then delivered.

This technology, developed by Gyroscope, has received 2019 FDA approval and is being used in the Lineage (formerly BioTime) cell therapy trial for atrophic AMD.

Dr Ho pointed out the importance of three-dimensional (3D) imaging in reaching the correct subretinal space with precision and safety. “3D imaging allows measurement of dosing, which is an important metric in a clinical trial,” he commented.

“Gene and cell therapy is happening,” he added. “Subretinal delivery of therapy via a vitrectomy and retinotomy is very familiar.”

However, the dosing can vary and efflux can occur, especially in cell therapy trials.

“The suprachoroidal approach has been approved by the FDA and is being used in an AMD clinical trial. Imaging will be important and we now have 3D imaging to facilitate quantitative dosing,” Dr Ho summarised.

Dr Ho is a consultant to AGTC, Asclepix, Gyroscope, Iveric/Ophthotech, Lineage/BioTime, and RegenexBio.

Dr Khan has no financial disclosures related to this subject.

europe.ophthalmologytimes.com
Ophthalmologists should advise their patients to perform their due diligence when participating in patient-funded clinical trials on stem-cell therapies to treat glaucoma, according to Leslie Jones, MD.

Talking at the annual Sally Letson Symposium, Dr Jones, chairwoman of Ophthalmology at Howard University in Washington, DC, USA, said that clinicians should caution patients against trials that are not controlled. She noted that patient-funded trials have numerous weaknesses, such as the lack of randomisation and control arms, a disparity in access to the trials owing to their high fees, and an apparent risk of exploitation of vulnerable patients who are “reaching out for anything to improve their situation.”

A trial appearing on a registry does not guarantee its scientific validity, Dr Jones explained, adding that clinicaltrials.gov does not ensure random selection, informed consent or a proven effect of the therapy.

Unproven stem-cell therapy treatments are readily available in the USA and Canada. Patients should look for red flags before they opt for current stem-cell treatments, i.e., not being asked to provide informed consent, not being told about the possible harms associated with the treatment, and paying out-of-pocket for the treatment. Another red flag is the absence of other stakeholders in a trial, such as government agencies or research organisations.

The adverse events that have developed after visits to such clinics have been documented and include severe bilateral vision loss subsequent to intravitreal injections of autologous adipose-tissue-derived stem cells (N Engl J Med. 2017; 376:1047-1053).

Another instance involved a woman who had exudative macular degeneration and underwent bilateral intravitreal injections and later developed retinal detachments in both eyes (Ophthalmic Surg Lasers Imaging Retina 2017; 48:772-775).

Dr Jones noted that patients are paying a minimum of $5,000 per injection per eye.

The attraction of stem cells, or induced pluripotent cells created by various growth factors and transcription factors, is that they can revert back to the pluripotent state, where they can develop into any kind of cell, Dr Jones pointed out.

Several possible avenues of research are taking hold, such as differentiation of stem cells into trabecular meshwork, with a goal to lowering IOP and aiming to have the new trabecular meshwork function better than the existing one; use of supportive cells in the retina to protect against degeneration of retinal ganglion cells (RGCs); and differentiation of stem cells into RGCs so that damaged cells in the retina are replaced, with the hope that they would then re-establish axons and reconstitute the optic nerve.

Investigators have successfully transplanted RGCs that have survived, migrated and integrated into the retina in rodent models, but more investigations are needed before this research translates to clinical practice, according to Dr Jones.

Dr Jones noted that, when it comes to glaucoma, there is not enough known to get these stem-cell therapies to work in vivo in humans.

“What we will need are clinical trials which are randomly selected with a placebo arm, and these are generally very expensive and very slow to start,” she said. Technologies to image the health of RGCs in vivo are needed, Dr Jones concluded. “Candidate therapies that allow us to protect RGCs, rescue injured and dying RGCs, replace non-viable RGCs and regenerate the optic nerve (are needed), as are randomised, clinical trials with control arms to allow us to test the efficacy of new therapies in humans,” she said.

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This article is based on Dr Jones’s presentation at the 51st Sally Letson Symposium in Ottawa, Ontario, Canada. She has no financial disclosures related to her discussion.
Module bridges remote gap in learning and mentorships

Platform links healthcare specialists from around the world

Orbis International has one of the largest and most diversified ophthalmology resource offerings in the world, and what it offers is completely free, with the goal of using technology to scale up its efforts to eliminate avoidable blindness in developing countries.

Cybersight, founded by Gene Helveston, MD, in the late 1990s, is the free eye-health learning and mentorship telemedicine platform used by Orbis International to teach and disseminate information as part of its mission to prevent and treat avoidable blindness. Since the time when Dr Helveston sought to teach strabismus procedures to Cuban physicians, Cybersight has evolved substantially to incorporate the Cybersight Consult, Cybersight Learn and Cybersight Live Teaching components into its program.

