Myopia Dystopia

Are future generations doomed to an ever-worsening spiral of refractive error?

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* DMO-diabetic macular oedema; AMD-age-related macular degeneration; RVO-retinal vein occlusion.
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Clearly not. You’re reading this... But that’s not to say there isn’t room for some exciting digital publishing, as proved by The Ophthalmologist iPad app. Here, we take you on a whistle-stop tour of the navigation features.
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One of the most striking aspects of ophthalmology has been the intensity of manufacturers’ stated commitment to innovation. I see that message on the signage on almost all of the company booths at the big congresses, and it’s present in discussions at symposia and at meetings. It’s refreshing. But is it completely convincing?

“Innovation” is difficult to define precisely, but it has a noble, grand feel to it. As such, it’s a marketer’s dream. In my view, a lot of what is being termed innovation in ophthalmology would be more accurately described as incremental improvements to existing technology. For example, the FDA is adding better-trained staff and now offers fast-track assessments of new drugs and devices; this sounds like a practical improvement to me, but not an innovation — as it is sometimes presented as being. Similarly, innovations “in the cataract workflow” and “in titanium-handled instruments” are likely to be welcome developments, but they sound more like improvements than innovations.

This is not meant to be disparaging; in fact, the opposite. Improvements can be made by all of us, safely and (relatively) cheaply. And the combination of incremental improvements from multiple sources can amount to an innovation. Many problems are suited to such approaches. Think, for example, of the 75 percent of adult patients do not comply with their prescribed therapeutic regimens, including the 57 percent who admit that they forget to take their medications altogether. It’s going to take multiple incremental improvements to get patients taking the correct dosage of the correct medicine at the correct time; and what an impact it will have once we’re there!

Of course, there have been numerous “proper” innovations in ophthalmology over the past couple of decades, such as the revolutions in cataract, refractive and vitreo retinal surgery, and the transformation of the outcomes of patients with wet AMD. These developments have all been built on a single-minded focus on a novel solution, first by an individual and then from a team or a dedicated small company. This approach to innovation is a high-investment, high-risk pursuit, as a glance at the stem cell article on page 35 illustrates. Today it’s especially tricky, as the number of venture capital funds investing in health care is just one-third of what it was pre-2008. Hopefully the nadir has been reached and things will start to improve — as ophthalmologists are going to need two or three revolutions in the next decade to keep pace with demand.

My request: a focus on improvements to match that on innovation.

Richard Gallagher
Editorial Director
Marianne Shahsuvaryan
As an ophthalmologist, Marianne sees 15-20 patients each day; as a surgeon, she performs three operations per week. “Combining medical therapy and surgery is a privilege and gives me great satisfaction,” says the Professor of Ophthalmology at the Department of Ophthalmology at Yerevan State Medical University, in Yerevan, Armenia. “The most challenging thing about it all is to combine it all and do it all the best way.” Still, she also finds time for an eclectic range of hobbies which, she reveals, include knitting and billiards.
Read Marianne’s insights on treating macular edema following retinal vein occlusion on page 27.

Sebastian Waldstein
Having trained in Innsbruck, Oxford and Philadelphia, Sebastian is now the Laboratory Coordinator at the Christian Doppler Laboratory of Ophthalmic Image Analysis at the Vienna Reading Center, Department of Ophthalmology, Medical University of Vienna, Austria. There, his main research focus is optical coherence tomography image analysis. Outside of the hospital, Sebastian enjoys honing his classical piano and cooking skills.
He looks at predicting patient outcomes following anti-VEGF treatment on page 26.

Kristine Morrill
Kristine is a founding partner of medeuronet, a Strasbourg, France-based company. Medeuronet has a mission to accelerate time to market, ensure successful launches and drive profitable sales growth for innovative, start-up medical device companies. In addition, she works with physicians on developing effective practice marketing strategies. Outside of work, Kris loves to travel around France sampling and collecting fine wines and improving her gastronomic skills.
Kristine’s recipe for do-it-yourself market research can be found on page 40.

Irv Arons
Irv Arons’ Journal (irvaronsjournal.blogspot.com/) is a well-read blog that reports on new drugs and devices for the treatment of retinal diseases, including age-related macular degeneration (AMD). Until his retirement, Irv was a consultant to the ophthalmic and medical laser industries, working for management consultants Arthur D. Little for 25 years and running his own company, Spectrum Consulting, for 11 years.
In this issue, Irv presents an infographic overview of the stem cell clinical trials for ophthalmic conditions, see page 36.
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Blindingly Obvious Progress

Analysis of a rich long-term epidemiological dataset reveals that interventions have significantly reduced the probability of open-angle glaucoma-related blindness

The past fifty years have seen significant changes in the practice of ophthalmology. New diagnostic tools, pharmacological interventions, and surgical techniques have all been developed, and clinical trial and post-marketing surveillance data have almost always shown these to be of benefit to patients. However, patients only receive interventions if screening catches them or they present themselves to a physician, and drugs only work if patients take them as directed. Regimen non-compliance can strip the efficacy from even the most effective therapies.

So, have the advances of the last half-century percolated sufficiently through the health care system to make a difference at the population level? That question has been answered with a resounding “yes” in a recently-published analysis of long-term trends in glaucoma-related blindness (1).

The Olmsted County Study (OCS) data used was originally designed to follow the incidence of cardiovascular events, and was subsequently expanded to cover other disorders. The database has almost complete local medical history coverage of patients presenting to Mayo Clinic hospitals in the Olmsted County region of Minnesota, dating back for over six decades. Mehrdad Malihi, an ophthalmologist at the Mayo Clinic, Rochester, MN, and his colleagues analyzed OCS medical records in order to determine the historical incidence of open-angle glaucoma (OAG) diagnoses over two OCS time periods: 1965 to 1980 and 1981 to 2000.

Compared with the earlier period, the probability of glaucoma leading to blindness in at least one eye in the later period fell by almost one-half (see Figure 1). Between 1965 and 1980, the probability of OAG-related blindness was 25.8 percent; this dropped to 13.5 percent in the period 1981 to 2000 – and the difference was highly significant (p=0.01).

Progression to blindness also slowed significantly. The incidence of blindness within 10 years of first glaucoma diagnosis was reduced from 8.7 per 100,000 for patients in the LBJ-Nixon-Carter era, to 5.5 per 100,000 for patients diagnosed under the Reagan-Bush-Clinton administrations (p=0.02). As for many other diseases, older age was a significant risk factor for blindness (p<0.001), although gender was not.

This study demonstrates that the interventions made in timolol era worked (timolol was first approved for use in the US for glaucoma treatment in 1978).

Russell Young, Chairman of the International Glaucoma Association, in commenting on how the trend
might continue, observed that, “The combination of improved surgery and more convenient and effective eye drops may lead to further reductions in these figures in the future. However, these results are still highly dependent on the patient’s commitment to using their drops daily, which continues to be a significant issue. Thankfully, with patient commitment, this means the vast majority of patients with glaucoma can look forward to a decent quality of life for the rest of their days.”

MH

References

Figure 1. The probability of open-angle glaucoma (OAG)-related blindness has nearly halved between the period between 1965–1980, and 1981–2000.

The Pill and Glaucoma

Two studies have found a link between long-term usage of contraceptive pills and glaucoma

In 2011, Harvard Medical School researchers (1) reported that the use of oral contraceptives for five years or longer carried a 25 percent increased risk of primary open angle glaucoma (POAG). Now, a second study has provided supporting data: in a poster at the American Association for Ophthalmology conference (2), Wang et al. described a doubling in the prevalence of POAG among women who took oral contraceptives for three years or longer. The latest study used data from the US National Health and Nutrition Examination Survey (NHANES) to track self-declared glaucoma.

Future longitudinal studies and double blinded clinical trials are needed to detect any causative effect of longer term oral contraceptive use on the risk of glaucoma, the authors cautioned. In the meantime, suggests author Shan Lin of the University of San Francisco, “long-term oral contraceptive users who higher risk of glaucoma, such as women with a family history of glaucoma and those of African ethnicity, may consider being screened for glaucoma.”

