DIABETIC RETINOPATHY IN PAEDIATRICS

Management and treatment considerations

CATARACT & REFRACTIVE
Can Nd:YAG laser capsulotomies damage IOLs?

RETINA
The increasing potential of ERG in diagnostics

GLAUCOMA
Addressing leaking blebs post-trabeculectomy

CORNEA
The vicious cycle theory in dry eye disease

GENE THERAPY
Exploring cytokines as biomarkers for DMO
Effective DME treatment doesn’t have to be a burden.

OZURDEX® (dexamethasone intravitreal implant) 0.7mg

OZURDEX® (Dexamethasone 700 micrograms intravitreal implant in applicator)

Abbreviated Prescribing Information

Presentation: Single-use intravitreal implant in applicator. One implant contains 700 micrograms of dexamethasone. Disposable injection device, containing a rod-shaped implant which is not visible. The implant is approximately 0.46 mm in diameter and 6.0 mm in length.

Indications: Treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO), inflammation of the posterior segment of the eye presenting as non-infectious uveitis and visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy.

Dosage and Administration: Please refer to the Summary of Product Characteristics before prescribing for full information. OZURDEX must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose is one OZURDEX implant to be administered intravitreally to the affected eye. Administration to both eyes consecutively is not recommended. Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician’s opinion may benefit from retreatment without being exposed to significant risk. Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by treatment, should be retreated. Patients who experience a deterioration in vision, which is not slowed by treatment, should be retreated. Patients who experience a deterioration in vision, which is not slowed by treatment, should be retreated.

Contra-indications: OZURDEX should not be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored to allow for proper diagnosis and management of device migration. Use of corticosteroids, including OZURDEX, may induce cataracts (including posterior subcapsular cataracts), increased IOP, steroid induced glaucoma and may result in increased IOP levels. Cataracts should be used with caution in patients with a history of topical corticosteroid use.

Warnings/Precautions: Intravitreal injections, including OZURDEX can be accompanied with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aortic injection technique must always be used. Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Monitoring may consist of a check by ocular tonometry, immediately after the injection, tonometry within 10 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay. All patients with posterior capsular tear, such as those with a posterior lens (e.g. due to cataract surgery), and those who have an opening into the vitreous cavity (e.g. due to iridectomy) with or without a history of vitrectomy, are at risk of implant migration into the anterior chamber. Implant migration to the anterior chamber may lead to corneal oedema. Persistent severe corneal oedema could progress to the need for corneal transplantation. Other than those patients contraindicated where OZURDEX should not be used, OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored to allow for proper diagnosis and management of device migration. Use of corticosteroids, including OZURDEX, may induce cataracts (including posterior subcapsular cataracts), increased IOP, steroid induced glaucoma and may result in increased IOP levels. Cataracts should be used with caution in patients with a history of topical corticosteroid use.

Interactions: No interaction studies have been performed. Interactions are possible when intraocular injections are used in patients with a history of systemic corticosteroid use (e.g. due to autoimmune disorders). Intraocular injections may be used in patients with a history of systemic corticosteroid use who are also being treated with corticosteroids. Interactions: No interaction studies have been performed. Interactions are possible when intraocular injections are used in patients with a history of systemic corticosteroid use (e.g. due to autoimmune disorders). Intraocular injections may be used in patients with a history of systemic corticosteroid use who are also being treated with corticosteroids.

The most commonly reported adverse events reported following treatment with OZURDEX® are those frequently observed with ophthalmic steroid treatment or intravitreal injections (elevated IOP, cataract formation and conjunctival or vitreal haemorrhage respectively). Less frequently reported, but more serious, adverse reactions include endophthalmitis, necrotising retinitis, retinal detachment and retinal tear.

Effective DME treatment doesn’t have to be a burden.

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

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Welcome to 2021 and the promise that a new year holds. Think back to 12 months ago and how the world was in the early stages of the coronavirus disease 2019 (COVID-19) pandemic. Now, consider how in the span of 9 months, we are seeing the first of several vaccines begin to be approved for emergency use in the UK and the US. The next step of the process—distribution of the vaccine—will be as challenging as the development phase, if not more so. But there is no doubt, science and technology will rise to the occasion.

As for the future of eye care, this issue of Ophthalmology Times Europe® touches upon advances in paediatric ophthalmology. As we learn from Dr Richard W. Hertle, it takes a village to beat visual system diseases in paediatric patients. Community involvement and research continue to boost treatment in children. In our cover story, Prof. Winfried Amoaku speaks to the risks and management of diabetic retinopathy in paediatric patients. Diabetes mellitus can lead to significant eye morbidities with long-lasting effects, including diabetic retinopathy.

In cataract and refractive surgery, Dr Dan Z. Reinstein discusses how non-linear aspheric corneal ablation can be used to treat presbyopia. The approach yields high patient satisfaction in emmetropic, myopic and hyperopic eyes. Dr Andreas F. Borkenstein and Dr Eva-Maria Borkenstein weigh in on Nd:YAG laser capsulotomy in intraocular lenses. Is it safe or dangerous? Poorly focused YAG shots lead irrevocably to a permanent defect in the IOL material and thus to possible effects on the quality of vision with straylight or glare, they note. In a recent study, the differing amounts of damage that Nd:YAG causes in a range of hydrophilic and hydrophobic acrylic lens materials was assessed.

Turning to retina, we learn more about the increasing potential of electroretinopathy (ERG) in diagnosing a wide range of eye conditions. Dr Ruth Hamilton provides an update on the progress that has been made with ERG and its future potential. In addition, Dr Netan Choudhry highlights the treatment of persistent vitreous opacities with a YAG vitreolysis method. A study found that YAG laser vitreolysis was less invasive than pars plana vitrectomy.

In glaucoma, Prof. Neeru Gupta addresses the challenge of late-onset bleb leaks. Minimally invasive conjunctival surgery option is an efficient procedure in patients.

Shifting our focus to cornea, ophthalmologists have seen several new therapeutics for the treatment of dry eye disease in recent years. Dr Cynthia Matossian highlights how a novel chondroitin formulation contributes to cyclosporine efficacy. A multicentre study showed improvements in symptoms after 3 months of treatment. In addition, Editor Caroline Richards conducts an interview with Prof. Christophe Baudouin, who explains how dry eye disease can become a vicious cycle. There is a complex interplay between a series of self-stimulating biological events, he notes.

In gene therapy, Dr Andric C. Perez-Ortiz provides an update on how investigators explore pathogenic cytokines as biomarkers for diabetic macular oedema (DMO). Results of a study analysing cytokine levels in the aqueous humour and serum of patients with non-proliferative diabetic retinopathy with and without DMO support further research investigating transforming growth factor-β-induced Gene Human Clone 30 (BIGH3) as a potential biomarker for DMO.

Lastly, with the global impact of DMO and diabetic retinopathy, four international specialists gather virtually to discuss current challenges, ranging from diabetic eye examinations, collaborations among eye health physicians, COVID-19 and available and upcoming treatments.

Along with the breakthroughs we are witnessing in COVID-19 vaccines, the innovations that ophthalmologists are realising are medical marvels in their own right. The future is looking bright!
New standards have emerged for treating visual diseases in paediatric populations during the previous two decades, thanks to community involvement and external funding of research, according to Dr Richard W. Hertle, who described the progress achieved in various diseases as a result of these factors. Such progress is likely to continue in the future and spark continuing improvements in the treatment of a range of disorders.

Dr Hertle is chief of paediatric ophthalmology and director of the Vision Center at Akron Children’s Hospital in Akron, Ohio, United States. He is also director of the hospital’s paediatric ophthalmology fellowship programme, the Dr Robert “Boomer” and Jill Burstine Chair in paediatric Ophthalmology, and a professor of surgery at Northeast Ohio Medical University in Rootstown, Ohio.

Retinopathy of prematurity
Numerous studies of retinopathy of prematurity (ROP) have evaluated interventions such as cryotherapy, supplemental oxygen, light reduction and early laser treatment, which reduced blindness caused by abnormal development of blood vessels in thousands of infants annually to about 500.

A more recent treatment is injection of intraocular bevacizumab (Avastin, Genentech), which, when compared with laser therapy, has been found by physicians to be equally efficacious, with the same long-term benefits and fewer adverse effects, Dr Hertle said.\(^2\)

Major findings in retinopathy of prematurity studies included the following:

1. Cryotherapy decreased blindness by 50% in infancy and 17% by age 10 according to the study ‘Cryotherapy for Retinopathy of Prematurity’;\(^1\)

2. Supplemental oxygen therapy did not stop progression of ROP (as seen in ‘Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity Study’) and nor did reduction of ambient light (‘Light Reduction in Retinopathy of Prematurity Study’);\(^1\)

3. Early laser application reduced blindness by another 5% (‘Early Treatment for Retinopathy of Prematurity [ETROP] Study’); and\(^1\)

4. Artificial intelligence and use of telemedicine approaches for evaluating acute ROP decrease blindness worldwide.\(^1\)

In short

Community support is the most important factor in ascertaining effective treatments for paediatric eye diseases.

