**Issue Feature**

Top ophthalmic challenges in 2017
Medical, surgical options at forefront

**Retina**

Managing giant retinal tear re-attachment
Case involves incidental subfoveal perfluorocarbon heavy liquids

**Cornea**

Bowman layer graft in keratoconus
Transplant promising to stabilise ectasia

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**Cataract & Refractive**

**AD-IOL mimics natural lens movement**

Novel concept for accommodating IOLs captures, transforms zonular movement into axial shift

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**Caption**

A. The foldable implant is positioned into the capsular bag with a restraining device that keeps the optic temporarily in a flat position. B, C, and D. The activated optic mimics movement of the crystalline lens. (Images courtesy of Dr Paul M Beer)
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Top ophthalmic challenges in 2017: What to watch in the year ahead

Changing healthcare environment, medical/surgical options at forefront

OTE Staff Reports

As the year 2016 winds to a close, thoughts begin to turn to the next challenges for ophthalmology in the new year.

Top of mind for many are concerns over the diagnosis and management of retinal disease, glaucoma, and cornea/anterior segment disease, along with a watchful eye on a new administration in the United States.

Five members of the Ophthalmology Times Europe Editorial Advisory Board share their perspectives on the top challenges that ophthalmologists likely will face in 2017.

Dr Stefánsson: The global pandemic in diabetes produces an epidemic of diabetic eye disease that strains ophthalmology resources.

There were 150 million diabetic patients in the world in the year 2000 and now there are 430 million. Two-thirds of type 2 diabetics develop retinopathy and one-third reach sight-threatening retinopathy in their lifetime.

Screening and preventive treatment is the way to go, but global resources cannot deal with annual screening of this enormous group of patients.

Also, the ophthalmology resources to provide lifelong intravitreal injections for tens of million of patients with diabetic macular oedema are not available.

Eye clinics around the world are already strained by the treatment load of intravitreal anti-vascular endothelial growth factor (VEGF) injections for wet age-related macular degeneration (AMD). Aging populations will increase the number of patients over the coming decades. At the same time, this treatment should be made available to more wet AMD patients and at optimal frequency. Various treat-and-extend protocols are a compromise between healthcare resources and patient needs. Many elderly patients are receiving fewer injections than what would give them best vision outcome.

While anti-VEGF injections have been a godsend for patients with wet AMD, diabetic macular oedema, and other retinal diseases, the fact remains that many patients have a modest or
Dr Augustin: Ocular imaging tools to better evaluate both therapeutic strategies and the pathophysiology of many diseases are rapidly expanding and improving. Especially, improvements in optical coherence tomography (OCT) imaging of the posterior and anterior segment need further critical evaluation.

This is not only true for OCT angiography (OCTA), which may add additional knowledge on perfusion characteristics of different layers of the posterior segment, but also for higher resolutions and imaging modalities. Those are swept-source OCT and the “en face” presentation.

Dr Holló: OCTA for glaucoma (and retina) has been gaining increasing interest and importance. Of the different OCTA systems currently available, the AngioVue OCTA provides the most developed, quantitative evaluation on disc and peripapillary angioflow density, and provides data for various sectors of the peripapillary as well for different layers, separately.

It was recently shown that the measurement is reproducible, able to separate glaucoma eyes from normal eyes, correlates with the corresponding retinal nerve fibre layer thickness (RNFLT), visual function ad visual field damage, and shows improvement after significant reduction of IOP.

The value of OCTA vessel density change in early detection of glaucomatous progression (in comparison to that of RNFLT change) is a particularly important question, to which follow-up studies need to be done in the next years.

Dr Kermani: The number of patients receiving intravitreal operative medication (IVOM) for wet AMD is increasing every year. In my clinic, I do see cases with therapy refractory to wet AMD more often. What are we going to do with them? Continue with IVOM after 15 to 20 injections? What kind of life quality is this? And at what costs? A life before and after the next injection.

Brachytherapy in combination with vitrectomy was an alternative, but the company failed to perform proper studies and busted. Oraya? It has become quiet around this radiologic approach. Not a good sign.

There are rumors of a new brachytherapy approach. This time vitrectomy is not necessary. The approach is ab externo. Let us see what they are coming up with, and hopefully, this time the company takes care that the studies are performed with quality and care.

Dr. Augustin: We have alternatives for several diseases, such as diabetic macular oedema, macular oedema due to retinal vein occlusion, and wet AMD. This means that we must evaluate the outcome early in the treatment course and decide to switch to other approaches if appropriate.

In addition, combination treatments are under consideration. Those strategies should be evaluated further.

Besides those diseases which can be already treated with evidence-based strategies, another challenge is dry AMD. We are expecting results from several studies for the treatment of this disease entity.

Hopefully, we can also expect alternatives.

Furthermore, we still need clear measures for a better evaluation of such a treatment. Several measures, such as autofluorescence, did not prove to be a reliable measure because of many uncertainties.
Dr Holló: Although their role is now established in the treatment of glaucoma, more extensive and early use of fixed-combination drugs is expected for the next years. All glaucoma patients need long-term medication, may potentially undergo filtration surgery, and will develop age-related dry eye, etc.

Thus, wider use of preservative-free, fixed-combination glaucoma drugs is definitely expected.

‘Wider use of preservative-free, fixed-combination glaucoma drugs is definitely expected.’
— Dr Gábor Holló

I expect further intensive discussions on the various minimally invasive glaucoma surgery (MIGS) devices since new implants are in the pipeline. But at the same time, I am sure that MMC trabeculectomy and glaucoma drainage devices will preserve their leading role in the surgical treatment of glaucoma for several years.

Patients’ adherence to topical glaucoma medication is suboptimal and needs to be improved. To this, new methods are needed, and the role of compliance trainings need to be better evaluated. Influence of cultural background on the effectivity of compliance trainings needs also to be analysed.

This is essential since many ophthalmologists are not fully familiar with the instrument (software) provided options, and the understanding of the background mathematical basics also remains suboptimally understood.

Haag-Streit published its new Visual Field Digest (a completely renewed 6th edition) which is available as a book and is freely downloadable from its website ([www.haag-streit.com/haag-streit-diagnostics/campaigns/visual-field-digest]). This book is very didactic and comprehensive, and guides the reader stepwise across the different stages of understanding visual field analysis, progression analysis, and automated kinetic perimetry, and presents several typical cases to improve readers’ skills on using modern visual field testing technologies.

Dr Alio: Femtosecond laser-assisted cataract surgery (FLACS) has become one of the hot topics in the last years in cataract surgery. However, its lack of cost effectiveness, the time that it requires, and the space in the operating room have become serious issues against its global adoption.

The only issue in which it seems to be offering a real advantage is in capsulorhexis. Devices, such as the Zepto or Capsulaser, are challenging the performance of capsulorhexis with a far lower cost for ocular surgeons, which would avoid FLACS to be adopted.

It is time to offer real evidence about the effectivity of FLACS or to reduce its excessive cost, or otherwise its progression will be challenged.

Dr Augustin: During the American Academy of Ophthalmology annual meeting, the question of whether FLACS is worth the considerable cost was the subject of a debate. One major issue is the longer procedure time and the high cost which must be covered by the patient. The potential advantages, such as a precise capsulotomy and reduced endothelial loss, are not unequivocally accepted.

Overall, the evidence for other advantages seems also to be very weak. Even a meta-analysis on the comparison of FLACS with manual surgery suggests that the advantages and disadvantages of FLACS may cancel each other out.

One final conclusion of this debate was that FLACS may find its place for severe cases as a niche product.

Next year, surgeons need to further evaluate this procedure.
THOUGHTS ON Presbyopia

**Dr Kermani:** In my opinion, it is the presbyopic patient who is emmetropic. Kamra failed to convince. Raindrop? “I do not like plastic in the cornea,” Prof Kanellopoulos from Athens says, and I agree. I would rather wait a few years to see what will come up with this new method, regardless if it is approved by the FDA.

So what is the alternative? Prof. Waring is paving the way. Is it only presbyopia or is it lens deficiency syndrome? Prof. Waring’s concept of lens deficiency syndrome is more than a euphemism. It makes sense and patients understand it.

If presbyopia is the earliest onset sign of cataract development, then it is not a matter if we propose lens exchange, the matter is when we are proposing lens exchange. Why would we want to let our patients suffer, until vision has decreased below 20/40? With modern laser technology and IOL design, refractive lens exchange might also become the method of choice for the emmetropic presbyope.

**Dr Alio:** Presbyopia IOLs have been progressing with sophisticated multifocality optics, such as the varifocal (Oculentis), extended depth of focus, and trifocals.