While the studies provide no information on the causation of POAG, the link with estrogen will surely spark interest. Giving estrogen to menopausal animals helps prevent glaucoma. “Estrogen receptors are present on retinal ganglion cells,” notes Lin, “and the hormone is thought to have a protective effect.”

RG

References
**Smart(phone) Ophthalmoscopy**

An iPhone, an app, and a 20 D lens, along with a bit of practice, will get you fundus photographs in a pinch

If you think that taking images of the retina requires an ophthalmology clinic decked out in expensive instrumentation – a condensing lens and coaxial light source, a dedicated image acquisition device, all linked to a computer – think again. The rise of smartphones that can shoot high-definition video, take even higher-resolution still images and provide a constant light source from a LED flash, means that everything but the specialized optics can be accomplished with a high-end iPhone or equivalent.

These recent capabilities haven’t escaped the attention of medical diagnostic equipment manufacturers. One, Welch Allyn, lets you pair their €540 PanOptic Ophthalmoscope with an iPhone 4 or 4S with a professional-looking €65 adaptor and its associated free app (Figure 1a). Image acquisition, storage, and distribution are all performed on the smartphone – increasing convenience and cutting costs (the total purchase price excluding the iPhone is only €605).

Now, three Boston-based ophthalmologists have lowered the bar even further. Luis Haddock, David Kim and Shizo Mukai of the Massachusetts Eye and Ear Infirmary have come up with a solution that is cheaper and more portable (1). It involves holding a €20, 20 D lens in front of the eye, and using the iPhone to video the images of the lens (Figure 1b–d).

When this has been tried before, results were unsatisfactory, primarily because the in-built Apple iPhone Camera app was poor. Apple’s app did not to allow users to adjust focus or contrast whilst filming, leading to blurry images that were full of glare. Luis, David and Kim’s solution is simple: buy a better camera app. They chose FiLMiC Pro, which currently retails for €2.99 on the Apple iPhone App Store. It enables focus and exposure adjustments during filming. The results are great – both with and without Koeppe lens use, and the group have been able to capture excellent, high-quality fundus images in children under anesthesia and in awake adults.

“Our technique provides a simpler and higher-quality method to more consistently produce excellent images of a patient’s fundus,” said Shizuo Mukai, explaining that “this technique has been extremely helpful for us in the Emergency Department setting, in in-patient consultations, and during examinations under anesthesia, as it provides a cheaper and portable option for high-quality fundus-image acquisition for documentation and consultation”.

Looking to justify the purchase of the latest smartphone? Upgrading your iPhone is likely to improve the camera in the device – and with it, the quality of your ophthalmoscopy. **MH**

**Reference**

Are you ready

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Do Something, Diabetics!

The American Academy of Ophthalmology urge patients with diabetes to take some simple steps to prevent vision loss. The most important: visit your ophthalmologist

In general medicine, diabetes mellitus appears to be a risk factor for almost everything, including cardiovascular disease, renal failure, neoplasms and neuropathies. Diabetes is a massive healthcare issue in the US: 25.8 million Americans are diabetic. In ophthalmology, it’s a major risk factor for the development of cataracts, glaucoma and diabetic retinopathy, and it’s the leading cause of new blindness of people aged 20 to 74 years in the USA – diabetic retinopathy alone currently afflicts 7.7 million US citizens.

Understandably, the American Academy of Ophthalmology (AAO) is urging patients with diabetes to take action to preserve their vision. They recommend that patients with diabetes should do the following:

- Get a comprehensive dilated eye examination from their ophthalmologist once a year,
- Maintain close-to-normal blood glucose levels
- Maintain healthy blood pressure and cholesterol levels
- Quit smoking
- Exercise regularly

The first point is the most important for retaining vision. Ophthalmologists are no strangers to diabetes, making the first diagnosis of the disease in almost half of all cases. In performing fundus imaging, eye care specialists can spot the early stages of diabetes-related damage to the retinal vasculature, commonly before any other symptoms of diabetes are seen. And it’s the power of this humble imaging technique that makes tracking the progression of diabetes-related ocular diseases easy, allowing timely interventions to save sight... but only if patients present to the clinic for assessment. John Kitchens, a retina specialist and AAO clinical spokesperson, remarked that, “Far too frequently patients with diabetes come to me when it’s too late. If only they had acted sooner and had a simple dilated eye exam each year, we could have intervened and saved their vision.” MH
Big Pharma Loves Ophtho Even More

Yet more ophthalmology acquisitions and licensing deals were announced this month...

As patents expire and pipelines dwindle, the pharmaceutical industry has looked at where the future medical needs are, and has identified ophthalmology as a market that’s both growing and lucrative. We’ve already covered the big mergers, acquisitions and partnerships announced this year in the September issue (top.txp.to/0113/203) but another two have recently been announced.

InnoCore Pharmaceuticals has revealed that it has signed an exclusive license and collaboration agreement with Allergan. The companies are currently working together on utilizing InnoCore’s long-acting drug delivery platforms for the delivery of Allergan’s ophthalmic drugs. Smarter drug delivery mechanisms have already given a new lease of life to older drugs, particularly corticosteroids, as demonstrated with Alimera’s Iluvien and Allergan’s own Ozurdex.

The overlap between ophthalmology – principally cataract and refractive surgery – and aesthetic procedures has been becoming greater, and some of the technologies that underlie them are similar. This might explain why the Frankfurt-based Merz Pharma Group, a pharmaceutical company with no prior presence in ophthalmology (but that does market a dermal filler product), has announced their acquisition of Anteis SA, a Swiss biotechnology company that has wide portfolio of injectable, transformable biopolymers for use primarily in surgical ophthalmic and aesthetic procedures. MH

Gazing into the MYRROR

Bayer and Regeneron have presented the phase III trial data for aflibercept treatment of myopic choroidal neovascularization

The latest data from the MYRROR trial indicate that there may soon be a new treatment option in town for myopic choroidal neovascularization (mCNV).

As previously reported in the evaluation of aflibercept versus sham treatment for CNV, aflibercept-receiving patients experienced a mean improvement in best-corrected visual acuity (BCVA) at week 24 of 12.1 letters from baseline, compared to a loss of two letters in those receiving sham injections (p<0.0001). What’s new is that the vision gains with aflibercept seen at week 24 were maintained until week 48 – despite patients receiving the drug almost exclusively within the first quarter of the study (a median of two aflibercept injections in weeks 0–12, and a median of zero injections thereafter).

“Early and effective treatment options are urgently needed for patients with mCNV to avoid permanent vision loss,” said Bayer HealthCare’s Chief Medical Officer, Kemal Malik. “These data show the disease may be successfully managed with an acute treatment regimen in the majority of subjects; however, it is still critical that treatment be administered early in the onset of the disease for maximum benefit to the patient.”

Notably, Bayer intends to submit its first application for regulatory approval for the treatment of mCNV in Asia before the end of 2013 – a region (as detailed in our feature article (on page 16) that has a particularly high incidence of both myopia and mCNV. If successful, aflibercept may help slow or even halt the progression of a widespread disease that, left untreated, causes blindness within a decade. MH
Myopia Dystopia

Five questions that must be answered on the causes and consequences of near-sightedness

By Richard Gallagher

If you are not nearsighted yourself, someone close to you will be: there is nothing more commonplace. Compensated for with a pair of spectacles or contact lenses it is, at worst, a mild inconvenience to most of us.

Why then is there a spreading unease across the world – culminating in near-panic in certain East Asian countries – over myopia? The answer is that this most homey of medical conditions is transforming rather quickly into an irascible monster. Its prevalence is through the ceiling. A recent survey in South Korea revealed the almost surreal fact that essentially all 19 year-old males there are myopic. Their military has compulsory conscription at that age, and 96.5% of conscripts are myopes.