Strabismus/amblyopia
The Pediatric Eye Disease Investigator Group in the US, a collaborative that conducts multicentre clinical research in strabismus, amblyopia and other diseases treated by paediatric ophthalmologists, functions internationally with hundreds of physicians. These trials, funded by more than $65 million raised since inception of the group in 1997, have developed new treatment protocols for strabismus, amblyopia, nasolacrimal duct obstruction, myopia, hyperopia and uveitis.\(^3\)

Dr Hertle further recounted major findings of this group that were not the standard of care before the clinical trials, including the following:

1. Patching for 2 hours is as effective as patching for 6 or 8 hours in patients with moderate amblyopia;

2. Patching over 6 hours works as well as full-time patching in patients with dense amblyopia;

3. Atropine use can be as effective as patching; and

4. Spectacle use alone can treat amblyopia without patching or drops in strabismic amblyopia.\(^3\)

Community involvement is the most important factor to beat childhood visual system disorders.
“The changes in the current standards of practice in common eye diseases are the result of these large clinical trials,” Dr Hertle explained. “We are moving from anecdotes to the ability to practice rigorous ways to treat amblyopia and strabismus.”

**Congenital cataract**

The Infant Aphakia Treatment Study evaluated the use of an IOL compared with a contact lens during the first 6 months of life to treat unilateral congenital cataract. The results showed equal vision with both.

**Convergence insufficiency**

Children aged between 9 and younger than 18 years diagnosed with this disorder, which is present in 5–7% of children, were treated in a multicentre, randomised clinical trial to determine the effectiveness of four therapies: office-based vergence/accommodative therapy plus home reinforcement; home-based pencil push-ups; home-based computer vergence/accommodative therapy and pencil push-ups; and office-based placebo therapy.

“The results showed that doing therapy in the office with home reinforcement was better than any other type of therapy, including pencil push-ups,” Dr Hertle said. A separate convergence trial that included 221 patients showed that convergence therapy to treat attention and reading was ineffective for attention and reading and only helped convergence.

**Community support**

When considering all the studies performed in thousands of patients with a variety of visual diseases, the community support was the most consequential factor. “By allowing the family and their children to participate in these trials and the grants, gifts, endowments and time, we were able to progress in paediatric eye care,” Dr Hertle said.

**REFERENCES**

Risks and management of diabetic retinopathy in paediatric patients

Insulin pumps, digital technology and outcome analyses are useful tools

By Prof. Winfried Amoaku

Diabetes mellitus (DM) is a metabolic disease of high glucose levels or poor glucose utilisation that leads to significant morbidity, particularly kidney, eye, heart and cerebrovascular disease, and premature mortality. Type 1 diabetes is one of the most common chronic diseases in children and represents a global public health challenge; the prevalence of type 2 diabetes ranges from 1 to 51 per 1,000. Although children and adolescents with type 1 diabetes are threatened daily with acute complications of hypoglycaemia and ketoacidosis, it is the long-term microvascular and macrovascular complications of the disease that place them at the greatest risk of serious morbidity and early mortality.

Diabetic eye disease in the young
DM can affect any ocular tissue, although the retinal microvascular changes of diabetic retinopathy (DR) are thought to be the most important long-term complication. DR, which can occur in all types of DM, can have a debilitating effect on visual acuity and ultimately lead to blindness in some cases.

The risk for and time to develop DR is variable, but it may already be present at the time of DM diagnosis. A Danish prospective cohort study that followed children and adolescents with type 1 diabetes for 8 years reported the prevalence of any level of DR as 17.7% in children aged 12–15 years and 45.4% in the 16–20 years age group, increasing to 67.6% after 20 years. A multicentre study based in north-west England reported a DR prevalence of 11% in children with T1 DM. Of these, 44% had background DR whilst 56% had pre-proliferative DR, with early age at diagnosis and poor metabolic control as independent risk factors.

Shibeshi et al. reported a DR prevalence in children in Ethiopia of 4.7% including two individuals who had maculopathy associated with vision loss. A recent study from the United States in young people reported an incidence of DR in 20.1% and 7.2% over a median period of 3.2 years in type 1 diabetes and 3.1 years in type 2 DM. DR risk depends on age at DM onset or diagnosis, duration of disease and glycaemic control. A population-based study from Australia reported that 24% of children and adolescents with type 1 diabetes developed DR after 6 years of DM; a similar study in Sweden reported a DR incidence of 27% after 13 years of DM. Prepubertal DM duration is strongly associated with the development of DR.

Management
GENERAL
The general management of DM in young patients has improved recently, supported by advancing technology. The development of insulin pumps, digital technology and outcome analyses have led to significant improvements in glycaemic control.

Control of blood pressure and serum lipids is also necessary. Close working with diabetologists as well as renal paediatricians is important in achieving the best outcomes.

SCREENING
The current UK guidance is for annual screening from 12 years and above, based on the low prevalence of DR in younger children. A close check should be kept on patients aged younger than 12 years by the diabetologist and appropriate teams.

IN SHORT
- Diabetes mellitus, which is a common chronic disease in children, can lead to significant eye morbidities with long-lasting effects, including diabetic retinopathy. Treatment should be tailored to the individual patient.
The current UK guidance is for annual screening from 12 years and above.

referrals to the Eye Clinic effected as necessary.

The American Academy of Ophthalmology recommends that annual eye examinations in children should start 3–5 years after the diagnosis of type 1 DM. The International Diabetes Federation/International Society for Pediatric and Adolescent Diabetes guideline from 2017 recommends that eye examinations for children with type 1 DM commence at 11 years of age and after 2 years of DM duration; in children with type 2 DM, screening should commence from diagnosis. In populations where DR onset is earlier or more common in children, screening programmes should be appropriately directed at the vulnerable population. Evaluation for other eye changes may be initiated by paediatric diabetes teams as appropriate.

Colour fundus photographs have traditionally been used to document DR. Optical coherence tomography (OCT) and OCT angiography (OCTA) are non-invasive state-of-the-art imaging techniques that are very useful in evaluating the status of the macula and specifically in quantifying diabetic macular oedema (DMO). Recently, the advent of spectral domain OCT has allowed diabetic neurodegeneration to be identified, which is thought to precede clinical DR detection.

TREATMENT
Unfortunately, the literature on treatment of DR in the young is limited because clinical trials for DR treatments recruit participants aged 18 years or older. The standard treatment for focal DMO located more than 500 microns from the foveal avascular zone edge is focal laser photocoagulation, as per the ETDRS protocol. However, laser photocoagulation should be avoided in diffuse oedema.

Where the DMO is diffuse, or patient cooperation unlikely, pharmacotherapy is more appropriate. Vascular endothelial growth factor (VEGF) blockage through intravitreal injections of
anti-VEGF agents is now well established as a treatment for DMO in adults, but its safety and efficacy has not been established in children and adolescents. Some limited data on the use of ranibizumab (Lucentis, Genentech/Roche) for the treatment of choroidal neovascularisation in patients between the ages of 12 and 17 years showed that it was well tolerated.

Similarly, no data exist for use of intravitreal steroids in DMO in the young, although non-randomised study data exist for dexamethasone in non-infectious uveitis in a similar age group. As intravitreal steroids are cataractogenic, their use in young diabetic patients is best avoided. However, it may be reasonable in older children if the DMO is unresponsive to other therapies, or if a young diabetic patient has undergone cataract surgery.

It has been suggested that blockade of the renin–angiotensin system with angiotensin-converting enzyme (ACE) inhibitors even in the absence of hypertension may slow progression of DR, although this was not supported in a study of adolescent diabetics. In summary, as there are limited trial data to guide treatment decisions in young patients, treatments for DR in this patient group should be individually tailored.

REFERENCES


In this new Modern Retina™ Viewpoints series, Dr. Rishi Singh, Dr. Anat Loewenstein, Dr. Paul Chous and Dr. Steven Ferrucci join as a panel of experts in ophthalmology and optometry to review the diagnosis and treatment of diabetic eye disease, including emerging agents in the field.

EXPLORE THIS SERIES

europe.ophthalmologytimes.com/viewpoints-dme-dr
Presbyopia combined with any refractive error has been a significant treatment challenge for refractive surgeons. Traditionally, the principles used for monovision contact lenses have been applied to corneal refractive surgery. However, this retains many of the limitations found with such contact lenses, including loss of fusion and stereoaucuity. Multifocal corneal ablation profiles have also been suggested; however, although an overall improvement in visual acuity has been recorded for both near and distance vision, the efficacy has remained relatively low, and safety and quality of vision can be compromised. A better solution that offers improved visual results and greater tolerance is still required.