These three technologies provide advantages and disadvantages, with a clear progressive increase in their adoption by surgeons and patients. The outcomes have been increasing and the particular role of each technology is unclear.

It is my opinion that trifocals and varifocals are superior to extended-depth-of-focus lenses. In this year, I expect that evidence will support one or the other in a way that surgeons can have independent and well-supported information on what to use.

Among the many techniques suggested for the compensation of presbyopia, intracorneal inlays have always been on the stage due to their minimally invasive character, their reversibility (in part), and the accessibility of the technique as it does not require high technology or sophisticated surgery.

However, in spite of all these theoretical advantages, the lack of reproducibility, the frequent intolerances happening in patients, and the explantation rate which is definitely higher than that reported by company-sponsored studies have made this topic not to be progressing adequately.

During 2017, I hope real evidence will arise in favor of intracorneal inlays—particularly the Kamra, the Raindrop, and Flexivue, which are those most extensively used. Lack of evidence will limit adequate expansion into the market and what is true is that previous evidence provided by the companies has not been backed by real results. This is the time to prove this.

Among the new emerging topics, and still not in practice, is the pharmacological therapy of presbyopia. Some companies are developing at this moment some topical treatments to increase the accommodation by reactivating the ciliary body (FOV presbydrops) or soften the lens (Encore Vision study), while others are simply using myotics.

These drugs should be used binocularly as pharmacological monovision is not, in my opinion, attractive for refractive surgeons.

If this is really on a practical basis helping patients with early and intermediate presbyopia, this can become a huge issue and indeed studies supporting or providing evidence on this alternative treatment of presbyopia will be most welcome and of huge interest.

‘If presbyopia is the earliest onset sign of cataract development, then it is not a matter if we propose lens exchange, the matter is when we are proposing lens exchange.’

— Dr med Omid Kermani

How did ophthalmology evolve in 2016? In a view from across the ocean, Editorial Advisory Board members from sister publication Ophthalmology Times shared thoughts on what advances they were anticipating, and what hurdles they would face in 2016. OphthalmologyTimes.com/2016Evolve
Dr Kermani: Tear film deficiency again was in focus in 2016 at our clinic. We invested in TearLab and learned a lot about tear film deficiency and osmolarity. The challenge will be advanced treatment of tear film deficiency.

There are many new options from steaming goggles to light pulses. Which is the best? Do we need a combination of therapies as Prof. McDonald proposes? Nutritional additives, local pharmaceutic and physical therapy, as well as systemic treatments with hormones? It seems to develop a subspecialty in our field.

In my city, the university hospital has inaugurated a dry eye outpatient department. Last week, I tried to get an appointment for a patient suffering from severe refractory dry eye. She was ready to pay private. Next open appointment was in April 2017. This tells you what is going on with dry eye. Challenges and opportunities.

Ectasia-angst! What a beautiful word creation. I read this in an article from Prof. McDonald.

Prof. Brad Randleman added the 40% rule to his risk score table, noting that the sum of flap thickness and ablation depth should not exceed 40% of total corneal thickness.

Very helpful for risk assessment; yet, can we prevent ectasia? One-third of ectasia cases had normal corneas prior to surgery. Ectasia has prevalence also with SMILE. No big difference.

What is needed is ectasia prevention in order to overcome ectasia-angst. LASIK Xtra could be the way to go. The company, however, fails to deliver studies to bring science into the discussion. So this would be a challenge for 2017. Who is coming up with scientific proof that LASIK Xtra works?

Dr Alio: Small incision lenticule extraction (SMILE) has become one of the top issues in refractive surgery. The possibility to use only one femtosecond laser for all refractive surgery, avoiding excimer costs, is attractive on top of the minimal invasiveness of the procedure.

However, SMILE has not yet been demonstrated to be superior to LASIK or to provide evidence about its better performance than excimer laser surgery. This is indeed an obstacle to its progression and, in my case, an obstacle for patients to choose the technique as it is less known.

Following the innovation that came with the invention of SMILE, now is the time to bring evidence about its superiority or not. If not superior, then SMILE will have the advantage of costs as once the hyperopia is accomplished, one femtosecond laser will fit all corneal procedures, including refractive ones.
Almost a decade ago, Dr Paul M Beer, set out to develop a pseudophakic IOL for in-the-bag implantation that would replicate the movement of the young crystalline lens.

At the XXXIV Congress of the European Society of Cataract and Refractive Surgeons in Copenhagen, Dr Beer reported on his success using “Zonular Capture Haptics” (ZCH) to create accommodating-disaccommodating IOLs (AD-IOLs).

Two AD-IOL prototypes are in development. The first is based on axial shift of a single foldable monofocal optic that would meet FDA label requirements. It has been implanted in six animal eyes so far, demonstrates continued efficacy after more than 1 year of follow-up, and is ready for resizing for human eyes.

The second, which is at an early prototype stage, is a dual-mode AD-IOL that combines axial shifting and optic shape changing mechanisms. Based on “in silico” studies, the dual-mode implant is estimated to produce 10 to 14 D of accommodation. Preclinical animal studies are targeted to begin in the first quarter of 2017.

“ZCH is an enabling technology that harnesses the fibrosis of the capsular bag and responds to ciliary muscle contraction in an unprecedented way, converting zonular forces into optic movement,” said Dr Beer, founder and chief executive officer, Z Lens LLC, St. Petersburg, Florida, USA. Dr Beer, who is a retina specialist, noted that compared with a cataract surgeon, he approached the development of an accommodating IOL with a fundamentally different perspective about the capsular bag.

“Because my encounter with capsular bags is usually months or years after cataract surgery, I see the capsule as a tangibly stiff disc that holds an IOL in a rigid straitjacket, restricting implant movement,” he explained.

His solution for enabling axial shift was to cut the fibrosed capsule into sections that could separate, thereby activating optic movement. In addition, Dr Beer thought to harness the fibrosis of the capsular bag so that the tissue could be utilised like Velcro straps to attach the zonules to individually mobile haptics.

**In Short**

Accommodating-disaccommodating IOLs are being developed that mimic the movement of the young crystalline lens through the use of “Zonular Capture Haptics” technology.
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His first prototype AD-IOL is a foldable implant positioned into the capsular bag during cataract surgery with a restraining device that keeps the optic temporarily in a flat position. In its resting state, the IOL functions like a monofocal lens.

After allowing 4 to 6 weeks for the capsule to collapse, fibrose, and adhere to the haptics, radial capsulotomies are created in a non-invasive procedure using a laser (Nd:YAG or femtosecond), releasing optic mobility for restoration of accommodation. B, C, and D. The activated optic then mimics the movement of the crystalline lens, vaulting forward when the ciliary body contracts with accommodation and flattening out during disaccommodation.

Findings from animal research
Animal studies evaluating the AD-IOL were conducted by Dr Paul Kaufman and Mary Ann Croft at the Wisconsin National Primate Research Center, University of Wisconsin-Madison, USA. Using electrode stimulation of the Edinger-Westphal midbrain nucleus to stimulate physiologic levels of accommodation and carbachol for pharmacologic stimulation, optic axial shift, haptics flexion, and refractive change were measured using anterior segment OCT, ultrasound, Scheimpflug imaging, and Hartinger objective refraction.

The collected data confirmed that the AD-IOL moves as intended after initial activation and at 1 year after cataract surgery. With electrode stimulation in a series of eyes, the AD-IOL demonstrated a maximum axial shift of 0.8 mm and maximum haptic flexion of 20°.

“Using monkey biometric data, we would predict about 1 mm of axial shift translates into about 1 D of accommodation,” Dr Beer said. “Using Hartinger refraction, however, we observed mean...
accommodation of about 2 D using electrode stimulation and up to 4 D using carbachol.”

Second-generation device
The Dual Mode AD-IOL incorporates a small, reservoir-free, fluid-filled optic vesicle that is thicker at the apex. The optic is pulled flat by stretched haptics during disaccommodation. During accommodation, the haptics come closer together so that the optic is compressed and its curvature increases.

Dr Paul M. Beer
E: drbeer@zlensllc.com
Dr Beer holds two patents on the AD-IOLs. Dr Kaufman and Ms Croft have no relevant financial interest to disclose.

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Evolutions in laser technologies making cataract surgery safer

Superior outcomes can be achieved precisely, consistently, predictably

By Dr H Burkhard Dick

Although femtosecond laser-assisted cataract surgery is now commonplace, using laser to assist with the steps of cataract surgery is still a relatively new concept. The first platforms reached the commercial market only about 5 or 6 years ago. Since then, however, they have undergone remarkable innovations that have served to refine their functionality and performance.