And it can be much more than a mild inconvenience. High myopia, usually defined as a spherical equivalent >6.00 diopters, is said to affect around 2 percent of the population in the United States and Europe – and 21.6 percent of those Korean conscripts. High myopia is a major cause of legal blindness due to increased risk for premature cataracts, glaucoma, retinal detachment and macular degeneration. As Ian Flitcroft of the Mater Hospital in Dublin, Ireland puts it, “Three diopters of myopia is worse for your eyes than 20 cigarettes a day is for your heart.”

Now, the scary part. We have no clear understanding of the mechanism by which myopia develops, which means we can do absolutely nothing to prevent it from occurring, and once it starts we have precious little idea about how to contain it.

This article poses five questions concerning the myopian dystopia that is enveloping us and looks at science and medicine’s present day best answers. The questions are:

1. What are the current and likely future impacts of myopia on health and the economy?
2. What is the mechanism by which myopia develops?
3. What factors contribute to susceptibility to myopia, and how do they do so?
4. What are the current and potential treatments for myopia?
5. How do we move towards prevention of myopia?

How thoroughly we can answer these questions, and how quickly we can implement potential solutions, will determine the impact that myopia will have on the current and future generations. The one certain thing right now is that this is not your father’s near-sightedness.

Question 1. What are the current and likely future impacts of myopia on health and the economy?

The reach of myopia is well illustrated in adolescents (Figure 1). Following well-documented increases in prevalence over the last three to four decades, currently 25 to 50 percent of adolescents in the West and between 60 and 100 percent in East Asia are myopic. The burden extends well beyond the period of transition to adulthood, of course, and back-of-the-envelope calculations suggest that there are 200 million myopes in the world today; by 2020, there may be 900 million.

The prevalence in young adults results from a gradual increase in cases per year throughout childhood. Myopia often becomes apparent in school-age children, although the problem may have its roots even earlier in life. Indeed, the prevalence of myopia in Singapore Chinese children aged 6 to 72 months stands at 11 percent.

Rates vary dramatically with ethnicity and with location, providing clues to the genetic and environmental factors that underlie the epidemic. Chinese children are more likely to be myopic than any other ethnic group, while the prevalence in Asian children generally is higher than in European children.

There is also a distinct division between urban and rural areas. Population studies of paired groups with similar genetic backgrounds in India, Nepal and China, for example, consistently demonstrate a lower prevalence of myopia in children from rural locations.

The most serious concern is the rising numbers of patients with high myopia. This is a feature across the world but is most pronounced in East Asia, where a number of studies have reported prevalence exceeding 20 percent; in the West,
the figure is in the low single digits. High myopia especially involves the macula. Potential complications include choroidal neovascularization, myopic chorioretinal atrophy, myopic macular retinoschisis, myopic macular holes, lacquer cracks and posterior staphyloma. The optic nerve may also be affected, causing myopic conus and myopic optic neuropathy. And a final problem is that the results of refractive surgery are less predictable. This alarming menu illustrates the need for concerted action on the part of public health organizations everywhere.  

In looking at the economic impact, the spotlight must first be shone on developing countries. “Avoidable distance vision impairment,” caused by problems that are readily addressed with spectacles and contact lenses in other parts of the world, has been estimated to cost $202 billion per annum by The International Agency for the Prevention of Blindness (IAPB). But the economic cost is dwarfed by the humanitarian toll of uncorrected refractive errors. The problem could be eliminated, according to IAPB, by an investment of $28 billion to establish the required eye care services. To promote this solution, IAPB proposes to integrate eye care into the United Nation’s post-2015 Millennium Development Goals. It is a logical fit, given that the Millennium Goals are geared to improving economic, social and health outcomes.  

How about the developed world? A survey in the United States estimated that in 1990 the price of correcting vision impairment owing to refractive error was between $3.9 billion and $7.2 billion. This figure was based on the direct costs of providing spectacles to everyone over the age of 12 who need refractive correction to achieve good distance vision. While this is a big number, it is dwarfed by the heavyweights of healthcare, the chronic diseases: for example, spending on dementias including Alzheimer’s disease topped $200 billion in 2012, while diabetes cost $245 billion and heart disease and stroke combined accounted for $312 billion.  

Given a doubling in the number of myopes since the study was published, plus the fact that no costs beyond the provision of eyeglasses were included, it is not hard to imagine that the annual cost to the US of refractive errors runs to several tens of billions. (As a whole, eye and vision disorders cost about $140 billion in 2012). And these costs will continue to climb steeply if solutions are not forthcoming.  

**Question 2. What is the mechanism by which myopia develops?**

Despite a century of interest in refractive development, the etiology of myopia is still not fully understood. Now, with
the prevalence skyrocketing, the search for answers is more urgent than ever.

What is known is that myopia results when an eye is too long for its optical power or optically too powerful for its axial length. The components of the optical system, such as axial length, refracting power of the cornea and depth of the anterior chamber, must remain in sync as the eye grows to ensure that objects are brought into sharp focus. The hypothesized mechanism by which this is brought about is called emmetropization, a term derived from the Greek emmetros, meaning “well-proportioned” or “fitting”. Identifying aspects of the visual experience that might aid, or hinder, the process of emmetropization provides clues as to why myopia develops. Several factors have been identified; the mechanism du jour is that outdoor light exposure helps maintain emmetropia. Spending too much time indoors, and not enough time outdoors promotes myopia.

There are a couple of mechanistic explanations for this indoor/outdoor light phenomenon. These explanations are not mutually exclusive. One is the huge disparity in the level of light exposure. Outside, light level readings are in the range of 50-100,000 lux; indoors, values are less than 1,000 lux, and mostly closer to 500. Increased exposure to sunlight promotes dopamine neurotransmission in the retina; in animal models, dopamine signaling is associated with an inhibition of axial elongation. Thus, a child exposed to a sufficiency of outdoor light is less likely to develop myopia than if he or she spends most of the time indoors.

Another possible mechanism involves peripheral vision. An outdoor vista, such as that experienced at the ocean or in the countryside provides dioptric continuity throughout the visual field: both central and peripheral vision are clear, unblurred. This state may help maintain symmetry of the eyeball, and promote emmetropia. Indoors, dioptric stimuli vary widely across the visual field. Central vision may be focused on a television screen or words on a page, but a wide range of light sources and objects at different distances means that the peripheral retina is likely to be defocused. Studies in animal models indicate that this kind of optically-imposed defocus impacts upon central refractive development: when the periphery of the eye is defocused, refractive errors are more likely to occur. Hence, the child spending his or her time indoors is more inclined to be myopic.

Increased understanding of the factors that influence refractive parameters and how these interact should lead to more effective treatments to slow myopia progression or to prevent its onset.

**Question 3. What factors contribute to susceptibility to myopia?**

Nature or nurture? There is clearly a mix of genetic and environmental components involved in the development of myopia, but the contribution of each, and the ingredients that make up that contribution, are still being teased out.

Back in 2005, a meta-analysis of some 300 papers downplayed the role of hereditary factors. It noted distinct variations in prevalence between genetically similar cohorts in different environments: for instance, the high prevalence of myopic Indians in Singapore (70 percent of 18-year-old men), while in India itself the rate was roughly 10 percent. The simplest explanation of such findings is that a massive environmental effect is swamping the genetic influence.

So, was mother right when she said, “Don’t stare at the television too long or your eyes will go square”? No. Despite the folklore of “screens damaging eyes,” which has been passed down the generations in the form of watching TV, playing video games, working with personal computers, to today’s use of smartphones, their impact appears to be minimal. What Mother failed to identify is the crystal-clear relationship between education (and socio-economic status) and myopia prevalence in children. “Education” likely means “more reading,” supporting the idea that “nearwork” is a significant risk factor in myopia. Additionally or alternatively, increased indoor activity means less outdoor activity. As noted above, a strong body of evidence links outdoor activities, such as sports (though not indoor sports) and the amount/duration of sunlight exposure, to reduced risk of myopia in children. Thus, for “environmental factors,” read “lifestyle”; an important distinction when comparing myopia incidence on a global scale.