Laser blended vision

It is helpful to consider presbyopia as the inability to accommodate rather than a decrease in depth of field of the eye. This decrease can be overcome, at least in part, by using an optimised ablation profile that controls postoperative spherical aberration, thus increasing the depth of field of each eye without significantly compromising visual quality, contrast sensitivity or night vision. The optimisation is based on the patient’s age, refraction, preoperative spherical aberration, tolerance for anisometropia and treatment centred on the corneal vertex.

We learned in the 1990s that spherical aberration increased in myopic ablations, leading to a decrease in visual quality and contrast sensitivity. My early work in wavefront-guided repair of night vision disturbances using what was at the time the highest resolution aberrometer (210 µm) coupled with Gaussian small-spot (0.7 mm) high repetition rate excimer laser ablation taught me that even a modest (27%) decrease in harmful levels of spherical aberration restored contrast sensitivity and night vision quality to normal.

This led me to consider up to approximately 0.6 µm of spherical aberration (Optical Society of America, 6 mm) as tolerable – this level can be filtered by the brain. This led to the concept of using spherical aberration to increase the depth of field of the eye. Within a few years, several researchers were able to experimentally duplicate this concept using adaptive optics systems and to demonstrate that extended depth of field increased linearly with the increase in spherical aberration, but only up to a certain point. Most important to note here is that adaptive optics studies proved that the depth of field increased with both positive and negative spherical aberration, showing that the effect was due to the spherical aberration itself rather than a zonal change in refractive sphere power (e.g., in positive spherical aberration, the larger the pupil, the more myopic the sphere of the refraction).

These laboratory experiments confirmed our surgical clinical research findings that a ‘therapeutic’ range for spherical aberration producing extended depth of field existed, beyond which there were ‘toxic’ effects of halos and reduced contrast sensitivity. During my early work developing an algorithm for presbyopic correction, the initial aim was to be able to adjust depth of field enough to provide clear vision from distance through intermediate to near, creating an eye that could see 20/20 at distance and also see a computer screen and read J1. We discovered that with photopic pupil diameters, the depth of field could be safely increased to 1.50 D for any starting refractive error. Given a 1.50 D depth of field, it would not be possible to get full distance and full near vision monocularly; therefore, based on the time-tested concept of introducing a

IN SHORT

Presbyopia can be treated in emmetropic, myopic and hyperopic patients with refractive errors between +5.75 and -9.00 D using corneal non-linear aspheric ablation profiles to increase the depth of field in both eyes, in combination with micro-monovision. Patient satisfaction with this approach is high.
degree of anisometropia between the eyes, the non-dominant eye was set up to be slightly myopic, so that the predominantly distance (dominant) eye was able to see at distance to intermediate while the predominantly near (non-dominant) eye was able to see in the near range and up to intermediate.

Both eyes had similar acuity in the intermediate region, an optimal situation for stereopsis. Microanisometropia in this case draws on the inherent cortical processes of neuronal gating and blur suppression by ‘interocular rivalry’ (the ability for conscious attention to be directed to the specific area with the best image quality within the entire visual field of both eyes). This contrasts with other attempts to treat presbyopia by inducing a cornea with two distinct focal points within the same eye: ‘intraocular rivalry’.

A further component contributing to the increase in depth of field, which persists even in eyes that have lost the ability to change crystalline lens power during the accommodative effort, is the increase in depth of field afforded by pupil constriction during accommodation. The combination of controlled induced corneal aberrations and pupil constriction significantly increases the depth of field on the retinal image.

Intraretinal and cortical processing and edge detection are the final components of laser blended vision: the pure retinal image, which is modified by spherical aberration, is further enhanced by central processing to yield the perception of clear, well-defined edges. In principle, as described above, the depth of field can be enhanced through the introduction of either positive corneal spherical aberration, in which case corneal power increases with zonal diameter, or negative aberration, where power decreases with distance from the corneal vertex.6,7

Most patients have some nascent positive spherical aberration before treatment, which is added to by the positive spherical aberration induced by standard myopic ablation. The important thing is to control the induction of spherical aberration to avoid increasing it above the tolerance threshold, which can cause loss of contrast sensitivity and night vision disturbances and can result in a topographic central island. To account for this, the ablation profile includes a pre-compensation factor. A standard large zone (7 mm) hyperopic ablation induces negative

It is helpful to consider presbyopia as the inability to accommodate rather than a decrease in depth of field of the eye.
spherical aberration that, in the case of hyperopic correction, is unlikely to increase above the tolerance threshold even with up to +7.00 D correction because most patients start with some positive spherical aberration and the range of hyperopic treatments is smaller than the range of myopic treatments.\(^9\) In emmetropic patients, you cannot rely on the ablation inducing spherical aberration, so the spherical aberration component of the calculation is increased.

This has an impact on the refractive accuracy. As emmetropic patients have high expectations and low tolerance to refractive inaccuracy, the best option is to increase the depth of field somewhat and make sure that the micro-anisometropia component is as accurate as possible.

The ablation profiles, taking age and preoperative spherical aberration into account, are referred to as non-linear aspheric ablation profiles because the spherical aberration component is governed by a non-linear function.

**Results**

The outcomes using Presbyond laser blended vision with the MEL 80 excimer laser (Carl Zeiss Meditec) have been published for myopia up to –8.50 D,\(^9\) hyperopia up to +5.75 D,\(^10\) and emmetropia.\(^11\) All treatments were performed as bilateral simultaneous LASIK.

For inclusion, patients had to be medically suitable for LASIK, presbyopic with corrected distance visual acuity (CDVA) no worse than 20/25 in either eye and have a tolerance of at least -0.75 D anisometropia. The standard micro-monovision protocol corrected the dominant eye to plano and the non-dominant eye to –1.50 D irrespective of age.

At 1-year follow-up, binocular uncorrected distance visual acuity was 20/20 or better and binocular uncorrected near visual acuity was J2 or better in 95% of myopes, 77% of hyperopes and 95% of emmetropes. Retreatment rate was 19%, 22% and 12%, respectively, although this would have been 5%, 6% and 4% had the criterion for retreatment been 20/32. The safety in terms of CDVA and contrast sensitivity was the same as for standard LASIK, with no eyes losing more than one line.

Mean mesopic contrast sensitivity either remained the same or improved slightly at 3, 6, 12 and 18 cycles per degree for all three populations. Stereaoacuity, although slightly reduced, has been shown to be maintained at a functional level of 100–400 seconds. Similar results have been reported by other groups.\(^12-15\)

The principle of correcting refractive error while modulating spherical aberration to benefit the depth of field can be equally applied to cataract surgery with IOL placement. A previously pseudophakic patient can be treated by laser blended vision protocols to set a total final spherical aberration of the eye that gives an extraordinary range of vision.

Performing cataract surgery on a patient with prior laser blended vision in the cornea enables the choice of a monofocal IOL of appropriate asphericity to leave the eyes with optimised spherical aberration, without resorting to diffractive optics and all of the quality of vision and adaptation issues that are introduced by intraocular rivalry, reduced contrast and the selective quantisation of the reading distance.

**Conclusion**

The combination of micro-anisometropia with increased depth of field through appropriate non-linear aspheric ablation profiles substantially improves visual outcomes in comparison with the conventional monovision approach. This can be achieved in the cornea and also in conjunction with cataract surgery.

Trials show that laser blended vision is effective in presbyopic patients with refractive errors between +5.75 and –9.00 D, including emmetropic presbyopes. With the safety advantages of modern femtosecond LASIK, the rapid bilateral surgical procedure and a recovery time of a few hours, patient satisfaction is extremely high.

**REFERENCES**


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Nd:YAG laser capsulotomy in intraocular lenses: Safe or dangerous?

Raman spectroscopy, electron microscopy, wavefront measurements offer clues

By Dr Andreas F. Borkenstein and Dr Eva-Maria Borkenstein

Neodymium:yttrium aluminium-garnet (Nd:YAG) laser capsulotomy is a safe, effective, quick and relatively easy gold-standard outpatient procedure for the treatment for posterior capsule opacification (PCO) following cataract surgery. It improves visual acuity and may also have positive effects on glare and contrast sensitivity in some patients.

However, there are reports of complications associated with the method such as corneal injuries; pupil blockage; iritis; increases in intraocular pressure (IOP); vitreous prolapse; retinal damage; and luxation/decentration of the IOL or damage to the IOL material (pitting). Pitting occurs in 15–33% of eyes during Nd:YAG laser posterior capsulotomy.