The incorporation of laser cataract surgery (LCS) into regular practice has fundamentally changed how the surgery is done, while also introducing the possibility of performing new techniques. These new techniques have, in turn, made the platforms more versatile and the surgery safer, while also making cataract surgery accessible to populations who may have been previously disqualified.

As important as LCS has been for the cataract surgery field, there are important differences in the platforms available on the market. The individual features of a platform affect how it functions in the operating room: the features interact and complement each other to add to the platform’s overall capabilities.

Rationale and benefits for cataract surgery

I was one of the first surgeons in Europe to start performing LCS on a routine basis, because I believed it was a better way to do the surgery.

For example, a perfectly cut and centred capsulotomy gives a better chance of achieving the IOL’s optimal effective lens position after implantation. Pristine sideport, main, and arcuate incisions offer a means to address astigmatism at the time of surgery and reduce surgically induced astigmatism.

I was also intrigued by the possibility of using the laser to fragment the lens and thereby reduce ultrasound power while potentially lowering the time spent performing intraocular manoeuvres.

As to whether the LCS lived up to my expectations, the short answer is yes. In fact, in my hands, LCS is an upgrade over manual techniques for several reasons. Although my LCS cases did take a little longer while I was getting used to the new way of operating and figuring out the platform, in the long term, LCS actually improved my surgical efficiency. There is no difference in the time taken for the procedure with LCS (from suction on to wound closure) compared with manual, and no difference in cortex removal time. The overall procedure time is equivalent to manual because ophthalmic viscosurgical device (OVD) use can be minimised or eliminated and the need for ultrasound to emulsify the lens is significantly reduced.

My hunch about the intrastromal incisions also proved correct. Histology studies indicate that laser-cut incisions are precise and accurate, with no apparent damage to the cornea. LCS is associated with faster visual rehabilitation, less deviation from the refractive target and earlier postoperative refractive stability than manual surgery.

In short

- Laser techniques have fundamentally changed the cataract surgery landscape.
- New, versatile platforms have made surgery safer and provided superior clinical outcomes precisely, consistently and predictably.
Performing LCS may increase prostaglandin levels in the eye, which could induce miosis, particularly when cutting the anterior capsulotomy. To counteract this and maintain mydriasis, it is highly recommended to use a non-steroidal anti-inflammatory drug three times on the day of surgery.

However, this is a relatively minor concern, especially considering that LCS does not induce any additional endothelial cell loss and can reduce postoperative inflammation compared with manual surgery.

**Platform benefits**

When I became interested in adding laser to my cataract surgeries in 2011, I chose the Catalys system (Abbott) because it offered several features I believed would be advantageous for the surgery.

For instance, the system was introduced with a non-applanating liquid interface that holds the eye firmly in place to minimise eye movement during the procedure.

This is important, as respiratory movement of the eye during the capsulotomy step has been suggested as a potential risk factor for capsule tear. The liquid optic interface also minimises increases in IOP.

The system also came equipped with an advanced imaging system, which I foresaw would be important for scanning the eye and preparing the treatment plan.

The accuracy of the imaging would also be crucial for individual capsulotomy centration. Over the years, 3-D spectral-domain optical

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**FIGURE 1**

A. Posterior laser capsulotomy. B. Full fragmentation. C. Anterior capsulotomy. D. Live OCT Intrastromal incision. (Images courtesy of Dr. H. Burkhard Dick)
coherence tomography (OCT) has been added to make the imaging capabilities even stronger.

The system is also extremely fast, with the ability to achieve a full lens fragmentation in less than 30 seconds in most kinds of cataracts. Treatment time may be a little longer in higher-grade cataracts.

However, the laser fragmentation option is much more gentle than the turbulence that would be created by using ultrasound energy to emulsify dense cataracts, and so a slightly longer fragmentation cycle with laser is still preferable over manual techniques in these cases.

These features on their own are important; how they can be used in tandem to complement one another may be even more important.

I have been involved in several research efforts aimed at understanding how the various features can be utilised to optimise patients’ outcomes and facilitate greater efficiency in the operating room. As I have learned, the features can be harnessed to create new surgical techniques that make the surgery safer and easier to perform in routine cases and especially in complex ones.

One example is the ability to perform cataract surgery without the use of OVDs. Because the femtosecond laser can be used to emulsify the lens, which in turn reduces the reliance on ultrasound energy, OVDs may not be necessary to protect the corneal endothelium during the capsulotomy and fragmentation steps. An intra-individual comparison of 74 eyes of 37 patients randomised to either standard phaco with OVD or LCS without OVD indicated no difference in endothelial cell loss and a trend toward lower IOP in the group without OVD.

Another example is to use laser-cut capsulotomies as a rescue technique in cases in which the initial capsulotomy is too small. A case series demonstrated the ability to safely perform phaco and IOL insertion before using laser to enlarge the capsulotomy without causing a capsule tear. Such a technique may be applicable and beneficial for eyes in which there is a small anterior capsule opening.

A potential benefit of laser-cut capsulotomies is the ability to achieve an IOL’s effective lens position more rapidly after implantation, thus ensuring faster visual recovery and more predictable outcomes. However, while all of the femtosecond laser platforms on the market offer the ability to cut a capsulotomy, the onboard imaging capabilities of the Catalys with regard to its 3-D SC-OCT creates particularly precise positioning.

Another example of complementary functions and their application to cataract surgery is in the ability to perform a posterior capsulotomy. Because this platform’s imaging system can map anterior and posterior capsulotomies, there are several ways to perform a primary posterior capsulotomy with the Catalys, both in adults and in paediatric eyes. The fluid interface means that it is also possible to first aspirate the cataract then safely re-dock the eye, cut a posterior capsulotomy and perform a bag-in-the-lens implantation.

Overall, the unique features of Catalys have permitted the expansion of indications for LCS and have made the procedure safe for even complex cases, such as brunescent and intumescent white cataracts in paediatric patients with Marfan syndrome, eyes with a small pupil and following trauma cases involving penetrating injury to the cornea and capsule.

A potential benefit of laser-cut capsulotomies is the ability to achieve an IOL effective lens position more rapidly after implantation.

The Catalys system recently underwent a software upgrade to version cOS 3, which served to strengthen the existing functionality while improving workflow.

The biggest upgrade is the addition of streaming OCT, which is of particular benefit to detect eye movement during the incision stage. Aided by an internal guidance system, the cOS 3 upgrade reduces the time needed for incision computation and requires fewer operator adjustments and modifications to the baseline protocols.

The usability of the system with the cOS 3 upgrade is enhanced by the addition of several automated treatment plans, including an option to align the capsulotomy over the scanned capsule using the live OCT feature. The wealth of additions is not overwhelming, however, and the system can be easily integrated for use in all types of cases, from routine to complex.
The capsulotomy is performed in less than 1 second with minimal cavitation bubbles and even dense, grade 4 cataracts can be fully fragmented with the laser.

The docking process has also been enhanced in an effort to reduce residual forces during the “lock” step. This feature has implications for reducing micromovements of the eye during the procedure to minimise the risk of capsule tears. These additions add to the already innovative and validated liquid optics interface, which induces minimal changes in IOP and no corneal folds, thereby yielding a clear optical path for laser delivery.

What these upgrades add to an already innovative platform is an increased chance to achieve superior clinical outcomes precisely, consistently and predictably. I have found the cOS 3 upgrade easy to integrate and having it available is a tremendous benefit when I am implanting a premium IOL for which the accuracy of each step is crucial.

When I am able to deliver on the results promised to my patients after surgery, it yields a premium experience, whereby the surgeon can feel satisfied with the result and patients go home happy with their new postsurgical vision.

REFERENCES


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Dr Dick is chairman of the Ruhr University Eye Hospital in Bochum, Germany. He did not indicate financial interest relevant to the subject matter.
Giant retinal tears pose outsize challenges for physicians, including the risks of hemorrhage, heavy fluid droplets, and macular holes, according to Dr Gerardo Ledesma-Gil.

“These surgeries are complicated and you have to take your time,” said Dr Ledesma-Gil, a retina fellow at the Instituto de Oftalmología Fundación Conde de Valenciana, Mexico City, Mexico. “If something goes wrong, be calm and make another plan.”

Giant retinal tears are rare, he added. In 2010, the British Giant Retinal Tear Epidemiology Eye Study (Invest Ophthalmol Vis Sci. 2010;51:4781-4787) found an incidence of 0.094 retinal tears per 100,000 people. Although retinal attachment was achieved in 94.7% of patients, only 42.1% achieved vision of 20/40 or better.