Environmental factors alone cannot, however, explain why so many individuals within a single family present with myopia; there must be a substantial role for genes. Altogether, an extraordinary 68 genes across all chromosomes have been associated with refractive error, including 20-some recent additions from the international Consortium for Refraction and Myopia (CREAM) and the company 23andMe, who corroborated each other’s findings.

Interestingly, no significant genetic differences between Europeans and Asians were discovered. The bad news is that many of the genes have very slight (though additive) effects, ruling out a simple solution. The rather better news is that they can be mapped onto functional pathways, giving pointers on how to improve our basic understanding and, by extension, our ability to treat this perplexing condition. The pathways
include neurotransmission, vitamin A (retinol) metabolism, eye development and remodeling of the extracellular matrix.

Rapid progress is being made on the environmental component too. Randomized clinical trials are underway to more precisely pin down the impact of sunlight, bright light, and/or outdoor exposure; some of these studies use wearable light sensors in place of questionnaires to capture data more rigorously.

The ultimate goal will be to integrate the two streams of information, pinpointing unfavorable combinations of genetic predisposition and environmental factors that are particularly risky for the development of myopia. At that point, improved therapeutic options may come into focus.

**Question 4. What are the current and potential treatments for myopia?**

Spectacles, contact lenses and intraocular lenses bring the image closer to the retina, helping to render a sharp, focused image. For patients with low, non-progressing myopia (-3.00 diopters or less), that’s great. But for those with mid or high myopia, and especially for children with progressing myopia, strategies that reduce the rate of progression are highly desirable.

Here’s a selection of effective approaches:

**Behavioral interventions**
A meta-analysis of studies that looked at the effect of increased outdoor time on children’s risk of myopia (2) concluded that each additional hour spent outside per week reduces the odds of myopia by two percent. There are several potential (and non-exclusive) explanations for this, including the aforementioned increased exposure to sunlight. For example, pupils are more constricted outdoors than indoors, which increases the depth of focus and reduces blur, slowing eye growth. Another theory points to an assumed reduction in nearwork given that more time is spent outdoors, while a further suggestions is that physical activity itself prevents myopia.

**Pharmacological interventions**
Pharmacotherapy with muscarinic receptor antagonists like atropine and pirenzepine has been evaluated, initially because accommodation appears to play a role in the progression of myopia.

The use of 1% atropine is effective in slowing childhood myopia progression. However, the decision to administer drugs to children over an extended period must always be approached with care. Atropine’s side effects include blurred vision, increased light sensitivity and constantly dilated pupils, making it commercially impractical. More recently, 0.01% atropine has been evaluated; it also slows the development of myopia, but with less cycloplegia and better tolerability. A further bonus is that there are lower levels of rebound progression on the termination of treatment. Pirenzepine has also been evaluated in a randomized placebo-controlled trial: relative to placebo, a 2% gel formulation administered twice-daily almost halved the rate of myopia progression in children.

**Optical interventions**
Orthokeratology – or overnight vision correction – uses specially designed rigid gas-permeable contact lenses that reshape the cornea, reducing the extent of myopia and correcting vision in the short-term for adults. In children, there is an additional benefit: the rate at which the eye’s axial length elongates is reduced, slowing the development of myopia. A recent study showed that progression of myopia in children wearing orthokeratology contacts was significantly less than a control group over a two-year evaluation. Orthokeratology is said to be effective up to -4.00 diopters.

Bifocal soft contact lenses (BSCLs) with a distance center may provide a similar effect as corneal reshaping. One comparison of BSCLs against single-vision soft contact lenses (SVSCLs) in children showed significant slowing of both myopic and axial length progression. Soft multifocal lenses appear to have similar effects in children; in a recent clinical trial, the rate of myopia progression was halved, and axial elongation reduce by one third compared with SVSCLs.

**Surgical interventions**
For adults (though not for children save in a small number of special cases) there are several surgical techniques that can be employed. They have no effect on the underlying posterior segment pathology: existing axial eye elongations are not reversed, the vitreous chamber continues to lengthen unabated, and the risk of posterior segment sequelae remains.

Laser procedures have been used to treat nearsightedness in
around 50 million adults over the past 20 years. The cornea is reshaped by removing a small amount of eye tissue using a highly focused laser beam. Recent developments include the cutting and extraction of a lenticule, a disc-shaped piece of corneal tissue.

Phakic intraocular lenses (IOLs) are gaining currency for moderate and high myopes. The implanted lenses have the advantage of being removable, and their effects reversible.

**Question 5. How do we move towards prevention of myopia?**

Since axial lengthening of the eye isn’t reversible, the only way to prevent myopia is to stop it developing in the first place. That means intervention in children, as soon as signs of nearsightedness appear – which could be in infancy.

At present, no single strategy can prevent childhood myopia. However, shrewd combinations of current tactics, based on novel clinical algorithms and public health initiatives, are having a marked impact. Perhaps the best example is from the Singapore Health Promotion Board which for many years has rigorously assessed vision in schoolchildren and spent millions of dollars on national myopia prevention programs to educate the public.

Regular screening of children’s vision – something that’s already practiced in many urbanized parts of the world (where the issue is most acute) – is an essential part of any strategy. This must include not only school visits by optometrists but assessment of younger, pre-school children and even babies. Myopia develops most rapidly in the initial couple of years – and it’s during this period that interventions can make the biggest difference. The emergence of Myopia Control Clinics, such as the one at the University of California Berkeley (www.caleyecare.org/myopia-control-clinic), will help ensure efficient delivery of treatment to myopic children and young adults. “In addition to providing conventional glasses to correct myopia,” their website explains, “doctors will be offering treatments for controlling the condition’s progression, ranging from special contact lenses to prescription eye drops.”

Refractive interventions in children – from orthokeratology to soft bifocal contact lenses – certainly have a place in a myopia control strategy. Such approaches work for many children, but the extent to which they prevent myopia progression is unpredictable. It’s an area that is continually evolving, and more effective contact lenses are likely to be introduced periodically.

Other components of a fully integrated strategy are more easily stated than implemented. For example, having children spend more than two hours a day outdoors does seem to prevent – or at least substantially retard – the development of myopia. However, today, the average American kid spends under 30 minutes a week in unstructured outdoor play, while devoting seven hours indoors in front of electronic screens. In other countries, parental obsession with academic attainment is an equally large obstacle to outdoor play. It is going to take a concerted and creative marketing campaign to nudge families into changing their lifestyles. Again, Singapore offers an example of one way forward. The program there was initiated around 15 years ago, built around the message to take breaks from nearwork. Since the importance of outdoor exposure became known, some eight years ago, programs directed at parents, schools and schoolchildren themselves have made outdoor activities an essential part of the day. In the past five years, the rates of myopia have almost stabilized, contrasting dramatically with the rapid growth in the previous three decades.

Notably lacking from most current myopia prevention strategies are pharmaceutical interventions. While atropine and pirenzepine are effective, their anticholinergic side effects have precluded prescription (though hopes for 0.01% atropine remain high). The search for new agents that have a better therapeutic index with fewer side effects is underway and may benefit from the growing body of genetic information. Who would bet against such remedies being found? The size of the market provides great incentive to industry.

The “database state,” where healthcare, governmental and commercial records are all maintained electronically, means that almost population-wide assessments of public health and the impacts of interventions can be made rapidly, and far more easily than what was previously the case.

The highly myopic eye is a vulnerable eye. Reversing the prevalence of myopia – across the entire globe but especially in East Asia – presents a monumental social, scientific, medical and political challenge. The lack of a “magic bullet” and of a sophisticated knowledge of the mechanism by which myopia develops complicates matters. But the stakes are high. There is a real prospect of everyone being nearsighted in certain locations, including huge numbers of high myopes who will have significant vision-related problems. A solution seems to be emerging but it will require great discipline and deep pockets to implement. Hopefully, innovations will continue to bring that solution within more certain reach.