In the past, incorrect and inaccurate focusing of the laser beam was identified as the main cause of pitting. In several cases, time pressure could be determined as the main cause for these iatrogenic defects. Pitting is supposedly not visually significant, although rarely the damage may cause sufficient glare, straylight and image degradation to require the damaged IOL to be explanted (Figures 1–2).

**Techniques**

The two primary YAG types are the cruciate pattern and the circular pattern, and each has its benefits and downsides. In the cruciate method, the YAG laser is used to create a cross pattern, which then allows the resultant capsule flaps to retract out of the visual axis.

Laser spots are placed through the centre of the IOL. Therefore, care must be taken to properly aim the laser to avoid pitting the optic in the central visual axis.

The circular technique creates a circular cutout, which then allows for a round posterior capsular opening. With this method, laser shots do not need to be placed in the central optical zone but can instead be aimed at the periphery.

Thus, the chance of central pitting and negative effects on the optics is lower. Some data also found that the frequency of IOL damage depends on the specific IOL design. A design separating the posterior capsule from the IOL (ridge) is less prone to damage than lenses with a close apposition between the IOL posterior surface and the posterior capsule.

Current attempts to reduce or prevent PCO by having posterior capsule adhesion to the IOL might complicate laser treatment and increase rates of damage in the future. Nd:YAG rates commonly reported before 1992 were between 20% and 33%, while Nd:YAG rates for IOLs implanted 10 years later were below 17%. In the past, numerous studies on various IOLs showed very different, unsteady results of Nd:YAG and PCO rates (5–2%) 3–5 years after surgery.

**Comparison study**

We recently conducted a study to assess differences in Nd:YAG-induced defects between hydrophilic and hydrophobic acrylic IOLs and describe optical and surface properties. The main aim was to increase awareness of the need to approach Nd:YAG laser
capsulotomy with a greater level of caution. We recognised that hydrophilic and hydrophobic IOL materials seemed to be affected differently by Nd:YAG treatment according to wavefront aberrations and in slit lamp examinations. A total of 12 different monofocal IOLs from nine manufacturers were evaluated. All five hydrophilic lenses had a refractive index of 1.46 and a water content of 26%. Of the seven hydrophobic IOLs, two were yellow and one had an additional heparin coating.

Refractive index varied between 1.47 and 1.55 and the water content was less than 1% except for one lens which was 4% water. All lenses were manufactured with a 360° sharp edge and had a spherical power of 21.5 dioptres.

Reflected-light microscopy and an environmental scanning electron microscope (ESEM) were used to visually analyse the defects. Additionally, wavefront measurements were taken for exact power mapping of the IOL optic and Raman spectroscopy was performed. Vertical and horizontal dimensions of the defects were analysed and compared, and Raman line scans assessed the chemical changes in the defect area and surrounding area.

In photomicrographs of the hydrophilic and hydrophobic IOLs after laser treatment, pits created by the laser were observed on both types of materials. The damage appeared to be bigger and more intense within the hydrophobic lenses than in hydrophilic ones. In the hydrophobic lenses the pits looked similar to the branches that appear when glass breaks and could be seen even with less magnification, while in the hydrophilic ones, they were not as visible.

These smaller zones of damage appeared like bullet holes with a smoother rim. An additional observation was that shots made directly next to already existing defects produced larger craters. This could be caused by a change in the material surrounding the defect (surrounding area).

The ESEM images confirmed the results and showed deeper and greater damage in hydrophobic materials than in hydrophilic. Damage to hydrophilic lenses seemed to be more circular while those in
hydrophobics were more frayed (Figure 3).

In Raman spectroscopy, defects were found to have different depths, with deeper pits seen in hydrophobic lenses (Figures 4–5). Raman line scans showed the area of defect in terms of chemical changes. These areas were found to be bigger than the visible defect area and, again, this effect was greater in the hydrophobic lenses.

Regarding the level to which the optical properties of the IOL changed after the treatment, a difference was noted within each group but it was not a significant one. Wavefront analysis revealed unusual white spots, besides the well-known colour map of the power of the lens. These spots occur when an area of the sensor has not been illuminated, since the light beam deflection at a defined point of the lens is so large that it no longer falls into the corresponding microlens, as in the case of damage and material defects.

Our results may support the assumption that the differences between the materials are mainly due to the differing water content. Defects can be seen very well even within standard slit lamp examination. We also found evidence that the material at the point of entry (area of the shot) and surrounding area changes chemically due to the procedure. These changes seem to be greater than what is visually observable.

If we analyse a hydrophobic lens as an example, the visible damage was measured at 81 µm (vertical) and 95 µm (horizontal), however, the chemical changes increased these to 120 µm (vertical) and 124 µm (horizontal), which was an enlargement of 48% and 31%, respectively. This means that the area of the defect in the IOL was not 7,600 µm² (visible area) but 14,800 µm².
Defect length (μm)

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<tr>
<td>50</td>
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<td>p = 0.036</td>
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(FIGURE 5) Measuring the defect length showed differences in horizontal and vertical visible damage lines in hydrophilic and hydrophobic material. (All images courtesy of Dr Andreas F. Borkenstein and Dr Eva-Maria Borkenstein)

Ophthalmologists should be as cautious as possible when performing laser capsulotomy. It is important to consider the position of the defect and the IOL type and model. The results of this study support the clinical experience that iatrogenic-induced YAG shots in IOLs behave similarly to other defects and clouding/haze in such lenses, such as scratches (after improper folding of the IOL or incorrect manipulation with a spatula or forceps), glistening or calcification in IOLs.

In all cases, the extent and severity as well as the position/area in the IOL optic is most important. When it comes to clinical symptoms, there is a wide variability, ranging from no effects or mild symptoms to severe clinically significant effects on the overall quality of vision.

Concluding thoughts and future perspectives

Ophthalmologists should be as cautious as possible when performing laser capsulotomy. In the worst-case scenario, an improper YAG-procedure can lead to major clinical effects and permanently influence the optical quality. For such patients, explant of the IOL may need to be considered, but this has a further risk of complications. Therefore, it is important that patients are informed about all the potential dangers before they undergo a supposedly short and simple YAG procedure, and that the doctor is aware that these tiny defects could actually have a greater impact than is often thought.

Ophthalmologists should also consider the position of YAG laser. Laser shots do not need to be placed in the central optical zone but in the periphery, so the chance of central pitting and negative effects on the optic is lower. Moreover, the procedure should not be performed under time pressure.

If for any reason the lens is bombarded and defects do occur, the doctor should halt the procedure immediately. To continue operating would be irresponsible and could amount to an ‘ophthalmic terrorist attack’, which will certainly have clinical implications.

Further investigation via in vitro and in vivo studies is needed. Additional aids could be developed by companies to further minimise the risk. For example, an acoustic signal could be used to draw attention to a patient’s head movements or warn that the focus of the laser beam is incorrectly adjusted. In addition, an ocular measuring device would help to avoid pitting the central, and most important, area of the lens and at the same time achieve a sufficiently large capsulotomy.

REFERENCE


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The increasing potential of ERG in diagnosing a wide range of eye conditions

Easier, more accessible functional studies have been made possible

**By Miss Sally Justus; Reviewed by Dr Ruth Hamilton**

**SALLY JUSTUS, BA**
Miss Justus is an MD/MBA candidate at Harvard Medical School, United States. She studied inherited retinal degenerative conditions at Columbia University Irving Medical Center in New York City before beginning her medical training. Miss Justus is a consultant of GP Communications; GP Communications is a consultant of LKC.

**RUTH HAMILTON, PHD**
Dr Hamilton is a consultant clinical scientist at Royal Hospital for Children, Glasgow, UK, where she directs the paediatric visual electrophysiology service. Dr Hamilton has no financial disclosure and no financial or proprietary interest in any material or method mentioned. Neither Dr Hamilton nor ISCEV approve or endorse specific instruments for electrophysiological recording.

**ELECTRORETINOGRAPHY (ERG) HAS COME A LONG WAY** since its inception in the mid to late 1800s, when the notion of recording the eye’s electrical activity as a measure of its function was revolutionary. It was not until the 1900s that this technology was applied to patients in a clinically relevant manner (Figure 1).

Standardisation of testing protocols by the International Society for Clinical Electrophysiology of Vision (ISCEV) enabled the development of clinical practice guidelines for the administration and interpretation of ERG so that patients would benefit from its diagnostic insights.

Today, the test has a wide range of applications such as inherited retinal conditions, medication-induced retinopathy, diabetic macular oedema, vein occlusions, arteriosclerotic retinal damage and Vitamin A deficiency, among others. I had the pleasure of speaking with Dr Ruth Hamilton, the newly elected president of the ISCEV and the secretary of the British Society for Clinical Electrophysiology of Vision (BiSCEV), about the progress that has been made with ERG and its future potential.