**Patient case**

Dr Ledesma-Gil’s patient was a 29-year-old male who underwent phacoemulsification in 2009 as treatment for injuries from blunt trauma to the eye.

Five years later, the man presented with a giant retinal tear and retinal detachment. Surgeons began their treatment with pars plana vitrectomy (PPV). They used perfluorocarbon heavy liquids to flatten the retina, allowing them to observe its anterior edge.

After an air fluid exchange, they tried to re-attach the anterior edge. During this procedure, a subretinal hemorrhage occurred. However, the surgeons were able to control it and remove all the clots.

“In that part of the surgery, the heavy liquids came under the retina incidentally,” Dr Ledesma-Gil said.

When the surgeons noticed the heavy liquid under the retina, they drained it surgically and performed another air fluid exchange.

Using an endoprobe to deliver laser, they re-attached the retina, then infused silicone oil as a long-acting tamponade.

During a follow-up to this surgery, the surgeons noticed two elevations on the retina. Investigating with optical coherence tomography (OCT), they found one subfoveal perfluorocarbon droplet and one under the nasal region of the retina.

Fearing that the droplets could damage the retina, the surgeons performed a PPV revision, giving them a clear view of the droplets.
Surgeons made a second hole and drained the second droplet from the nasal area of the retina. Finally, they used gas for a temporary tamponade and achieved complete macular attachment.

Using a 42-gauge needle, they made a small hole in the area surrounding the droplet under the macula to attempt its removal, but were fearful of making the hole too close to the fovea.

As a consequence, they could not reach the droplet with the needle and had to use a silicon-tipped cannula to move the droplet to the needle. After several attempts, they succeeded in draining the droplet.

They made a second hole and drained the second droplet from the nasal area of the retina.

Finally, they used gas for a temporary tamponade and achieved complete macular attachment.

However, in a postoperative exam the patient’s final visual acuity in the affected eye was 20/400. Although this was an improvement over his vision before the surgery, it was disappointing, Dr Ledesma-Gil said.

Using OCT, the surgeons confirmed that they had completely removed the droplets. Though they found a macular hole, they decided to take no further action.

“It was probably the droplet itself and the retinotomy that made the hole,” Dr Ledesma-Gil said. “A combination of factors led to the hole formation.”

What to do differently?
If he had to do the procedure over, Dr Ledesma-Gil said he would take a slightly different approach, perhaps using gas to move the droplet rather than a cannula.

The physicians explained to the patient what happened, and because he has good vision in his other eye, he is satisfied, Dr Ledesma-Gil said.

*DR GERARDO LEDESMA-GIL*
This article was adapted from Dr Ledesma-Gil’s presentation at Retina Subspecialty Day during the annual meeting of the American Academy of Ophthalmology. He has no financial interest in the subject matter.

www.oteurope.com
SD-OCT enhances visualisation earlier in disease process

By Lynda Charters; Reviewed by Dr Anat Loewenstein

Spectral-domain optical coherence tomography (SD-OCT) has become indispensable for visualising the fovea and diagnosing retinal diseases. Importantly, detailed visualisation facilitates diagnosis during the early disease stages, according to Dr Anat Loewenstein.

**Solar maculopathy**

The first case (Figure 1 on page 22) illustrating the importance of high-detailed imaging was that of a 29-year-old male, as described by Dr Loewenstein. The patient’s past ocular medical and family histories were not remarkable.

The patient reported blurry vision in both eyes over the past 4 days with a yellow spot centrally. He denied any recent exposure to drugs, however, he had used cocaine and cannabis “crystal” 1 year previously.

SD-OCT examination showed a normal flat macula with a small yellow spot centrally. However, there was a stop in the photoreceptor continuity in the ellipsoid and inter-digitation zones.

“A hyper-reflective material was seen emerging from the retinal pigment epithelium [RPE] toward the outer nuclear layer,” said Dr Loewenstein, professor of ophthalmology, deputy dean of the medical school, Sackler Faculty of Medicine, Tel Aviv University, Israel, and chairman of ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv.

The patient later admitted to lying on the beach exposed to sunlight for the entire day when symptoms began. The diagnosis was solar retinopathy, secondary to sun gazing.

During follow-up, SD-OCT showed the hyper-reflective material was absorbed with abrupt continuation of the photoreceptor layer in the fovea and the external limiting membrane (ELM) was preserved. This status was maintained at 2 and 4 months of follow-up.

“Solar retinopathy occurs mainly during celestial events—such as eclipses, religious rituals, and sunbathing—and in psychiatric patients,” Dr Loewenstein said. “The light is of low power but exposure was usually for a long duration. The light intensity is amplified by the cornea and the lens by a factor of 10,000. The pathophysiology includes both thermal and photochemical damage. While recovery is possible, permanent damage is a possibility.”

The importance of SD-OCT is underscored in this case by the defects that were visible in the ellipsoidal zone as well as the strong correlation between the disruption of the inner photoreceptor junction and the worsened vision.

**Laser-induced retinopathy**

A second case (Figure 2 on page 22) was that of a 15-year-old boy who experienced an acute
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decrease in vision in both eyes after staring at a laser pointer. The patient’s medical and ocular histories and that of his family were unremarkable.

The macula was flat with a yellow spot in the fovea. Similar to the first case report, SD-OCT showed the contour of the fovea was normal with a stop in the photoreceptors continuity in the ellipsoid and interdigitation zones and the presence of a hyperreflective material emerging from the RPE toward the outer nuclear layer.

SD-OCT follow-up of this patient showed the reabsorption of the hyperreflective material, abrupt discontinuation of the photoreceptor layer in the fovea,
and preservation of the ELM. “The size of the outer macular hole in the right eye decreased between the examinations at 2 weeks and 2 months,” Dr Loewenstein said.

“Laser-induced retinopathy is caused by the coherent, monochromatic, unidirectional, minimally divergent laser beam,” she said. “The exposure to the light is short, about 0.25 second, as a result of the blink reflex. The light intensity is intensified by the cornea and lens by a factor of 10,000. The pathophysiology includes thermal damage primarily in the RPE, and photochemical and mechanical plasma formation damage.”

The vast majority of patients (95%) with laser-induced retinopathy experience improvement; 32% have vision better than 20/40.

In this case, SD-OCT showed defects in the ellipsoid zone, hyper-reflectivity at the retinal surface, and retinal or intraretinal hemorrhages and even neovascularisation.

**Hydroxychloroquine retinopathy**

Another case was a 29-year-old woman who had been treated for 13 years with prednisone, azathioprine (Imuran, Aspen Australia), and hydroxychloroquine for systemic lupus erythematosus.

The patient presented with the complaint of a central visual defect.

Examination showed a paracentral scotoma that developed between 2004 and 2013. This was the consequence of retinal toxicity resulting from hydroxychloroquine.

“In this case, SD-OCT showed loss of the perifoveal and macular ellipsoid zones, thinning of the outer nuclear layer, and sparing of the fovea with establishment of the ‘flying saucer’ sign,” Dr Loewenstein said.

“Hydroxychloroquine maculopathy is characterised by a bull’s eye appearance and a dense central scotoma,” she said.

The drug was discontinued but the damage was permanent.

Dr Loewenstein summarised that SD-OCT has dramatically enhanced the ability to diagnose foveal disorders even during the stage when they are not visible using other technologies.

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**DR ANAT LOEWENSTEIN**

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Dr Loewenstein is a consultant to Allergan, Alcon Laboratories, Bayer Healthcare, Notal Vision, and Novartis. Michaela Goldstein, MD, and Dafna Goldenberg, MD, from Dr Loewenstein’s department participated in the care of the patients under discussion.
As a leader in ophthalmology, Bayer HealthCare understands the importance of taking responsibility to drive science for a better life. This means addressing unmet needs through scientific progress and innovation and facilitating medical education and knowledge sharing. As such, Bayer HealthCare supports multiple projects and initiatives worldwide as well as partnering with multiple organizations to help improve the lives of people living with a visual impairment or blindness.

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JUMP-STARTING INNOVATIVE IDEAS IN OPHTHALMOLOGY

Global Ophthalmology Awards Program (GOAP) from Bayer
Tri-weekly injection of topotecan is safe and effective as monotherapy for management of refractory vitreous seeds in retinoblastoma. Such findings are according to a retrospective study conducted by ocular oncologists at the National Retinoblastoma Foundation, Centre for Sight Superspecialty Eye Hospital, Hyderabad, India.

The review included 17 eyes, all International

**IN SHORT**

- A retrospective study reviewing outcomes of 17 consecutive eyes with retinoblastoma treated for refractory vitreous seeds found intravitreal topotecan was safe and resulted in complete regression in all eyes after a mean of three injections.