**References**


JETREA® (ocriplasmin) Intravitreal (IVT) Injection
The first pharmacologic treatment for vitreomacular traction (VMT) in adults, including when associated with macular hole of diameter ≤400 μm

- In clinical trials, a single injection of JETREA® (ocriplasmin) Intravitreal (IVT) Injection was shown to resolve VMT and to help close macular hole as compared to placebo
- 26.5% of patients treated with JETREA® achieved resolution of VMT at Day 28 (vs 10.1% with placebo)
- 40.6% of patients treated with JETREA® with full-thickness macular hole (associated with VMT) achieved closure of macular hole of diameter ≤400 μm at Day 28 (vs 10.6% with placebo)

Predicting outcomes of anti-VEGF treatment

Anti-VEGF therapy is the standard of care for patients with neovascular age-related macular degeneration. Patients in clinical trials have great outcomes; often in real life outcomes aren’t as good, raising the question: why?

Loss of Traction

Vitrectomy is far from pleasant, recovery can be slow and uncomfortable, and it was the only option to treat vitreomacular traction or macular hole. Ocriplasmin may be about to change that...

Treating Macular Edema Following RVO

Intravitreal steroid implants and anti-VEGF therapies have transformed the treatment macular edema following retinal vein occlusion. There is, however, still room for improvement…
Loss of Traction

Focal adhesion of the vitreous to the macula carries the risk of traction-mediated damage and often requires surgical intervention. Now, a single injection of an enzyme called ocriplasmin — which cuts the ties between the vitreous and macula — will spare some from an unpleasant surgical procedure.

By Mark Hillen

Vitrectomy is the standard surgical intervention for the treatment of vitreomacular traction (VMT) and macular hole (MH) — completely removing the vitreous often works well. The procedure itself isn’t particularly pleasant and it carries a risk of complications. In addition, the majority of phakic patients who undergo vitrectomy will require cataract surgery within the next couple of years – so if the lens isn’t replaced during the procedure, it will in all likelihood have to be later. If the vitrectomy has been performed to treat MH, a gas bubble is often placed in the vitreous cavity to encourage the hole to close. To keep the bubble in place, many patients have to lie face down for fifty minutes of each hour for up to — and sometimes over — a week. This is obviously uncomfortable and greatly inconvenient.

As the eye ages, syneresis and synchisis (vitreous body liquefaction and collapse) commence, a process that, typically, is benign. If concurrent syneresis and weakening of vitreoretinal adhesion occur, the posterior vitreous cortex may separate from the internal limiting membrane. Eventually, this will result in posterior vitreous detachment (PVD); again, typically a benign development.

Incomplete posterior vitreous separation, however, leaves residual sites of vitreoretinal and vitreomacular adhesion (VMA). VMA is not ideal. In the early stages its influence on vision is minimal but as it progresses metamorphopsia can develop.

Tim Jackson, consultant eye surgeon at King’s College Hospital, London explains that, “A continuum exists between VMA, VMT and MH. VMA can progress into VMT, as adhesions to the retinal surface carry pulling forces — traction — that damages the retina. This can ultimately pull a hole, turning it from VMT to MH.” This damage can then lead to tractional macular edema. There is potential for irreversible vision loss, hence the surgical intervention. “If a patient presents with MH, provided it’s treatable, they will usually undergo vitrectomy,” Jackson says. However, as this intervention carries significant risks, and the recovery can be burdensome, the standard of care for VMT has been watchful waiting — delaying surgery until the disease had progressed to a point where it was severe enough for the benefits of vitrectomy outweighed the risks. With MH, the benefits already outweigh the risks, so vitrectomy is performed whenever possible — “we don’t watch and wait with macular hole,” adds Jackson.

The standard of care may be about to change. A new therapeutic option, ocriplasmin (Jetrea®, Bayer HealthCare/Thrombogenics), is now available that might avoid the need for surgery in some cases. Ocriplasmin is a recombinant truncated form of human plasmin, a serine protease that’s best known for dissolving fibrin-rich blood clots. It retains plasmin’s proteolytic activity; when injected intravitreally, it degrades protein components of the vitreous body and the vitreo-retinal interface (VRI), namely laminin, fibronectin and collagen. Thus, it dissolves the protein matrix responsible for VMA and VMT, liquefying the vitreous and, in so doing, ending the disease state (Figure 1). Furthermore, the drug raises the concept of treating VMA before it progresses to VMT — in theory, improving outcomes and minimizing risks.

Fibronectin, laminin and collagen are present throughout the eye, raising the potential for adverse events. Ocriplasmin is a new product, so post-launch safety and efficacy information is sparse. The phase III trial (known as MIVI TRUST) that formed the basis of ocriplasmin’s regulatory approvals provided a good sense of the safety and efficacy of ocriplasmin, and post-marketing studies are said to be consistent with trial data.

Clinical trial data

MIVI TRUST comprised two multicenter, randomized, double-blinded trials (1). It compared the efficacy and safety of ocriplasmin with placebo injections for the treatment of symptomatic VMA. Resolution of VMA, as determined by optical coherence tomography (OCT), was the primary efficacy assessment. By this measure, ocriplasmin was significantly better than placebo injection; 26.5 percent of patients in the ocriplasmin group achieved VMA resolution — with release being achieved within 1 week for 72 percent of these patients. The placebo injection group

At a Glance

- VMA can be benign, but its seriousness increases as it progresses to VMT
- The standard of care treatment, vitrectomy, is both risky and unpleasant, needing weeks of recovery
- Ocriplasmin is an intravitreally-administered protease that dissolves the protein matrix responsible for vitreomacular adhesion and traction
- Not all patients will benefit, but those who do are spared vitrectomy
fared less well; VMA resolved in only 10.1 percent of patients. Similarly, ocriplasmin use was associated with full-thickness MH closure in 40.6 percent of patients at day 28, compared with 10.6 percent of patients who received the placebo injection \( p<0.001 \). Gains in visual acuity of ≥3 lines occurred in 12.3 percent of patients in the ocriplasmin group compared with 6.3 percent of the placebo injection group \( p=0.02 \). Many patients with VMA have only mild to moderate impairment of visual acuity (VA), making a 3-line VA gain hard to achieve.

The rate of ocular adverse events was higher in patients treated with ocriplasmin than in the control group (68.4 percent versus 53.5 percent, \( p=0.001 \)), although ocriplasmin was associated with a reduced risk of serious adverse events, such as MH and retinal detachment.

The data showed that across the whole trial population, just over one in four patients who received ocriplasmin experienced resolution of VMA, raising the question: why did some people benefit and others not? Part of the reason is adhesion size, with smaller adhesions more likely to be effectively treated.

A MIVI TRUST subgroup analysis showed that VMA resolution occurred with ocriplasmin only 10.3 percent of the time if the adhesion size was greater than 1500 μm, but occurred 33.6 percent of the time if the adhesion size was 1500 μm or smaller (2). A similar story was seen with MH size: if the hole was 250 μm or less, ocriplasmin treatment resulted in resolution 58.3 percent of the time; if it was larger, resolution occurred in 24.8 percent of cases. That knowledge of who will do well is valuable; according to Jackson, “That makes a big difference. The headline figure of 26.5 percent is fine, but if we can hit a 50 percent success rate by selecting the right patients, then ocriplasmin injections become an even more attractive intervention.”

So ocriplasmin – like vitrectomy – isn’t for everyone. It appears that two patient populations will benefit most. The first is those with VMT that hasn’t yet progressed enough to justify surgery, as the risks of vitrectomy outweigh the benefits… but the benefit-risk balance of ocriplasmin favors its use. The second is patients with VMT or VMT and MH who require surgery – as if ocriplasmin works, it avoids vitrectomy.

Vitrectomy success rates are unaltered by prior ocriplasmin use. Virtually all patients can go home after an ocriplasmin injection, and the MIVI TRUST data shows that if the injection is successful, it will be obvious within a week (and by 28 days at the longest). If ocriplasmin therapy doesn’t succeed, little is lost apart from the cost of ocriplasmin and the clinic visit. Jackson summarizes it thus: “If it works, great, you’ve saved yourself an operation, and if it doesn’t, you’ve not lost anything by trying”.