**JUSTUS: ERG is sometimes thought of as difficult to administer, difficult to interpret and irrelevant for most ocular complaints, and instead better suited for the retina clinic and research studies. How would you respond to individuals who feel this way?**

**HAMILTON: ERG has great promise to assist in clinical decision-making for patients with various ophthalmic conditions, but you are right that it is sometimes seen as a niche tool for use only by retina specialists and researchers. This reputation was likely born from the complexity of performing and interpreting the test, the length of time it can take to administer and the costs of devices. However, multiple studies suggest that ERG testing may be useful as a screening tool for bread-and-butter general ophthalmology diagnoses such as diabetic retinopathy (DR), glaucoma and hereditary diseases.**

**JUSTUS: What is holding the use of ERG technology back and what would need to change to make it more accessible to both clinicians and patients?**

**HAMILTON: To realise the full potential of ERG, the use and interpretation of the test must be simplified. Until recent developments, the ERG protocols required dilation and significant times for set up, which places an administrative burden on clinics and is fatiguing for patients. Electrodes had to be in contact with the eye to detect a signal, which is uncomfortable for adults and nearly impossible without sedation in children. Interpretation of the data was challenging for non-specialists given variations in waveforms based on the protocol used. Finally, the size of the equipment, its lack of transportability and the need for specially trained technicians to perform it also limited the accessibility of this technology.**

**IN SHORT**
Recent improvements in electroretinography are making the technique more accessible for general use. It has a wide range of clinical applications.
**JUSTUS:** What progress has been made in recent years to address these limitations?

**HAMILTON:** Devices now exist that are more comfortable, do not require dilatation, are transportable, can be used without specialised training and provide simple-to-interpret, reproducible data. In my clinic we use the RETeval (LCI), the Espion (Diagnosys LLC) and the RETIport/scan (Roland Consult).

**JUSTUS:** I understand these devices have been explored for the screening and diagnosis of a wide range of conditions. For example, the RETIscan has been used to assess the value of multifocal ERG in predicting visual declines in early age-related macular degeneration and it seems particularly useful in children, owing to the comfort of its external sensors. Do you predict other developments for these devices?

**HAMILTON:** I think advances in ERG testing technology will be particularly useful for improving access in resource-limited settings and in developing nations that may not have the financial, technical or human resources to establish their own conventional ERG centres.

**JUSTUS:** Hand-held ERG devices have been found to be sensitive enough to detect functional changes before observable structural changes can be appreciated on fundus examinations. Nevertheless, I imagine the traditional ERG will still be more suitable for tough cases, especially if there is a high noise-to-signal ratio. The value of the portable ERGs, then, is not to fully replace the traditional system, but to spread the use of the test in ophthalmology, whereas more complex ERGs, such as the multifocal ones, can continue to be the standard of care in specialty clinics. Would you agree?

**HAMILTON:** Yes, and the faster, easier-to-use devices can identify patients with abnormalities who will need further study, thereby reducing the burden placed on the healthcare system by prioritising advanced testing for the patients who need it most.

**JUSTUS:** What do you think the future holds for ERG technology?

**HAMILTON:** One day, ERG may well have a use in primary care offices to screen patients for conditions like DR and glaucoma based on their risk factors and family history, just as an electrocardiogram would routinely be ordered in patients with cardiovascular risk factors, but there is a need for further improvement before this becomes a reality. Developing artificial intelligence software to automatically grade the waveforms would enhance standardisation across platforms and make interpretation more efficient. The results could be compiled into an international repository where mathematical modelling might enhance the diagnostic robustness of testing. This harmonised reference data would enable further refinement of the protocols and technology. In this manner, clinical practice would be able to match the rigours of research standards, which arguably will result in better outcomes for patients.

For ERG technology to provide the most good for the most patients, it must make the leap to being comfortable, portable, standardised and accessible. Fortunately, we are off to a great start to make this ideal a reality for patients around the world.

**REFERENCES:**


Multiple studies suggest that ERG testing may be useful as a screening tool for bread-and-butter general ophthalmology diagnoses.
YAG laser vitreolysis is a less-invasive option than pars plana vitrectomy for patients who are affected by vitreous opacities (floaters), according to Dr Netan Choudhry of Vitreous Retina Macula Specialists, Toronto, Canada. Although floaters are typically clinically inconsequential, a small subset of patients have debilitating symptoms that interfere with their vision and require treatment.²

During the American Society of Retina Specialists virtual annual meeting, co-author Dr Collier Jiang, University of Calgary Department of Ophthalmology, presented outcomes from the VOYAGE study evaluating the impact the surgical procedure has on visual outcomes and on optical coherence tomography (OCT) imaging in patients with symptomatic vitreous floaters. As background, Dr Jiang said few publications exist on the treatment since it is so new, and those that have been published have shown varying degrees of visual function improvement after the procedure. “Up to this point, we really have not had an objective way of evaluating the opacity, what it looks like, where is it, what it is doing … what the end point for treatment is,” Dr Choudhry said.

Study design and results
In the VOYAGE study, 35 patients (mean age 59; 43% female) with symptomatic floaters (n=40 eyes) were treated with YAG laser vitreolysis. All patients had a dilated eye examination to confirm the floaters as well as receiving pre- and post-treatment ultra-widefield imaging.

Best corrected visual acuity (BCVA) was measured and swept-source OCT conducted prior to and after treatment. Dr Jiang noted that five patients received bilateral YAG laser vitreolysis due to symptomatic vitreous floaters in both eyes.

All treatments were performed by a single surgeon using the Ultra Q Reflex Laser (Ellex) after dilation and anaesthesia, using a single mid-vitreous contact lens that was applied to the cornea using GenTeal ointment (Alcon). “The energy level was initially set for 5 mJ and titrated up to a maximum of 20 mJ to achieve plasma formation with the creation of bubbles and opacity destruction,” Dr Jiang said. Patients were re-treated if they reported ongoing symptoms during follow-up; 37% of eyes required a second treatment and 35% required a third treatment.

Overall, patients experienced an improvement in mean BCVA after the first YAG treatment compared with baseline (0.14 ±0.20 logMAR units vs 0.11 ±0.20 logMAR units, respectively), however BCVA was not significantly different after the second and third treatments compared with baseline. Furthermore, just over half of the patients (55%) reported an improvement in their symptoms after their final YAG treatment, Dr Jiang said.

“Overall, this study showed a significant improvement in mean BCVA after the first YAG laser vitreolysis treatment compared with baseline,” he said. “Ninety percent of patients reported resolution of their symptomatic visual disturbance after the final treatment session. There were no retinal detachments or retinal tears.”

IN SHORT

A study found that YAG laser vitreolysis was less invasive than pars plana vitrectomy for patients with vitreous opacities.
Imaging floaters in clinical practice

The VOYAGE study “used a variety of novel imaging techniques to quantify and follow changes in the vitreous opacities,” Dr Jiang said, adding that scanning laser ophthalmoscopy and dynamic OCT visualisation were particularly useful tools. For example, he said by increasing the gain by 55% to 75% from an unaltered swept-source OCT scan, clinicians are able to view the opacities that were previously unable to be imaged.

Furthermore, “dynamic OCT imaging can capture the movement of the patient’s vitreous in real time and help localise vitreous opacities during treatment,” he said. “OCT can provide useful information. When the depth is increased to 6 mm, we can identify some vitreous opacities that may have been missed with the standard 3 mm depth.”

Dr Carl Regillo, Wills Eye Hospital, led the paper discussion, and noted that about two-thirds of patients needed re-treatments. “Why aren’t we doing this across the board? Most vitreoretinal surgeons are not doing YAG vitreolysis. Is it time consuming? Is it challenging?” he asked.

“These procedures can take some time, probably 10 to 15 minutes,” Dr Choudhry said. “The reason that it was broken up into, on average, two sessions, was because after a certain amount of power was administered to the eye, there was a risk of an increase in IOP. We wanted to limit all complications or [adverse] effects.”

Dr Choudhry elaborated on the unique imaging used, noting that swept-source OCT was vital to “identify the opacities that the patients were complaining about and then titrate the treatment to the end point of the disappearance of those opacities, to know that we have hit an end point for the therapy.” In terms of clinical practice implementation and patient selection, he noted that not every patient who has floaters needs treatment.

“I have been doing [YAG vitreolysis] for the past year-and-a-half successfully in the patients [who] really need it,” he said. “Of course, in the world of optics, the definitive result will always be with the complete clearing of the vitreous, but if we can avoid vitrectomy and the small risk of complication from vitrectomy in those patients [who] are good for this procedure, then why not?” Dr Choudhry did note, however, that vitrectomy is the first and only option for certain opacities of the amorphous variety or multiple diffuse floaters.