**FIGURE 1** Technique of intravitreal topotecan chemotherapy.  
A. Transconjunctival pars plana intravitreal injection of topotecan at a dose of 30 μg in 0.15 ml with a 30-gauge needle.  
B. Needle withdrawal through the first ice ball of cryotherapy.  
C. Triple freeze-thaw cryotherapy at the injection site.  
D. Forceps-assisted jiggling of the eyeball following the injection for an even dispersion of topotecan.  
(Images courtesy of Dr Santosh G Honawar)
Classification for Intraocular Retinoblastoma Group C or D, with persistent or recurrent vitreous seeds after standard intravenous chemotherapy ± local therapy. Tri-weekly topotecan 30 mcg/0.15 mL was administered until there was complete regression of the seeds and was followed by an additional injection for consolidation of probable microscopic residual seeds.

Complete regression of vitreous seeds was achieved in all eyes after a mean of three injections, and 7 eyes (41%) required just two injections. No ocular/systemic complications were noted during a mean follow-up of 12 months.

“To our knowledge, we are reporting the first case series of intravitreal topotecan as monotherapy in the management of refractory vitreous seeds in retinoblastoma, and our results indicate topotecan is a potent agent providing impressive control of refractory vitreous seeds,” Dr Raksha Rao said.

“Our results . . . are comparable to those previously reported for intravitreal melphalan,” Dr Rao said. “However, the mean number of injections required was lower using topotecan than with melphalan, and according to previous reports and our own experience, intravitreal melphalan also causes few ocular side effects.”

**Treatment protocol**
The treatment protocol for retinoblastoma at the center where the study took place begins with triple drug intravenous chemotherapy or superselective intra-arterial chemotherapy. Periocular carboplatin or topotecan are administered if viable diffuse vitreous seeds are present after three cycles. Intravitreal chemotherapy is administered in eyes that have persistent or recurrent vitreous seeds after the completion of intravenous or intra-arterial chemotherapy.

“Initially, we were using melphalan for intravitreal therapy, but we switched to topotecan because of the need for multiple injections with melphalan and the
retina

development of complications, including iritis, posterior synechiae, and retinal pigment epithelial mottling,” Dr Rao said.

The treatment protocol for retinoblastoma at the center where the study took place begins with triple drug intravenous chemotherapy or superselective intra-arterial chemotherapy.

“Topotecan has known activity as a treatment for retinoblastoma when given by intra-arterial injection, periorcular injection, or with melphalan in an intravitreal injection,” she said. “The latter combined treatment was also . . . associated with minimal ocular or systemic side effects.”

Patients in the series were predominantly female (76.5%) and had a mean age of 35 months. All patients had at least 6 cycles of intravenous chemotherapy with a mean of 10 cycles.

Three eyes had persistent vitreous seeds and 14 had recurrent vitreous seeds. The vitreous seeds were diffuse in 13 eyes and focal in 4 eyes. The intravitreal topotecan was given through a tranconjunctival pars plana route using a 30-gauge needle at a site based on patient age.

A safety-enhanced technique was used wherein the needle was withdrawn through the first ice ball formation of cryotherapy, followed by two more cycles of freeze and thaw.

Then, forceps-assisted jiggling of the eye was done to disperse the drug evenly in the vitreous cavity.

One eye with a recurrent retinal tumor was enucleated at 5 months’ follow-up, and histopathology showed no tumor cells in the needle track.

“We have extended the use of intravitreal topotecan to Group E eyes for refractory vitreous seeds following intravenous and intra-arterial chemotherapy,” said Dr Santosh G Honavar, director, ophthalmic and facial plastic surgery and ocular oncology, Centre for Sight Superspeciality Eye Hospital. “To date, 36 eyes have received intravitreal topotecan monotherapy at our center, and we have achieved 100% success in vitreous seed control, and 98% eye salvage in these advanced tumors.”

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This article was adapted from Dr Rao’s presentation at the American Academy of Ophthalmology meeting. She and her co-investigators have no relevant financial interests to disclose.
The pathogenesis of diabetic macular oedema and retinal vein occlusion is associated with increased levels of vascular endothelial growth factor (VEGF), placental growth factor (PGF), and other inflammatory factors that are key targets for the treatment of retinal disease.

Aflibercept, which was specifically designed to bind VEGF and PGF with high affinity, can enable treatment interval extensions in the clinic with vision gains comparable to those seen in clinical trials. Aflibercept provides rapid and sustained vision gain in both ischaemic and non-ischaemic retinal vascular diseases and significantly reduces the severity of diabetic retinopathy.

Unravelling the role of cytokines in retinal disease

Dr Aude Ambresin from Lausanne University and the Jules Gonin Eye Hospital provided a brief description of how retinal vascular disease develops.

Impaired retinal blood flow leads to hypoxia, then the hypoxic cells release inflammatory cytokines, such as interleukin-6 (IL-6) and upregulate VEGF, PGF and VEGF receptor (VEGFR) 1. This causes activation of microglial cells, apoptosis of endothelial cells, and pericyte drop off, coupled with opening of tight junctions and neovascularisation—all of which lead to chronic inflammation and breakdown of the blood–retinal barrier.

The end results are vessel leakage, oedema, and vision loss. The pathogenesis is similar for diabetic macular oedema and retinal vein occlusion in that both involve inflammation and ischaemia leading to endothelial damage.

Dr Ambresin went on to summarise the evidence, both preclinical and clinical, for the involvement of VEGF and PGF in retinal vascular disease.

VEGF-A overexpression promotes vascular permeability and angiogenesis; PGF has also been shown to be pro-angiogenic, and promotes leukocyte infiltration and vascular inflammation. Preclinical animal models have demonstrated that VEGF and PGF contribute to the breakdown of the blood–retinal barrier in two ways: first, via the loss of pericytes from retinal capillaries and second, by increasing vascular permeability, which leads to exudation of fluid into the subretinal space and results in macular oedema.

A preclinical model of diabetic retinopathy in mice, the Akita mouse, showed that when PGF is knocked out all measures of diabetic retinopathy decrease almost to the level seen in wild-type mice.

VEGF-A and PGF synergise to activate VEGFR-1, leading to angiogenesis, neovascularisation, and inflammation.

Experimentally induced choroidal neovascularisation (CNV) in mice is associated with significantly elevated levels of VEGF-A and PGF.

The elevation of VEGF and PGF has been further examined in clinical studies: the degree of ischaemia and severity of disease correlates with levels of VEGF-A and PGF in both retinal vein occlusion and diabetic retinopathy. Levels of PGF and VEGF are significantly higher in the vitreous of patients with active diabetic retinopathy than those with quiescent disease.

VEGF-A and PGF synergise to activate VEGFR-1, leading to angiogenesis,

IN SHORT

Aflibercept, an anti-VEGF agent, can enable treatment interval extensions and provide rapid and sustained vision gain in retinal vascular diseases as well as significantly reducing the severity of diabetic retinopathy.
neovascularisation, and inflammation. This synergy has been demonstrated in several preclinical studies.

For example, whereas inhibition of VEGF-A significantly reduced the increases in vessel density in a mouse model of CNV, inhibition of PGF had no real effect. However, co-inhibition of VEGF-A and PGF reduced vessel density by significantly more than inhibition of VEGF-A alone. 1

Dr Ambresin finished by touching on galectin-1, which is a potential modulator of neovascular retinal disease. Expressed in endothelial cells, it interacts with VEGFR and its overexpression has been linked to pathological neovascularisation. Elevated levels of galectin-1 have been reported in the plasma of patients with type 2 diabetes. 1

In cultured retinal endothelial cells, galectin-1–mediated phosphorylation of VEGFR-2 was inhibited by aflibercept and this inhibition was associated with reduced cell proliferation.

The dual action of aflibercept
While currently available anti-VEGF agents inhibit the VEGF-A isoforms, aflibercept is up to 92 times more potent an inhibitor than bevacizumab or ranibizumab, with higher affinity and a faster association rate; moreover, unlike the other two inhibitors, aflibercept also binds PGF and VEGF-B. 2

Professor Thomas Langmann of the University Hospital of Cologne described the structure and mode of action of aflibercept and discussed how they affect its clinical function. Aflibercept is a fusion protein that comprises two VEGF-binding portions derived from the extracellular domains of human VEGFR-1 and -2, connected via a human IgG antibody fragment [Figure 1].