Although post-marketing clinical experience is currently sparse, it looks like ocriplasmin will also save healthcare systems and society money. “You save money by avoiding vitrectomy – but the cost of vitrectomy is not just the surgical cost, it’s also the cost to the patient in terms of recovery time, lost work due to blurred vision after surgery, and the subsequent cataract surgery for those who need it,” Jackson explains. “You also have a quicker visual recovery than you’d see with vitrectomy.”

Future prospects

Looking to the future, one compound that is midway through its clinical trial program is Allegro Ophthalmics’ ALG-1001. The drug is a small-molecule, synthetic oligopeptide integrin receptor antagonist that has recently received FDA clearance to commence phase II trials for the treatment of symptomatic VMT and wet age-related macular degeneration.

Figure 1. Ocriplasmin lysing protein components of the vitreous body and the vitreo-retinal interface, specifically laminin, fibronectin and collagen, liquefying the vitreous and releasing vitreomacular adhesion/ traction.
Predicting Anti-VEGF Treatment Outcomes

Anti-VEGF therapy is the standard of care for neovascular age-related macular degeneration. Patients in clinical trials have certain outcomes; why might they be different in real life?

By Sebastian Waldstein

At a Glance

- Internet research by patients may lead them to have unreasonable expectations of treatment efficacy
- Not all patients are equal; concomitant diseases can affect their treatment outcomes and options
- Understanding what factors make a difference means you can manage patient expectations, and optimise the therapeutic regimens prescribed

“Doctor Google” provides unlimited information on almost any disease to patients and their families, so it comes as no surprise when patients, having cherry-picked from the web, have unrealistic expectations of how successful their treatment will be. Partly, this is due to marketing messages that are scattered across the web, but even publications containing well-designed clinical trial manuscripts can mislead avid patient Googlers. This is not because of any nefarious practices on the part of the researchers or the journal; rather, it’s often a failure of patients to notice the finer details of the patient population (inclusion and exclusion criteria, proportions of different patient types) within each trial.

Many patients may have poorer outcomes than the clinical trial cohort because they differ from the trial population – primarily by disease morphology. One particular misunderstanding is that some patients have the concept of average; clinical trials show average or median result data, and that’s what they expect to experience. However, every practicing ophthalmologist will see a vast range of treatment responses – few patients have an “average” response. Clinical trial data are not easily transferrable to the individual patient. This is important not just for managing patient expectations, but for the physician too. It is often crucial for determining the best therapeutic options, in terms of drug choice, dose and regimen, so that the patient achieves the best possible outcomes.

The AMD experience

In patients with neovascular age-related macular degeneration (AMD) there can be large disparities between the drug dosing regimens employed in the clinical trials (mostly fixed monthly or bimonthly administration) and real-world settings (where as-needed or treat-and-extend is mostly used). Timely management of patient expectations is necessary to ensure that they are satisfied with treatment outcomes. Moreover, adequate and realistic guidance for the choice of dosing regimen is essential for the treating ophthalmologist. Today, we are seeing analyses of individual lesion subgroups from within large-scale clinical trial populations beginning to be published. This is useful as it offers insight into the disease-specific mechanisms that can alter patient outcomes, and allows personalized choice of treatment as well as prognosis and counseling of patients.
prior to the procedure.

Our research group led by Ursula Schmidt-Erfurth has performed in-depth subgroup analyses of multiple multicenter trials. These trials enrolled more than 1500 patients, who received standard therapeutic regimens of European Medicines Agency (EMA)-approved drugs, using various dosing regimens. What follows is a brief overview of our findings (see Figure 1).

**Intraretinal cysts**

Intraretinal cysts (IRCs) at the time of presentation are a strongly negative predictor of visual function. They presage a mean reduction in visual acuity (VA) of about 1 line, and a below-average improvement in vision during therapy. Having said that, once anti-VEGF treatment has been initiated, over one half of all patients experience IRC resolution.

IRCs provide a classic example of the consequences of exudate entering neurosensory tissue, a sign of advanced disease. Choroidal neovascularization (CNV) typically develops below the retinal pigment epithelium (RPE) and subsequently invades the retina (Type I CNV). In patients who present with neovascular AMD and IRC irreversible damage has already happened, and anti-VEGF therapy will be substantially less effective than if it were administered at an earlier point during the progression of the disease.

**Pigment epithelial detachment**

VA gains with anti-VEGF therapy will be lower in patients presenting with pigment epithelial detachment (PED) than patients without. The reduction in VA gain is only half as bad as with IRC, but these effects are additive; a patient presenting with both will have particularly poor outcomes. Clinical trial data have shown that patients with PED and otherwise dry retina are particularly at risk of significant VA loss if placed on a reactive, discontinuous anti-VEGF treatment regimen.

Fibrovascular PED harbors the CNV lesions in the majority of patients (that is, Type I “occult” CNV). Intensive anti-VEGF treatment results in pronounced PED flattening. However, if the retina is otherwise dry and treatment is discontinued, the CNV lesion will reanimate and grow underneath the RPE as VEGF suppression declines—in other words the PED starts to expand again. However, PEDs usually develop rather slowly and it is not regarded as an indication for treatment in most clinical environments. Treatment is re-administered only if the RPE is breached and intra- and/or subretinal exudation occurs. In these cases, it is likely to be too late to prevent irreversible photoreceptor loss and neurosensory damage.

**Subretinal fluid**

The presence of subretinal fluid (SRF) is of limited prognostic value; patients with neovascular AMD and SRF alone typically exhibit excellent visual outcomes, with vision gains in the range of two or more lines, when treated with anti-VEGF therapy.

**Vitreomacular adhesion**

The status of the vitreomacular interface is one of the most difficult pathologies to interpret because vitreous configurations, which encompasses vitreomacular adhesion (VMA) and posterior vitreous detachment (PVD) may change over time.
time and one may develop one into the other (see “Loss of Traction,” page 24).

Generally, the prognosis of patients with neovascular AMD and PVD, which is roughly two in every three patients with AMD, is similar, no matter which dosing regimens are used. It’s a different story with VMA. Patients with any form of VMA have greatly different outcomes depending on whether fixed monthly (good outcomes) or discontinuous/quarterly anti-VEGF (poor outcomes) dosing regimens are used. These patients should rarely, and only reluctantly, be switched to an as-needed or a treat-and-evaluate regimen in clinical practice (1).

General recommendations for ophthalmologists

The following steps should be followed for prognosis of AMD after treatment with anti-VEGF agents and managing patient expectations:

• Ascertain the state of the retina using optical coherence tomography (OCT) imaging, to determine the pathology or pathologies.
• For patients who present with IRC – and particularly those with IRC still present after three doses of anti-VEGF – advise that their vision gains are likely to be substantially lower compared with other patients.
• If a decision is made to employ a discontinuous treatment regimen for patients with PED and/or VMA, follow up monthly with OCT-based assessment of their disease status.
• If a growing PED in a patient with neovascular AMD is observed, this should prompt retreatment, even if the retina is otherwise dry.

It is important to manage both your own and your patients’ expectations when undertaking a course of anti-VEGF therapy – partly for the patients’ own peace of mind, and partly for your own reputation and treatment planning. To achieve these twin goals, determine the best therapeutic regimen before commencing treatment and give your patients an honest assessment of what their vision is likely be after anti-VEGF therapy.

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References

Treating Macular Edema Following RVO

Intravitreal steroid implants and anti-VEGF therapies have transformed the treatment of macular edema following retinal vein occlusion. There is, however, still room for improvement...