REFERENCE

In the past, attempts at bleb repair after trabeculectomy and introduction of the use of mitomycin C (MMC) to improve surgical success rates resulted in blebs that were avascular and prone to leaks. According to Prof. Neeru Gupta, chief of glaucoma at the University of Toronto, Canada, and president-elect of the World Glaucoma Association, this situation is a “time bomb”. She said: “Left unchecked, it can lead to blebitis and possibly endophthalmitis, and myriad other problems, such as hypotony with associated anatomic disruptions such as vision-blurring corneal striae, shallow anterior chambers, buildup of excess fluid leading to dome-shaped choroidals and hypotony maculopathy.”

Techniques that have attempted to address the problem of leaky blebs include conservative treatment with antibiotics; aqueous suppressants; steroids; collagen shields; bandage contact lens; pressure patches; cyanoacrylate tissue glue; autologous blood; and argon laser or Nd:YAG laser. The microsurgical approaches include bleb resuturing and bleb excision and conjunctival advancement with or without various grafting techniques. Despite all of this, no procedure stands out as effective.

Prof. Gupta developed the minimally invasive conjunctival surgery incision-free procedure to address late-onset bleb leaks close to the limbus. A patient had a history of high myopia, advanced pigmentary glaucoma and retinal detachment treated with pars plana vitrectomy, and later with pneumatic retinopexy and cryotherapy. They had used multiple glaucoma medications for advanced glaucoma, thin corneas, bilateral cataracts and had remaining central islands of vision of 20/60 to 20/70.

Prof. Gupta performed bilateral trabeculectomies with MMC. Vision was stable with intraocular pressures (IOPs) of 8–10 mm Hg bilaterally. In 2012, however, the vision in the left eye decreased to 20/100 with an IOP of 2 mm Hg and an avascular leaking bleb. Three days later, the vision was 20/200 with an IOP of 0 mm Hg.

In surgery, Prof. Gupta acted to address this situation without undoing the previous treatments. Instead of excising the bleb and covering the area with conjunctiva, she injected subconjunctival lidocaine above the bleb.

She described the conjunctival epithelium as highly voluminous and able to move freely. With gentle tugging and without disturbing Tenon capsule, she pulled a sizable area of the conjunctival tissue to the limbus over the leaking area and put in a series of stitches (typically three to four) without using a great deal of pressure that resulted in a sealed wound.

The patient has done well during the ensuing 8 years. Prof. Gupta reported that she has performed this procedure in 14 cases and reported the results in the American Journal of Ophthalmology.1

In all cases, the patients have remained stable and medication-free from 2 weeks to 5 years later. She said that with time the transposed conjunctival tissue becomes translucent and seems to take on the characteristics of the early bleb that was leaking.

“It is short and incision free with good success; the bleb is preserved; the procedure is relatively simple, inexpensive, efficient and accessible; and the patients are comfortable postoperatively and can return to normal activities,” she said. They leave after the surgery with an antibiotic and a steroid. She advised that studies are needed to determine the long-term outcomes.

REFERENCE

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Prof. Gupta has no financial interest in this subject matter.
Novel chondroitin formulation contributes to cyclosporine efficacy

Multicentre study shows improvements in symptoms after 3 months of treatment

By Cynthia Matossian; Special to Ophthalmology Times

Topical cyclosporine A (CsA) has long been a mainstay of treatment for dry eye disease. In fact, for many years, CsA 0.05% (Restasis, Allergan) was the only treatment available to our patients, other than steroids or palliative artificial lubricants. More recently, we have seen the introduction of lifitegrast 5% (Xiidra, Novartis), multiple treatments for underlying meibomian gland dysfunction, and higher-concentration CsA formulations (Cequa, Sun Pharmaceutical Industries and Klarity-C, ImprimisRx), all of which have given rise to a more robust armamentarium of treatment options for dry eye disease.

CsA is an immunosuppressant that inhibits T-cell-mediated inflammation and cytokines, stimulates tear production and increases goblet cell density.\(^1,2\) Despite its success in the marketplace and in many of our practices, there are still challenges with its use, including the high cost of the prescription solution for patients and burning or stinging on instillation, which can discourage patients from continuing the drops long enough to see an effect. Additionally, it is challenging to formulate a topical CsA preparation because this molecule is not very water soluble.

I have been involved in a study to evaluate efficacy in a real-world clinical practice setting of a higher-

**IN SHORT**

In recent years, ophthalmologists have seen several new therapeutics for the treatment of dry eye disease.

**Severity of OSDI Score (frequency distribution)**

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<td>Mild (13 to 22)</td>
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<td>Moderate 23 to 32</td>
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<td>Severe (33 to 100)</td>
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*p=0.002*

*(FIGURE 1) After 3 months of treatment, the severity of dry eye was reduced, as shown by the change in the ocular surface disease index score from baseline. (Chart courtesy of Dr Cynthia Matossian)*
dose (0.1%) cyclosporine (Klarity-C) in a unique chondroitin sulfate formulation. Chondroitin sulfate, a compound developed decades ago by Dr Richard Lindstrom, Dr Herbert Kaufman and others, is the key ingredient in OptiSol-GS (Bausch + Lomb) and is used in several viscoelastic products.

It has some unique properties in that it is lubricating, anti-inflammatory, cell membrane-stabilising and corneal oedema-reducing. Klarity-C, the drug used in our study, is a preservative-free drop compounded in a 503B United States Food and Drug Administration (FDA)-regulated outsourcing facility.

503B pharmacies have to follow stringent quality and manufacturing requirements and are subject to the same FDA inspection and oversight as large pharmaceutical companies. However, compounded medications are typically more affordable than other branded drugs.

Study design and results
This was a retrospective, multicentre study which I conducted with Dr Jennifer Loh and Dr William Trattler. Adult patients with a dry eye diagnosis who were treated with Klarity-C twice daily were included. We reviewed patients’ charts to determine the change from baseline in ocular surface disease index (OSDI) scores and corneal staining after 3 months of treatment.

Fifty-one patients with dry eye (102 eyes) were enrolled. Patients ranged in age from 27 to 80 years, with a mean age of 62 years and 76% were women.

The OSDI questionnaire measures dry eye symptoms, including visual symptoms and ocular discomfort. Patients are asked to indicate whether they experienced any of the 12 symptoms all, most, half, some or none of the time during the previous week, and the answers are scored from 0 to 100, with a lower score being ideal.
At 3 months, patients’ mean OSDI improved from 37.57 to 23.83 (\(P < 0.001\)). Before starting treatment, 61% of the patients had OSDI scores in the “severe” range (33–100). By 3 months, patients scoring in the severe range declined to 20%, and more than one third of patients reported improvements in symptoms that put them in the normal (0–12) range (see Figure 1).

Fluorescein staining of the entire cornea was evaluated for each eye (\(n = 102\)). The mean staining grade improved from 3.57 pre-treatment to 2.17 (\(P < 0.001\)) at 3 months. I find corneal staining with vital dyes to be an excellent diagnostic tool. In the PHACO study, Trattler et al showed that staining is extremely common in older patients, with 77% of those presenting for cataract surgery demonstrating some corneal staining (central or peripheral), including 50% with central staining.1

One patient I treated in this study was a 71-year-old man who complained of blur, light sensitivity and irritation, which he described as a “sandy, gritty feeling.” He thought he needed stronger glasses because he had a hard time focusing to read. He was not on any ocular medications, including artificial tears. His medical history was significant for hypertension, and controlled on lisinopril 10 mg and metoprolol 25 mg. He went through a full dry eye evaluation.

Tear osmolarity (TearLab) was normal (300 oculus sinister and 301 oculus dexter), but an MMP9 test (InflammaDry, Quidel) was positive for the inflammatory marker in the tear film. He had 1+ central and inferior staining in both eyes and his OSDI score was 22.7, putting him in the mild-to-moderate category.

I also like to look at topography images in evaluating dry eye. Prior to treatment, the axial maps on the OPD-Scan III (Nidek Inc) revealed that this patient had tear film instability (see Figure 2). We could also see missing and warped squares on the Cassini ocular surface qualifier, supporting the finding of an unstable tear film.

After 3 months of treatment with Klarity-C, this patient’s tear film was still not perfect, but the topography images were better; his OSDI score had improved from 22.7 to 6.25—well into the normal category—and he now had only trace inferior staining, with no staining centrally. His symptoms improved, including the visual fluctuations that made him feel that something was wrong with his vision. He had no problems tolerating the drops.

CsA is a time-tested, effective treatment for inflammation in dry eye. Twice daily instillation of Klarity-C results in statistically significant improvement in OSDI scores and improvement in corneal staining and also offers patients a favourable tolerability and cost profile.

REFERENCES


It is challenging to formulate a topical CsA preparation because this molecule is not very water soluble.
How dry eye disease can become a complex vicious cycle

There is a complex interplay between a series of self-stimulating biological events.