Aflibercept binds the active dimers of VEGF-A or PGF on both

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**Figure 1** The structure of aflibercept

Aflibercept binds more tightly to VEGF than the native VEGF receptors

Aflibercept was specifically designed for high-affinity binding to VEGF and PGF

Aflibercept is a fusion protein for intravitreal injection that ‘traps’ VEGF-A and PGF molecules

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Fc, fragment, crystallizable; IgG, immunoglobulin G; PGF, placent growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Comparing duration of action, ranibizumab has been reported to suppress VEGF-A levels in the aqueous humour—VEGF levels in the aqueous humour correlate well with those in the vitreous and the retina—for a mean of 36 days.1

Accordingly, bimonthly injections are not appropriate. Aflibercept, however, suppresses VEGF-A levels for a mean of 71 days,4 which means that most patients are still experiencing suppression at the end of the recommended injection interval of 8 weeks.

A small crossover study of seven patients allowed aflibercept and ranibizumab to be compared directly:2 patients who had persistent active neovascular AMD with ranibizumab were switched to aflibercept. Suppression of VEGF levels lasted twice as long with aflibercept as with ranibizumab.

These extended cytokine suppression times suggest that treatment intervals can be extended. This was tested in clinical studies, where bimonthly dosing of aflibercept delivered similar improvements in visual acuity to monthly ranibizumab, and is supported by real-life clinical data: patients had vision gains comparable to those seen in clinical trials, which were maintained using a treat-and-extend protocol with mean injection intervals of approximately 3 months. Treatment intervals can be extended with aflibercept even in patients with a poor response to other anti-VEGF agents.

The action of aflibercept on retinal disease
Professor Peter Kaiser from the Cole Eye Institute in Cleveland, Ohio, USA, explored aflibercept’s action on retinal disease.

He reiterated that VEGF is not the only cytokine elevated in retinal disease and diabetes, but so too are others including PGF, IL-6, and IL-8, and showed clinical data that backed up the mostly preclinical data Dr Ambresin had shared.

He emphasised that levels of VEGF, PGF, and other inflammatory cytokines correlate with increasing severity of disease, such that patients with high ischaemic loads have extremely high levels of both VEGF and PGF.

Clinical studies in retinal vein occlusion or diabetic macular oedema using aflibercept have demonstrated a very rapid gain in visual acuity—improvements were seen after the first injection—that persists to at least 3 years. As well as the visual acuity gains, a dramatic reduction in retinal thickness is seen after just one injection. This gain is maintained such that the majority of patients actually have normal retinal thickness at 3 years.

Professor Kaiser emphasised that rapid treatment is important for central retinal vein occlusion.

“Historically we were taught that it didn’t really matter when you treated a patient because the outcomes were rather similar,” he said. “But if we look at the phase III studies with aflibercept this doesn’t hold . . . there’s a dramatic difference if you wait more than 2 months from diagnosis to institute treatment.”

Phase III studies showed a clinically significant improvement in diabetic retinopathy severity scores with aflibercept treatment, which continued to improve with longer treatment. About one-third of patients had an improvement after 1 year, which had increased to almost half by 3 years.

Retrospective studies examined the effect of switching to aflibercept in patients with retinal vein occlusion and diabetic macular oedema who were resistant to treatment with bevacizumab or ranibizumab. Patients who are hard to treat tend to have very elevated levels of VEGF and other cytokines, which is believed to be one reason why they don’t respond. Improvements in visual acuity and central retinal thickness were noted as well as extensions in the injection intervals.

In summary, aflibercept, which is a more potent inhibitor of VEGF than its competitors, with higher affinity and a faster association rate, and which also binds PGF and VEGF-B, can enable treatment interval extensions and provide rapid and sustained vision gain in retinal vascular diseases as well as significantly reducing the severity of diabetic retinopathy.

references

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As patients are turning to the Internet for health and medical information, ophthalmologists are increasingly facing the need to separate myth from fact on a variety of disease-related issues.

Dr Yvonne Ou, assistant professor of ophthalmology, University of California-San Francisco, USA, reviewed evidence regarding the effects of various lifestyle practices on glaucoma and IOP.

**Exercise**

Results from a number of studies indicate that aerobic exercise is associated with IOP lowering, and according to the findings of a meta-analysis ([Clin J Sport Med. 2014;24:364-372](https://www.ncbi.nlm.nih.gov/pubmed/24929026)), the change is greater among sedentary individuals than those who were already active and independent of exercise duration or intensity.

“Based on this evidence, I encourage my patients to get moving, especially if they are not already,” Dr Ou said. “For those who feel they cannot incorporate exercise into their lifestyle, I tell them that any kind of movement, even walking, may be beneficial. However, I also tell them they have to maintain their regimen because there is evidence showing as well that the effect of exercise on IOP does not persist when deconditioning occurs.”

Dr Ou added that advising patients to find an exercise partner is helpful as it can be a motivator for starting and adhering to an exercise program. In addition, it can enable patients with impediments to exercising, such as reduced visual acuity or visual field defects, to be more active.

Another common exercise-related concern pertains to the effect of head-down yoga poses on IOP. While it is already known that shoulder stands or headstands increase IOP, a recent study evaluating the effects of four common yoga positions on IOP was recently published ([PLoS ONE. 201;10(10):e0144505](https://www.ncbi.nlm.nih.gov/pubmed/29843452)).

Dr Ou noted that changes in IOP were the same among subjects with and without glaucoma, and among the positions evaluated, downward dog (Adho Mukha Svanasana) was associated with the greatest increase in IOP.

However, the study also found the effect on IOP is transient, and there are no data showing

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**IN SHORT**

- Regular exercise and consumption of green leafy vegetables may positively affect glaucoma progression. Effects of acupuncture and inverted yoga poses are also discussed.
that the yoga position-induced IOP changes are a factor for glaucoma progression.

Given this information, she acknowledged that it is difficult to advise patients. Until more data are available, the best thing is to consider any potential risk in the context of the individual’s stage of glaucoma and commitment to yoga.

“I have a patient with glaucoma who is a yoga instructor,” she said. “It is hard to tell someone whose livelihood depends on yoga to avoid head-down positions.”

**Diet**

Based on the results of several studies, Dr Ou encourages patients to eat a healthy diet that includes a variety of fruits and vegetables, especially green leafy vegetables. This advice comes from studies showing that consumption of a diet rich in green leafy vegetables, or with a higher dietary nitrate intake (for which green leafy vegetables are an excellent source), seemed to protect against glaucoma.

There is a biologic basis for the association considering that in one study, the reduced risk of glaucoma with increased dietary nitrate intake was greatest for glaucoma with early paracentral visual field loss at diagnosis, which has been associated with vascular dysregulation [JAMA Ophthalmol. 20015;134:294-303].

“We still need prospective studies to determine how eating green leafy vegetables affects glaucoma progression,” Dr Ou explained. “In the meantime, there is no harm to increasing intake of green leafy vegetables—although patients on blood thinners, such as warfarin, need to be aware that green leafy vegetables are high in vitamin K and should discuss any increase in their intake with their doctor so that medication dosages can be adjusted.”

**Acupuncture**

Patients interested in alternative therapies may ask about acupuncture for managing their glaucoma. Based on available evidence, the simple answer seems to be that it is unlikely to be beneficial.

Dr Ou noted that a recently published, well-designed prospective, randomised, masked, crossover study found that overall, diurnal IOP was unchanged in patients who underwent a series of 12 acupuncture sessions involving needle placement at eye- and non-eye-related acupoints [Am J Ophthalmol. 2015;160:255-265].

“This was a small study, and more data are needed,” she said. “At this time, however, we can’t say that acupuncture will help glaucoma patients.”

**Proactive practitioner**

In the interest of identifying low-ocular perfusion pressure as an underlying issue for glaucoma progression despite good IOP control, Dr Ou advised ophthalmologists to ask their patients about treatment for systemic hypertension.

Recently published results of the randomised SPRINT study [N Engl J Med. 2015;373:2103-2116] showed that in a population of patients with increased cardiovascular risk, intensive treatment targeting a systolic blood pressure (SBP) <120 mm Hg, significantly reduced cardiovascular events and cardiovascular event-related morbidity compared with standard treatment targeting SBP <140 mm Hg.

Although there was no difference between the two treatment arms in the incidence of serious adverse events, patients who had more intensive SBP lowering were more likely to report hypotension and syncope, Dr Ou said.

“These safety findings, which are not unexpected, are very relevant to patients with glaucoma because blood pressure drives optic nerve blood flow,” Dr Ou added.

“We know from epidemiologic studies that lower ocular perfusion pressure (mean, systolic and diastolic) is associated with worse glaucoma prognosis.