“All of these areas are about building capacity in human resources in the low- to middle-income countries in which we work,” said Hunter Cherwek, MD, who is vice president, clinical services, Orbis International.

According to Dr Cherwek, in the area of consultation, more than 150 top international ophthalmology experts are serving as mentors, and there have been more than 20,000 patient consultations undertaken for complex cases to date.

“We have been involved in 950 cases of retinoblastoma and linked doctors worldwide to St. Jude’s Hospital in Memphis and Toronto Sick Children’s Hospital in Canada,” he said.

Dr Cherwek noted that Cybersight Learn offers online courses and an open-access library in topics related to ophthalmology, nursing and associated fields. “Doctors can online free of charge and take multi-hour courses in, for example, phacoemulsification, small incision cataract surgery, pediatrics, and glaucoma,” he said.

Cybersight Live Teaching offers live lectures and surgical demonstrations through real-time video conferencing, Dr Cherwek explained, adding that it has been an explosive field for the company’s platform.

“We are using artificial intelligence to enable our consults not only to teach our doctors what the diagnosis is but also how the diagnosis was derived, what algorithmic thinking was used, and how the ocular structures and associated factors are viewed,” he said.

Growth spurt

The data collected from 2018 boast about the increasing numbers of surgeons taking advantage of the resources offered by Cybersight:

- 5,052 new users bring the total number of users to more than 12,000 globally;
- 2,160 patient consults; and
- 89 live webinars in 2,868 locations in 127 countries. The webinars and online courses trained 5,872 people in 165 countries.

The courses offered are not just for ophthalmologists but also include nurses, optometrists, schoolteachers and community village workers. The online courses that are proving to be of special interest are those providing instruction in phacoemulsification and small incision cataract surgery, the latter of which is the most highly accessed course.

Mobile access

For Dr Cherwek, the most exciting technological advances are smartphone apps being used, for example, to enable tribes to move their cattle from place to place in anticipation of changing weather patterns. The mobile utilisation of Cybersight has increased markedly from 2017 to 2019, compared with desktop access, he reported.

**IN SHORT**

- Cybersight platform of Orbis International links health personnel in low- and middle-income countries to healthcare experts worldwide for consultations and training.
“It is exciting to see how much we have been able to democratise education and open up access via cell phone technology,” he emphasised.

**Remote wet labs**

Dr Cherwek described the creation of academic bridges through the Cybersight platform with wet labs that have been established worldwide.

“We have normalised remote surgical mentorship in Peru and have the equipment ready to expand to Ghana, Cameroon, South Africa, Indonesia and Bolivia,” he said.

In this teaching model, international ophthalmology experts observe and mentor local surgeons in real time during live surgery, from thousands of miles away.

The digital wet lab model, he explained, is now in Peru and at Emory University, and new equipment is on site at Shroff’s Charity Eye Hospital in India. The wet lab courses now have standardised curricula, and individuals must be able to demonstrate knowledge and basic science competency before entering the wet lab in Peru. Based on this experience, the residents receive grades based on the Ophthalmology Surgical Competency Assessment Rubric (OSCAR) score and comments about their surgical performance and then review their surgical videos.

Dr Cherwek reported the results of a study in which 12 final-year residents who submitted 120 surgical videos were followed. The trainees’ average competency scores increased from 15.9 before training to 25.1 afterwards.

Among 60 resident surgeries performed after training, the patients’ vision exceeded 20/60 in 91.7% of cases, compared with 76% at baseline.

**Cybersight insight**

Cybersight is, first of all, a product that is free to people in low- to middle-income countries. However, it is ultimately a platform, according to Dr Cherwek.

With the Cybersight Consult function, the primary purpose is to link clinic personnel in these countries to ophthalmology experts worldwide. “We can now do this using digital photography and the Internet to link any two eye health professionals,” he said.

In Cybersight Learn, all of the content is free and is being translated almost instantaneously into more than 35 languages.

“This has become a learning management system not just of basic science but for evaluating residents’ wet lab training, OSCAR scores and videos,” he noted.

The Cybersight Live Teaching component provides live global webinars on clinical and surgical topics. Dr Cherwek acknowledged the work of Dan Neely, MD, a paediatric ophthalmologist who devotes 20% of his time to Cybersight, and is linked with all of the pediatric ophthalmologists he has trained in Mongolia, Peru, and elsewhere. From Indiana University, he has participated in surgeries in real time and provided surgical coaching.

**FIGURE 1** Cybersight is a health learning and mentorship telemedicine platform that physicians can access from anywhere. (Photo courtesy of Dr Cherwek)
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