By Caroline Richards, editor of Ophthalmology Times Europe®

I SPOKE WITH PROF. Christophe Baudouin, president of the European Dry Eye Society to find out more about the complex nature of dry eye disease.

Q. COULD YOU TELL ME MORE ABOUT THE PATHOGENESIS OF DRY EYE DISEASE?

Dry eye is a very complex disease. It is not just a question of lack of water and so it is impossible to treat patients just by lubricating the eye with water. It is a disease that involves a series of self-stimulating biological events, and the lack of tears, insufficient tear quality or their instability results in direct mechanical and/or osmotic stress, which causes further damage.

In addition, goblet cell loss results in further tear film instability or imbalance and thus, dryness. The drier the eyes become, the more inflammatory they become and the greater the inflammation, the more the eyes continue to dry out, i.e., a vicious cycle occurs (see Figure 1).

To give more context on the vicious cycle theory, the dryness of the eye stimulates the nerves, the inflammatory reaction and inflammatory cells, and those act as stimulation for further damage, and so tears and their quality are reduced further, resulting in the disease becoming chronic.

Overall, the disease is very complex, with many risk factors, causes and aetiologies having been defined. As a result, it is difficult to resolve.

Q. HOW ARE PRIMARY AND SECONDARY INFLAMMATORY PROCESSES INVOLVED IN THE DISEASE?

There is a constant state of inflammation with the most severe dry eye cases, and this can be primary; for example, as seen with Sjogren syndrome, where inflammatory cells infiltrate and block the lacrimal glands, as well as the conjunctiva and cornea, and thus invade the whole...
ocular surface. Secondary processes are also involved: the various types of stress including mechanical and osmotic factors also stimulates inflammatory cells and results in a chronic inflammatory state.

Q. WHAT DO YOU THINK FUTURE TREATMENT STRATEGIES NEED TO FOCUS ON?

The increasing interest in the idea of the vicious cycle allows us to discriminate between different levels of events: the mechanical stress, the osmotic stress and the inflammatory stress, for example. This new way of understanding the disease may allow the physician firstly to try to prevent the patient from entering the cycle, which is important and can be made possible by controlling the environment, improving the eyelid and decreasing inflammation. Secondly, each part of the loop can be targeted with a specific approach such as lubrication, eyelid hygiene, anti-inflammatory strategies and maybe even Omega-3.

And so there are different complementary approaches that can improve the patient’s symptoms. That said, sometimes it is difficult to help the patient and they can suffer a lot.

To discuss a further complication of dry eye, we are increasingly starting to understand the concept of neuropathic pain in dry eye disease. Sometimes, the overstimulation of the nerve causes chronic pain and so even when the cornea and tears have been improved, patients can continue to suffer.

And once neuropathic pain has been stimulated, it can be very difficult to control it. Therefore, a good future treatment approach would be to find the best ways of relieving pain symptoms either locally or systemically.

Another consideration is in how we treat and control inflammation. In Europe, there is only one ciclosporin formulation indicated for severe dry eye disease with corneal damage, Ikervis (Santen), whilst the United States market has the prescription eyedrop Restasis (Allergan).

Another medication for the treatment of signs and symptoms of dry eye, which is available in some countries, is lifitegast (Xiidra, Takeda Pharmaceutical), which blocks the activation of lymphocytes. Unfortunately, this drug is not available in Europe and so other anti-inflammatory strategies are needed here.

In addition, the eyelids are likely to be the location of a lot of inflammation and so represent potential targets. Various strategies to treat the eyelids have been developed, based on pulse light or warming and massaging devices, and are certainly a good way of relieving the patient’s symptoms.

Q. HAS THE INCIDENCE OF DRY EYE DISEASE RISEN DURING THE COVID-19 PANDEMIC AS SCREEN TIME HAS INCREASED?

We do not yet have epidemiological data to assess, however, it is clear that long hours working at, or reading on, a computer do affect dry eye and there is a clear association between the two. So, most likely, patients who have dry eye are suffering more during this time.

Furthermore, it has also been found that wearing a mask seems to interfere with eyelids and lead to meibomian gland dysfunction, perhaps by blocking the lymphatics at the level of the eyelids or by focusing an air flow on the eyes, so some people are finding that their dry eyes have been worsening due to their mask use.
Investigators explore pathogenic cytokines as biomarkers for DMO

Extracellular matrix protein BIGH3 can act in an autocrine, paracrine manner

By Cheryl Guttman Krader; Reviewed by Dr Andric C. Perez-Ortiz

BIGH3 (transforming growth factor-β-induced Gene Human Clone 30) is a promising serum biomarker for diabetic macular oedema (DMO) in patients with nonproliferative diabetic retinopathy (NPDR), according to Dr Andric Perez-Ortiz, who presented research at the Association for Research in Vision and Ophthalmology 2020 virtual annual conference. Dr Perez-Ortiz and colleagues conducted a case-control study analysing levels of BIGH3, transforming growth factor-β1 (TGF-β1) and transforming growth factor-β2 (TGF-β2) in the aqueous humour and serum of patients with DMO and unaffected controls.

The results showed that BIGH3 was the only cytokine that was present in significantly different concentrations in both fluids in DMO patients compared with controls, and the only cytokine with a positive significant correlation between its level in aqueous humour and serum. None of the three cytokines, however, correlated with macular thickness or optical coherence tomography (OCT) phenotype among patients with DMO.

According to Dr Perez-Ortiz, studies investigating expression and levels of these cytokines have all been performed in vitro. “The aim of our study was to measure the concentrations of TGF-β1, TGF-β2 and BIGH3 in aqueous humour of patients with NPDR—with and without DMO—and to assess their clinical applicability as serum markers by testing their correlation in aqueous humour and serum, and association with macular thickness and DMO phenotype,” said Dr Perez-Ortiz, an associate professor in the Department of Public Health at Universidad Panamericana in México City, Mexico and research fellow, Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, United States.

“The predictive capacity of BIGH3 certainly warrants further study,” he said. “Especially its sensitivity and specificity and/or predictive use as an early biomarker for DMO development.”

Interest in exploring the potential for TGF-β1, TGF-β2 and BIGH3 to serve as biomarkers for DMO is based on understanding of their role in the pathogenesis of DR and DMO. Dr Perez-Ortiz explained that pericyte dropout and increased inflammation and activation of proinflammatory transcription factors that induce monocyte and macrophage infiltration occur early in the pathogenesis of these diabetic eye diseases.

Macrophages predominantly secrete TGF-β1 and TGF-β2 that induce apoptosis of retinal pigment epithelium (RPE) and upregulation of the gene encoding for BIGH3.

BIGH3 is an extracellular matrix protein that can act in an autocrine or paracrine manner to induce apoptosis of RPE cells, pericytes and retinal endothelial cells time- and dose-dependently. The presence of BIGH3 has been observed in the histopathologic retinal section of a postmortem globe with documented NPDR deposited predominantly around retinal vessels and occasionally in choroidal vessels. “Hence it has been hypothesised that monocyte/macrophage-induced BIGH3 expression is an important progressive step in the pathophysiology of pericyte loss,” Dr Perez-Ortiz said.

Study design

The study investigating levels of the TGF-β cytokines and BIGH3 in patients with NPDR included adults aged 18 years and older with type 2 diabetes mellitus who were undergoing a surgical procedure (initiation of intravitreal injection for DMO patients and cataract surgery for controls). It included 26 patients with

IN SHORT

- Results of a study analysing cytokine levels in the aqueous humour and serum of patients with NPDR with and without DMO support further research investigating transforming growth factor-β-induced Gene Human Clone 30 (BIGH3) as a potential biomarker for DMO.
DMO and 27 who did not have DMO.
Patients were excluded if they had systemic inflammatory disease or a history of any vitreous procedure. The aqueous humour sample of approximately 1 µL was collected in all eyes prior to any surgical intervention, and the cytokine levels in serum and aqueous humour were quantified with cytometric-bead assays.

The two groups were similar in mean age (~ 63 years) and sex distribution, but the average time since diabetes diagnosis was significantly longer in the DMO patients than in the controls. As would be expected, maximum central macular thickness (CMT) was also significantly greater in the cases compared with controls. Among patients with DMO, cystic changes and spongiform changes were the most common phenotypes identified on OCT.

The cytokine analyses showed that the aqueous humour concentration of TGF-β1 was significantly greater in the DMO eyes compared with the controls, whereas the reverse relationship was observed in serum. TGF-β2 also was present in a significantly higher concentration in the aqueous humour of the cases compared with controls, but its concentration in serum did not differ significantly between the two groups.

Further analyses showed that the ratio of TGF-β1 in aqueous humour serum was disproportionately elevated in the DMO cases compared with controls. In addition, a significant positive correlation was found in the DMO group between aqueous humour concentration and maximal CMT. The correlation between serum concentration and maximal central macular thickness was negative for TGF-β1 and positive for TGF-β2.