“So when glaucoma is progressing despite good IOP control, ask patients to keep a blood pressure log so that you can identify diurnal fluctuation,” she said. “Then, communicate with the internist if you have any concern and think the patient’s glaucoma might benefit from less aggressive blood pressure control.”

Dr Ou added that while exercise also lowers blood pressure, ophthalmologists are not doing their patients harm by encouraging them to be physically active, considering data from the EPIC-NORFOLK eye study showing that active people had a lower risk of having low-ocular perfusion pressure compared with non-active individuals [Invest Ophthalmol Vis Sci. 2011;52:8186-8192].

The analysis also showed the difference between groups was mediated by diastolic blood pressure rather than IOP.
Exploring Bowman layer graft in eyes with keratoconus

Surgical transplantation showing potential to reduce, stabilise corneal ectasia

By Laird Harrison;
Reviewed by Dr Jack Parker

Isolated Bowman layer transplantation can reduce and stabilise corneal ectasia in eyes with progressive advanced keratoconus, according to researchers.

The technique “flattens the cornea into a more normal position,” said Dr Jack Parker, a researcher at the Netherlands Institute for Innovative Ocular Surgery (NIIOS), Rotterdam, The Netherlands. “It doesn’t give [these patients] perfect vision, but it keeps them from getting worse. It lets them continue wearing their contact lenses.”

In a published study, the procedure produced an average flattening of about 8 D in 20 eyes, and stabilisation after that (van Dijk K, Liarakos VS, Parker J, et al. Bowman layer transplantation to reduce and stabilise progressive, advanced keratoconus. Ophthalmology. 2015;122:909–917). There were two complications.

In keratoconus, the cornea gradually bulges outward in the shape of a cone, distorting patients’ vision. Glasses and contact lenses can correct mild cases, and hard contact lenses as well as implantation of intracorneal ring segments can help in moderate cases.

However, in severe cases, the distortion of the cornea may progress to the point that contact lenses become too uncomfortable to wear.

“The problem with patients who have keratoconus is that the cornea is changing shape,” Dr Parker said. “A lot of times you can help them with contact lenses, but if the cornea is getting worse they’ll outgrow their lenses.”

At that point, penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK) may restore some vision. These procedures, however, can come with the risk for infection and other complications; may not halt the progress of the disease; and can make the cornea vulnerable to injury, Dr Parker noted.

More recently, surgeons have used ultraviolet A radiation to induce collagen crosslinking in patients with mild-to-moderate keratoconus. This procedure can halt the progression of the disease, but patients with advanced keratoconus are not eligible for the treatment, Dr Parker said.

Bowman layer grafts
Dr Parker and colleagues are proposing Bowman layer grafts as an alternative. The Bowman layer—a smooth, acellular, nonregenerating membrane composed of collagen fibrils—lies between the superficial epithelium and the stroma in the cornea.
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Because it has no cells, the layer does not provoke a graft rejection when transplanted, Dr Parker said.

At baseline, their eyes had a $K_{\text{max}}$ of more than 67.5 D and a best spectacle-corrected visual acuity (BSCVA) of worse than 20/60.

‘The problem with patients who have keratoconus is that the cornea is changing shape.’

— Dr Jack Parker

Co-author, Dr Gerrit RJ Melles, MD, PhD, an ophthalmologist at the NIIOS in Rotterdam, came up with the idea of transplanting it into eyes with keratoconus, according to Dr Parker.

**About the study**

For the current study, the researchers operated on 22 eyes in 19 patients with progressive, advanced keratoconus. Ten of the patients were male and nine were female, ranging in ages from 17 to 72 years, with keratoconus stages III to IV.

All the eyes had documented evidence of keratoconus progression, defined as ≥1 D change in simulated keratometry (SimK) values, ≥2 D change in $K_{\text{max}}$, or both, and a history of subjective decline in visual acuity.

The surgeons removed the Bowman layers from donor corneas and created mid-stromal pockets up to the limbus over 360° under air using manual dissection. This procedure was similar to the procedure used to create a lamellar dissection plane in DALK, except that the dissection went to the mid-stroma.

The surgeons inserted the donor Bowman layer into the stromal pocket, then unfolded and centred it using a cannula and balanced salt solutions to manipulate the tissue.

The procedure is less invasive than PK or DALK “because you are doing no cutting or sewing,” Dr Parker said.

Although it is technically feasible to place a donor Bowman layer in its true, anatomic position in a keratoconic cornea, it cannot be fixated with currently available sutures or glues—making it difficult to obtain sufficient traction force across the cornea to flatten the central cone.

As the corneas healed, the donor Bowman layers attached to the patients’ corneas, and the incisions closed without sutures.

“We’re not really sure why it works,” Dr Parker said. “It seems
to provoke a healing response in the cornea.”

Out of the 22 transplantations, 2 resulted in complications. In both of these, the Descemet membrane was perforated during manual dissection. Both patients declined PK, preferring to wait for corneal clearance after re-endothelialisation for the perforation.

The main value of the procedure may be that it preserved an acceptable contact lens corrected vision while stabilizing the cornea.

After initial clearance, 1 eye showed progressive corneal decompensation for which PK has been scheduled. The cornea of the other eye cleared slowly and BSCVA improved during the first postoperative 6 months. The researchers excluded the 2 eyes from postoperative evaluation.

**Flattening effect**

Of the remaining 20 eyes, a mean follow-up of 20 months (range 12 to 36 months) showed a flattening effect in 18 eyes.

On average, maximum keratometry ($K_{max}$) decreased from 77.2 D to 69.2 D a month after the surgery. Anterior SimK decreased then also stabilised. In 2 eyes, the corneal curvature continued steepening for reasons that were not clear.

One eye had low visual potential because of a cataract, and another had preoperative visual acuity measured only with a contact lens.

In the remaining 18 eyes, BSCVA changed from 1.27 logarithm of the minimum angle of resolution (LOGMAR) before surgery to 0.90 LOGMAR 12 months after the transplantation, a statistically significant different ($p < 0.001$). After that, no change in BSCVA was observed.

Average best contact lens-corrected visual acuity (BCLVA) showed no change from before surgery to any time point after.

The transplantation caused the most flattening in corneas with a relatively steep $K_{max}$, combined with a flatter SimK and a small corneal apex-to-$K_{max}$ distance. This means the procedure worked best in the most advanced cases with the most central cones, researchers said.

Because the procedure resulted in stabilisation, it might be useful in managing keratoconus cases ineligible for ultraviolet cross-linking, Dr Parker said.

The main value of the procedure may be that it preserved an acceptable contact lens corrected vision while stabilising the cornea, he said.

Researchers have continued to transplant Bowman layers into patients with advanced keratoconus, Dr Parker noted, and now have follow-up data on 65 or more cases.

**DR JACK PARKER**

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This article was adapted from Dr Parker’s presentation of the Howard Lieberman Memorial Paper at the 2016 meeting of the American Society of Cataract and Refractive Surgery. Dr Parker has no financial interest relevant to the subject matter.

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Thriee-dimensional (3-D) printing can produce models of facial skeletons and guides to help orbital surgeons plan repair of complicated fractures, according to Dr Paul Langer.

“In the cases where we have used it, the alignments have been excellent,” said Dr Langer, professor of ophthalmology, Rutgers New Jersey Medical School, Newark, USA. “In our experience it’s been very, very helpful.”

Dr Langer and a resident, Dr Leon Rafailov, described their experience with the new technology.

“Typically, the fracture cases where we’ve used this technology are those with severe comminution or with fragments missing,” Dr Langer said. “That’s when the technology is most useful because we can anticipate what we’ll find at the time of the surgery.”

In simple trauma cases where there are only one or two fractures, 3-D printing is not necessary, he said.

Dr Langer’s institution does not own its own 3-D printer; it contracts with private companies that print the guides.

How it works
The process begins with computed tomography (CT) of the injury. The CT must have slices of 1.25 mm or thinner, Dr Langer said.

“Five-mm cuts will not be able to transmit enough information,” he said.

The surgeon then must send the CT scan by compact disc using overnight delivery to the 3-D printing company, which downloads it to make the virtual model. The surgeon then meets in a web-based conference with engineers from one of the companies. Together the surgeon and the engineer manipulate the images of the bone fragments to plan the surgery.

“It helps us to know ahead of time by moving the pieces virtually what will be missing or how the bones will fit together,” he said.

Moving actual bone fragments during surgery is difficult because they are connected to muscles and arteries.

Typically, the engineer will call back the next day with images of guides for approval. Dr Langer sometimes asks for more adjustments, such as space for more screws. When Dr Langer has approved the guides, the company prints them out in polyamide.