By Marianne L. Shabsheerayan

Retinal vein occlusion (RVO) affects 16 million people worldwide, usually the middle-aged or older. It is caused by thrombosis, the clogging of the retinal veins, which may occur in the four branch veins that drain blood from the capillaries of the retina – branch vein retinal occlusion (BVRO; Figure 1) – or in the central retinal vein formed by the combination of the four branch veins – central retinal vein occlusion (CRVO). Occlusion may be either ischemic or non-ischemic in nature, with the former having considerably poorer prognosis. Left untreated (or if treatment fails), persistent RVO can lead to macular edema (ME), the swelling or thickening of the macula caused by leaking blood vessels. ME is the primary cause of RVO-related blindness, neovascularization, and retinal detachment. Longer durations of RVO-related ME are associated with poorer outcomes.

Until fairly recently, there was little that could be done for a patient that developed ME after an RVO episode. The standard care was grid laser photocoagulation for ME in non-ischemic BRVO (1) and observation of macular edema in the case of CRVO (2). Today, it’s a different story: implantable and injectable drug-
based options are available, notably a dexamethasone intravitreal implant (Allergan’s Ozurdex) and inhibitors of vascular endothelial growth factor (VEGF), including an antibody (Genentech’s Lucentis [ranibizumab]) and a fusion protein (Bayer/Regeneron’s Eylea [aflibercept]). Recently, pars plana vitrectomy has also been shown to be effective for improving macular thickness, volume, and sensitivity in patients with macular edema secondary to ischemic CRVO (3).

Here I will cover the current state of the art, issues arising, and possible solutions to them.

**Current Therapeutics**

Dexamethasone is a potent, water-soluble corticosteroid with many therapeutic indications, mostly anti-inflammatory. As the sclerotic membrane of the eye hinders the egress of intravitreally injected drugs, this means that the steroids introduced into the eye act mainly on the eye – to great effect. The intravitreal dexamethasone-containing implant (Ozurdex; Figure 2), which was approved by the US Food and Drug Administration (FDA) in 2009, comprises micronized dexamethasone within a biodegradable copolymer of lactic and glycolic acids. The implant is inserted into the eye through a small pars plana puncture using a customized applicator system and, once in situ, it releases dexamethasone over a period of months.

Phase III clinical trials (4) demonstrated efficacy and safety of the dexamethasone intravitreal implant for the treatment of patients with ME due to CRVO or BRVO. Ozurdex is most likely to improve vision in patients who have experienced RVO-related ME of a relatively short duration. While treatment initiated up to three months after the onset of disease is still somewhat efficacious, further delay diminishes impact. The implant also appears to be effective in vitrectomized eyes with ME secondary to CRVO and in those with chronic edema from BRVO. However, early retreatment after 16 weeks (instead of 24 weeks) was required in 50% of CRVO and BRVO cases in order to maintain the improved functional and anatomical results.

Analyses of the initial and follow-on studies have suggested that the original treatment protocols could have been better (5–6%). It is not clear that Ozurdex implants remained effective for six months, the schedule employed in the original study, and authors of subsequent studies have suggested the following. Rejection at shorter intervals; as-needed retreatment protocols (particularly in CRVO); and combination treatment.

Anti-VEGF agents, the first of which was introduced in 2005, revolutionized the treatment of wet age-related macular degeneration (AMD). Their use in treatment of ME secondary to RVO has been more recent, but equally impactful. Tissue hypoxia due to primary vascular occlusive disease is the most common driver of VEGF synthesis; as RVO is associated with increased VEGF expression levels, the use of VEGF inhibitor drugs would, in theory, improve matters in RVO-related ME.

Ranibizumab, a monoclonal antibody fragment that binds VEGF-A, was approved by FDA in 2010 for the treatment of ME secondary to both BRVO and CRVO; European Medicines Agency (EMA) approval followed in 2011. Ranibizumab is effective over a 12-month period, but beyond this, patients with CRVO may require treatment administration more frequently than every three months, the current standard. Less frequent follow-up and fewer ranibizumab injections in the second year of treatment were associated with a decline in vision in CRVO patients, although stable vision was achieved in patients with BRVO.

Aflibercept is a protein engineered to inhibit both VEGF and a related angiogenic molecule, placental growth factor (PGF). The FDA approved aflibercept in September 2012 for the treatment of ME resulting from CRVO, and a regulatory submission has been filed with the EMA. Data from two ongoing Phase III studies of aflibercept in patients with CRVO (7–10) indicate that intravitreal injection of aflibercept improves visual acuity and central retinal thickness, eliminates progression resulting from neovascularization and is associated with a low rate of treatment-related ocular adverse events. Although efficacy starts to wane after 12 months of treatment, taken together, the results are encouraging for patients with CRVO and the longer duration of action of aflibercept in comparison with ranibizumab makes it an appealing option (11).

**Ongoing Concerns**

Each of the above therapy options has associated safety issues.
Ozurdex use can raise intraocular pressure (IOP). Clinical trial data have shown that 16 to 27 percent of Ozurdex-implanted subjects developed significantly raised IOP, with some requiring therapy to manage this, including one percent of patients who needed surgical intervention (4–6). In addition, 26 percent of patients who receive two Ozurdex implants formed cataracts; the rate was five percent in control patients. Postmarketing surveillance has also revealed that dexamethasone implants can become discolored, or even cause endophthalmitis.

For ranibizumab and aflibercept a range of safety concerns have been raised. There are serious but rare (fewer than one in a thousand injections) ocular adverse events relating to the intravitreal injection procedure, including endophthalmitis, rhegmatogenous retinal detachments, and iatrogenic traumatic cataracts. Side effects associated with the active agents include hemorrhage, eye pain, maculopathy, retinal exudates, increased intraocular pressure, optic disc vascular disorder, and retinal vascular disorder. Chronic use brings the risk of adverse events developing over a longer time-period, and tolerance and tachyphylaxis start to become issues (12). There is also a risk of cardiovascular side effects – atrial fibrillation and peripheral edema occur in up to 5 and 6 percent of patients receiving ranibizumab, respectively – and the potential for arterial thromboembolic events (ATEs), such as stroke, myocardial infarction, and vascular death. Finally, renal failure (up to 7 percent) and chronic renal failure (up to 6 percent) have also been reported.

There are economic and cost-effectiveness considerations to throw into the mix too. The introduction of anti-VEGF therapy for RVO has led to substantial increases in clinical workload – both in terms of carrying out the implant procedures and in ensuring that patients have adequate follow-up appointments. The introduction of anti-VEGF treatments for CRVO could further exacerbate pressure on clinic capacity in the hospital eye service.

Future directions

One way to reduce clinical workload and the impact on resources is to determine a patient’s best treatment regimen based upon their disease characteristics. Vision loss, visual acuity (VA) instability, or other signs of an active disease state could be used as markers for when an individual requires treatment, rather than using fixed dosing schedules. This should match patients to their best therapeutic option, reduce over- and under-treatment, minimize unnecessary drug exposure and optimize the benefit-risk profile of these interventions.

Today, there is also a focus on improving the efficacy and safety of these therapies by, for example, optimizing retinal bioavailability, which is hampered by the blood-retina barrier. Nanoparticle formulations combined with new delivery systems promise increased drug penetration at the target site, reduced dose required to achieve therapeutic effects, prolonged effects and reductions in toxicity and systemic side-effects (13).

Integrin peptides are a new treatment option currently under investigation. Integrins are transmembrane receptors involved in cell adhesion, signal transduction, cell proliferation, shape and motility; in the eye, multiple integrins are involved with angiogenesis. Allegro Ophthalmics have a small peptide (ALG-1001) that inhibits multiple integrin receptor sites, that is currently undergoing clinical evaluation for vascular eye diseases, including macular edema due to retinal vein occlusion. In preclinical studies, ALG-1001 has shown promise as a monotherapy and when combined with ranibizumab. Further studies are ongoing (14).

Dexamethasone intravitreal implants and anti-VEGF angiogenesis inhibitors have dramatically improved the management of ME following retinal vein occlusion. Yet unmet needs remain: drugs that are less invasive in administration, more effective over longer periods, and have better safety profiles are required. I am confident that we will have them, and soon. 

Marianne L. Shahsuvaryan is Professor of Ophthalmology at Yerevan State Medical University, Yerevan, Armenia.