The concentration of BIGH3 was significantly higher in both serum and aqueous humour in the DMO group compared with controls. The ratio of BIGH3 concentration in aqueous humour to serum was not significantly different comparing cases and controls, and it did not correlate with CMT or OCT subtypes in the eyes with DMO.

BIGH3 is an extracellular matrix protein that can act in an autocrine or paracrine manner to induce apoptosis of RPO cells, pericytes and retinal endothelial cells.

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Dr Perez-Ortiz has no relevant financial interests to disclose.
Considerations in diabetic macular oedema and diabetic retinopathy

Diagnosis, management and upcoming treatments for these patient populations

By Lynda Charters

Diabetic eye disease is the leading cause of blindness in working-age adults, which underscores the disease’s community impact. In the first Ophthalmology Times, Ophthalmology Times Europe, Optometry Times and Modern Retina Viewpoints series, four international experts discussed current physician challenges virtually, ranging from diabetic eye examinations, collaborations between MDs and ODs, COVID-19 and available and upcoming treatments. Here are some of the highlights.

Ocular examinations

Dr A. Paul Chous explained that for patients with diabetes, a good dilated stereoscopic view of the inside of the eye is imperative. Imaging is useful, especially in the baseline examination to facilitate later comparisons; he values fundus photography highly, particularly wide-field or ultra-wide field imaging, and performs optical coherence tomography (OCT) at every visit to detect subclinical diabetic macular oedema (DMO).

He also underscored the value of good case histories regarding glucose and blood pressure control and lipids. Knowing the previous patient values is helpful for providing better advice about examination frequencies and the odds of maintaining good vision.

Dr Anat Loewenstein also emphasised the importance of the clinical evaluation and wide-field photography for screening. She performs angiography on patients at baseline if they have diabetic retinopathy (DR) but not in those without DR.

Dr Steven Ferrucci finds OCT-A helpful with diabetic patients without oedema who have unexplained visual loss. OCT in these patients identified macular ischaemia.

Dr Rishi Singh noted the controversy surrounding the correct way to perform the diabetic eye examination. He finds OCT-A useful in patients with diabetes without DR but with temporal microaneurysms. OCT-A showed that such patients actually had juxtafoveal telangiectasia or another masquerade syndrome. He does not use OCT for patients with good vision.

ODs and MDs

Dr Ferrucci underscored the role of optometrists in instructing patients about asymptomatic DR and DMO. “Good vision on an eye chart or in the real world does not mean their eyes are healthy,” he said.

Education about metabolic memory is also important, i.e., early tighter blood glucose control has a protective effect decades down the line. Patients should also be educated about diabetes medications that can lower the risk of fatal infarctions/stroke.

All panelists urged consistency in messages to patients.

He encouraged ODs to obtain a second opinion if necessary. The American Optometric Association guidelines recommend referral to retinal specialists at the earliest signs of severe nonproliferative DR (NPDR), PDR and centre-involved DMO to discuss treatment options. Communication via letters to retina specialists can provide a brief patient background with ODs’ concerns.

All panelists urged consistency in messages to patients and that all primary eye care providers send a note to the primary care physicians (PCPs) informing them of the development of DR in their

IN SHORT

- In this Viewpoints series, four international experts discussed current physician challenges ranging from diabetic eye examinations to COVID-19.
patients, whether they need referrals to retina specialists and asking about the follow-up interval. DR is linked to other diabetes comorbidities and communication is an opportunity to collaborate with PCPs and other subspecialists, Dr Chous said.

The panelists also discussed challenges such as asymptomatic disease and the importance of routine check-ups to start treatment as soon as possible. Patients must be educated about the importance of eye care. Because of cognitive disabilities associated with diabetic encephalopathy, it is helpful to have family members accompany patients to discuss follow-up or referrals.

**Treatment guidelines and COVID-19**

Dr Chous believes that an annual examination by an optometrist is appropriate if a patient has mild or no disease and believes there is value in habituating patients to annual dilated examinations. With disease worsening, a referral is needed. Dr Ferrucci feels safe examining patients with mild or moderate NDR.

Dr Loewenstein follows patients with good visual acuity (VA) but if follow-up is problematic, she prefers to treat. In patients with central macular oedema, she generally treats if the patient has very good VA and noted that bevacizumab (Avastin, Genentech Inc.) and aflibercept (Eylea, Regeneron) are good options; in patients with 20/50 or worse, she prefers bevacizumab.

A major disruption of the pandemic has been the slowing of diabetic, routine and annual examinations. Dr Chous believes elderly diabetic patients should be informed of their increased risk for poor outcomes related to glycaemic control if they are hospitalised for COVID-19.

Poor glycaemic control translates to 5–10 times greater likelihood of a fatality. He assures patients that proper in-office disinfection protocols are followed and advises minimal face-to-face time because patient risk is higher in an enclosed room.

Dr Loewenstein offered patients three options during the pandemic: a safe office visit, a remote clinic off-site from the hospital and an injection clinic. She and her colleagues also conducted home visits during which patients could receive injections.

**Drug treatments**

Dr Loewenstein considers faricimab (Genentech) to be the most promising future drug for managing patients since it is anti-angiopoietin-2, enhances vascular endothelial growth factor (VEGF) activity and is anti-inflammatory. Brolucizumab (Beovu, Novartis) also seems promising, but Dr Loewenstein is concerned about the inflammatory response.

KSI-301 (Kodiak Sciences) and gene therapy are promising but not currently close to the stage of large-scale clinical use. The Port Delivery System with ranibizumab (Genentech) is being studied for diabetes; however, there are safety concerns.

Dr Chous mentioned that the retinal flavoproteins, while not specific to diabetes, are the earliest marker of photoreceptor oxidative stress in diabetes, and he looks to them as an early marker in improving glucose control and thus avoiding ocular damage. His goal is elimination of the need for ocular injections or photocoagulation.

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Faster SD-OCT system launched by Haag-Streit UK

Haag-Streit has announced the launch of a new spectral domain optical coherence tomography (SD-OCT) system, iVue80 OCT, in the UK. The device can take 80,000 A-scans per second and is three times faster than the original iVue model, according to the company, and provides new scan options and functions, along with a wider field-of-view.

The product provides retina, glaucoma and anterior segment scanning, and quantifies the thickness of the retina, nerve fibre layer (RNFL), ganglion cell complex (GCC) and the cornea. It is also designed to track change and predict trends in RNFL and GCC thickness, as well as measure angles to aid in disease diagnoses.

The company added that it is easy-to-use and suitable for all clinical practices and features a “streamlined interface and familiar slit lamp-style design”. Real-time en-face imaging displays a 12 x 9 mm view of the retina during acquisition, to assist the operator in scanning the desired location.

The firm added: “The optional addition of the iCam12 allows the user to upgrade to the iFusion80, combining the advanced capabilities of iVue80 with the high-quality imaging from iCam12 on a single, integrated, versatile platform.”

Norlase receives CE Mark approval for green laser system

Norlase has announced that it has been granted the European CE Mark for its all-in-one portable green laser and indirect ophthalmoscope, Lion.

The system is designed to be used in any location, enabling physicians flexibility as to where and when they treat their patients. According to the company, further features of the system include: reduced risk of fibre breakage and repairs due to lack of fibre tether; enhanced visualisation during treatment and diagnosis due to clear optics; rechargeable battery providing more than a day of continuous use; parameter settings operable through an intuitive user interface on a wireless tablet; and optional voice control providing touchless parameter adjustment during treatment.

The approval in Europe follows the October 2020 510(k) market clearance of Lion by the United States Food and Drug Administration and recent announcements of strategic global distribution partnerships to expand the family of green laser systems into new markets.

Roclanda approval gives glaucoma patients new combination option

The European Commission (EC) has granted a marketing authorisation for Aerie Pharmaceuticals’ fixed-dose combination of netarsudil and latanoprost (Roclanda) in all 27 countries of the EU, plus Iceland, Norway and Liechtenstein.

The ophthalmic solution is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.

The approval was based on recently reported interim top-line data from the Mercury 3 trial, which demonstrated that the product was efficacious and non-inferior to bimatoprost/timolol (Ganfort, Allergan). It follows the positive scientific opinion recommending approval of the drug’s marketing authorisation application from the European Medicine Agency’s Committee for Medicinal Products for Human Use the company received in November 2020.

Aerie stated that it is currently preparing for pricing discussions in Germany. Roclanda was approved by the United States Food and Drug Administration in March 2019 under the trade name Rocklatan for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

The company noted that since the EC decision was received after the end of the Brexit transition period, it will complete a further administrative step in order to obtain a license in the United Kingdom. No re-evaluation of clinical data by the UK Medicines and Healthcare Products Regulatory Agency is expected.
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