The 3-D printing company sends the guides to its representative, who delivers them to the hospital. Intraoperatively, Dr Langer lays the guides over the fracture to align the segments and screws the guide in place to temporarily hold the fracture segments in place. Then he screws a metal plate over the fracture and removes the guide.

The technology has also been used in surgery to aid in facial reconstruction after tumor removal.

“Otherwise, while you’re putting screws and plates on the bone fragments, you may move them and not get the contour or curvature you want,” Dr Langer said.

The 3-D printers can also produce acrylic facial skeletons, which are sterilised and used intraoperatively to guide fracture reduction, for example, by helping shape a metal plate.

“I can shape an implant exactly to the contour I want, then pull it off the printed skull and put it in the patient,” Dr Langer said.

Case example
In one case, Dr Langer operated on a 19-year-old
man with multiple periorbital fractures and significant comminution and misalignment of bones following a gunshot to the right face. After virtually manipulating the CT images on a computer, Dr Langer discovered there was a large bone fragment missing. He then worked with an engineer to design guides to realign the larger fracture segments.

The printing company then produced a model of the reconstructed facial skeleton showing the bone fragments realigned in their optimal locations. It also produced guides for the procedure.

Dr Langer corrected the defect in the right inferior orbital rim with a porous polyethylene implant. Postoperative CT showed excellent symmetry and alignment.

The technology has also been used in surgery to aid in facial reconstruction after tumor removal.

Currently, several companies are competing to provide this technology.

One drawback to this approach is the time required to send the CT scans by mail to the company, planning by web conference, and then shipping the 3-D models back to the hospital, Dr Langer said.

“If I see a patient today, I can’t operate tomorrow,” he said. “It’s usually 4 to 5 days.”

As the technology becomes more widely available, more hospitals may buy their own 3-D
plastics

Dr. Langer has also used 3-D printing to create implants.

For example, he recently operated on a woman who had been in a car accident years earlier. The original surgery to reassemble fragments of her skull left a divot in her forehead.

“So,” he said, “we created an implant that would smooth out that defect into an arc rather than a divot.”

DR PAUL LANGER
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This article was adapted from Dr. Langer’s presentation at the 2015 meeting of the American Academy of Ophthalmology. He did not indicate any proprietary interest in the subject matter.
Haag-Streit fundus device enhances clinical workflow

Haag-Streit UK (HS-UK) has announced the launch of the new Fundus Module 300 (FM 300) imaging device. The FM 300 allows the integration of non-mydriatic retinal imaging into a regular slit lamp examination, enhancing clinical workflow. The instrument can be quickly mounted on the slit lamp, ready to capture an image.

The compact fundus imaging solution provides high-quality retinal images that can rival those of a fundus camera, making it very cost-efficient, according to the company. Images can be transferred to the EyeSuite software, allowing easy documentation and increasing the quality and accuracy of referrals.

Sam Laidlaw, HS-UK Product Manager, said, “The FM 300 is an exciting addition to the HS-UK portfolio. It allows users of all Haag-Streit slit lamps to access simple and instant documentation of the retina, enhancing and extending the functionality of the slit lamp.”

For more information, go to www.haag-streit.com/haag-streit-uk

Allergan receives FDA clearance for gel stent, a surgical treatment for refractory glaucoma

Allergan plc announced the FDA has cleared the XEN Glaucoma Treatment System (consisting of the XEN45 Gel Stent and the XEN Injector) for use in the United States. The XEN Glaucoma Treatment System reduces IOP in patients and is indicated for the management of refractory glucomas, where previous surgical treatment has failed or in patients with primary open-angle glaucoma, and pseudoxfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy. XEN is implanted through an ab interno approach and reduces IOP by creating a new drainage channel with a permanent implant that becomes flexible. This provides a new treatment option for millions of Americans with refractory glaucoma.

“Allergan has a deep, long-term commitment to developing treatments for patients with glaucoma, a sight-threatening disease that affects millions in the United States and worldwide. We are thrilled to receive FDA clearance for the XEN Glaucoma Treatment System, which will provide a new treatment option for patients struggling to bring down their intraocular pressure,” said David Nicholson, Chief R&D Officer at Allergan.

In the U.S. pivotal trial conducted in refractory glaucoma patients, XEN reduced IOP from a mean medicated baseline of 25.1 (+ 3.7) mm Hg to 15.9 (+ 5.2) mm Hg at the 12 month visit (n = 52). The mean baseline number of IOP-lowering medications was 3.5 (+ 1.0) versus an average use of 1.7 (+ 1.5) medications at 12 months. XEN also allows for keeping post-operative options open, allowing physicians to utilize other IOP-reduction techniques in the event that they are still needed after surgery.

“XEN is a new option that provides an opportunity for surgical intervention in refractory glaucoma patients. XEN can effectively lower IOP, in fact, studies have shown that at 12 months using XEN, patients used, on average, less IOP lowering drops than they did before XEN was implanted,” said Dr Robert N Weinreb, chairman and distinguished professor of ophthalmology at the University of California, San Diego, USA.

Allergan plans to launch the XEN Glaucoma Treatment System in the United States in early 2017, according to a prepared statement. More than 10,500 XEN Gel Stents have already been distributed worldwide. XEN is CE marked in the European Union, where it is indicated for the reduction of IOP in patients with primary open-angle glaucoma where previous medical treatments have failed. It is also licensed for use in Canada, Switzerland, and Turkey.

For more information, go to www.Allergan.com
Avellino Labs to introduce keratoconus screening test; expected to predict elevated risk in Asian populations

Avellino Labs announced it will launch a keratoconus screening test in Korea, Japan, and China in the first quarter of 2017.

In a recent study, Avellino Labs used next-generation sequencing (NGS) to examine DNA collected from more than 200 keratoconus patients from different clinics and institutions from around the world, according to the company.

The company said it was able to identify four DNA variants within three different genes that conferred genetic risk factors in 9% to 21% of patients within the study group from Korea. These percentages imply a statistically significant increased risk for keratoconus. Avellino Labs intends to launch a test to screen for these four mutations for use in Korea, Japan, and China in the first quarter of 2017, according to a prepared statement.

Dr John Marshall, PhD, FRCPath, FMedSci, concurrently medical advisory board member at Avellino Labs and Frost Professor of Ophthalmology at UCL Institute of Ophthalmology and Moorfields Eye Hospital, commented, “At Avellino Labs we are excited to be able to offer the first genetic predictor of relative risk of keratoconus in Asian eyes, which often hits in the prime of life and progressively impairs vision over time. Most importantly, the Avellino DNA Test represents a sea change detecting keratoconus early in order to inform surgeons performing laser vision correction and to improve keratoconus patient care.”

For more information, go to www.avellinolabs.com

Oculus next-generation trial frame available

Lighter, trendier, simpler, more comfortable – this describes the new Universal Trial Frame from OCULUS, according to the company. For the new generation of the OCULUS Trial Frame, many suggestions from users were taken into consideration in order to create an even more comfortable method of subjective refraction for customers and eye care professionals, said the company.

New in an OCULUS Trial Frame are the 12 total slots for trial lenses: 6 for each side of the frame, 4 in front and 2 behind. This makes fine adjustment, with sph +/- 0.12 D or refraction with circular/linear polarizing filters, easier to carry out.

The new design with its optimized material mix is, like the rest of the UB 6, 100 % “Made by OCULUS.” All 166 individual parts of the new Trial Frame are crafted by hand with attention to detail, for guaranteed quality, according to the company.

Unique to this design: the gradation of the axis scales at 2.5° intervals. These are easy to read even in dark rooms. The operating elements have a new design and appear in a trendy, grey colour tone. The nose bridge can be adjusted in height and angle, and the nose piece is anatomically formed for better distribution of pressure.

The thumb wheel for adjustment of the earpieces has also been modified and can now be gripped more firmly. The earpieces have been changed substantially: the new flexible double earpieces adapt perfectly to every ear shape.

The optically available polarizing filters can be easily clipped on. There are two versions, linear and circular. Both offer an expanded viewing area for distance and near vision.

All OCULUS trial and special lenses in standard size 38 mm diameter are compatible with the new UB 6.

For further information, go to www.oculus.de
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For additional information or to schedule a demonstration, contact your Alcon representative.

*Post hoc analysis of postoperative UCVA compared to preoperative BSCVA of 230 eyes contained in the FDA T-CAT pivotal trial at 12 months. The primary end point evaluated changes in BSCVA.
1. Results from FDA T-CAT-001 clinical study for Topography-Guided vision correction (with the 400 Hz ALLEGRO WAVE® Eye-Q Excimer Laser).