References
The Lore of Levofloxacin

Experts from the four corners of the world shared their experiences at a recent symposium* on the prevention and treatment of ocular infections. Their unanimous view is that levofloxacin continues to be a logical and attractive choice for topical prevention of endophthalmitis following cataract surgery, and for the treatment of bacterial keratitis.

*The Oftaquix Symposium was held in Amsterdam on 7 October 2013.

Richard Abbott
Chair of the event, Abbott is the Thomas W. Boyden Endowed Chair in Health Sciences and is Clinical Professor of Ophthalmology at the Beckman Vision Center, University of California, San Francisco, USA. He is former President of the American Academy of Ophthalmologists.

The speakers were:

Alexander Doga
Professor of Ophthalmology and Deputy Director, Scientific and Clinical work at the Svyatoslav Fyodorov Eye Microsurgery State Institution in Moscow, Russia, and Vice President, Russian Society of Ophthalmology.

Tat Keong Chan
Senior Consultant, Refractive Surgery and Cataract/Comprehensive Ophthalmology Services, and Chairman of the Infection Control Committee at the Singapore National Eye Centre, Singapore. Chan is an international council member of the International Society of Refractive Surgery and a past Executive Committee member of the Singapore Society of Ophthalmology.

Roberto Bellucci
Chief of the Ophthalmic Unit, Hospital and University of Verona, Italy, and Professor of Anterior Segment Surgery at the University of Verona and at the University of Lugano, Switzerland. Bellucci is President-Elect of the European Society of Cataract and Refractive Surgeons.
The symposium addressed the use of levofloxacin in laser refractive surgery; in perioperative prophylaxis for cataract surgery, including the combination of topical treatment with intracameral cefuroxime; and in the treatment of bacterial keratitis.

Infection Prevention in Photorefractive Surgery
Alexander Doga described the collective experience of the dozen branches of the Svyatoslav Fyodorov Eye Microsurgery State Institution. Since 1989, more than 150,000 photorefractive surgery procedures have been performed, including photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK) and Femto LASIK surgery. Doga characterized the antibacterial protocols used as “straightforward”, noting that in cataract surgery, the institution follows ESCRS’s 2007 Guidelines on Prevention, Investigation and Management of Post-Operative Endophthalmitis (1). For photorefractive surgery this protocol is simplified to: preoperatively, levofloxacin eye drops applied at 1 hour and at 30 minutes before the operation along with 5% povidone-iodine application; postoperatively, levofloxacin is applied four times per day for five to seven days, and preservative-free artificial tears for a period of up to three months.

Turning to infectious keratitis (inflammation of the cornea), a potentially devastating complication of refractive surgery, Doga distinguished between early (1-2 weeks after surgery) and late (3-4 weeks or later) events. The former, which are often caused by gram-positive bacteria, are characterized clinically by multifocal infiltrates, deep corneal opacity, anterior chamber aqueous reactions; they require paralimbal injection. The latter tend to involve atypical mycobacteria or fungi, with clinical manifestations that include elevated lesions with margins that have a feathery appearance; they are treated with ciliary injections.

Reviewing the literature on infectious complications following refractive surgery, Doga noted that 12 percent of cases involve Gram-negative bacteria. This includes Pseudomonas aeruginosa, one of the most serious causes of postoperative infectious keratitis following PRK and LASIK. Prophylaxis with levofloxacin guards against both Gram-positive and Gram-negative bacteria, and Doga explained that a single drop of this antibiotic is sufficient to maintain, for six hours, concentrations at the ocular surface that inhibit most microorganisms. A further advantage of levofloxacin is that it displays low toxicity for ocular tissues in a range of in vitro studies. Doga concluded that topical treatment with levofloxacin is sufficient for safe and effective photorefractive surgery procedures.

Targeting Zero Infection in Cataract Surgery
Roberto Bellucci commented that as cataract surgery now provides postoperative vision that is better than the pre-cataract vision, more patients require early surgery. This trend, he argued, is limited by a number of factors, including intraoperative complications, postoperative infection and postoperative inflammation. Of these, endophthalmitis, which can be a devastating complication, is the major issue. Most cases of endophthalmitis, inflammation of the internal coats of the eye, are caused by bacteria already present in the conjunctiva of the patient so it is essential to make the area as sterile as possible before surgery. Bellucci explained that he treats both eyes of the patient, “to reduce the possibility that bacteria will be transferred by eye-rubbing.”

Although up to 94 percent of cases of infection are caused by Gram-positive bacteria, it is the Gram-negative cases that are the most troubling. “Bacteria, especially gram-negative bacteria, can destroy everything inside the eye within hours,” said Tat Keong Chan in his opening remarks, “You have to aim for zero infections.” He noted that the spectrum of bacteria implicated in serious ocular infections varies geographically, so there are no uniform practices: eye drops, intracameral and subconjunctival antibiotics, and various combinations of these, are all in use at different locations worldwide. At the Singapore National Eye Centre, where more than 12,000 cataract operations are performed annually, the incidence of endophthalmitis stands at just 0.05 percent over the last 22 years. This rate is similar to the lowest reported rates in the world.

Bellucci described certain risk factors for postoperative endophthalmitis, including capsular rupture, old age and being male. Chan mentioned three further risk factors following cataract surgery that were identified in an ESCRS multicenter study (2), namely the failure to inject intracameral cefuroxime; the use of clear corneal incisions without sutures; and the use of silicone intraocular lenses. Despite the evidence for the first of these factors, there remains no consensus on intracameral cefuroxime use in many countries (3). Obstacles to the widespread use of intracameral cefuroxime include legal barriers and lack of availability of the commercial preparation. Indeed, Chan’s center does not use intracameral antibiotics, while Bellucci’s does. In contrast, topical povidone-iodine has been universally adopted and postoperative topical antibiotics such as levofloxacin are used extensively.

Intracameral antibiotics alone are certainly not sufficient for prophylaxis, Chan stated, as they provide very high levels of the antibiotic in the anterior chamber for only a matter of hours, while the risk of contamination from leaking clear corneal incisions may persist for days. Sutureless, poorly constructed clear
Corneal incisions are especially prone to leak, and corneal incisions generally are truly vulnerable: the force generated by rubbing the eye for 2 to 3 seconds induces sufficient force to cause leakage from two-thirds of sutureless incisions and from a quarter of sutured incisions (4).

Other than the divergence in intracameral antibiotic use, the regimen for prophylaxis practiced by the two experts is remarkably similar, with levofloxacin playing a central role. The procedure includes:

- Topical levofloxacin every four hours one or two days pre-op, and every 15 minutes starting one hour before surgery
- Meticulous draping (complete isolation of lashes)
- Topical povidone-iodine: 10% on periorcular skin; 5% on ocular surface, for at least three minutes
- Limbal or corneal incision under topical anesthesia
- Routine stromal hydration of incision
- Ensure hermetic “watertight” seal of incision at the end of surgery
- Continued topical levofloxacin and topical steroids starting immediately at the end of surgery, every two hours on the day of surgery and every four hours thereafter
- Topical levofloxacin administered intensively (not less than QID dosage) and stopped abruptly with no tapering
- Telephone call to all patients to ensure strict compliance of the dosing schedule

Looking at recent developments in cataract surgery, Bellucci expressed the hope that microincision cataract surgery (MICS) and femto lasers will reduce complications, that disposable instruments will reduce toxic anterior segment syndrome (TASS) and that preloaded IOLs will reduce contamination. However, both speakers underlined the key role of levofloxacin in prevention of endophthalmitis. It should be used, they say, because it very effectively kills bacteria on the surface of the eye, kills bacteria that get inside the eye, and is effective and safe.

**Therapy of Bacterial Keratitis**

Half a million cases of bacterial keratitis are reported annually worldwide. If untreated, these would result in progressive tissue destruction, corneal perforation and extension to adjacent structures, causing loss of vision. Indeed, in excess of one million people worldwide suffer from decreased vision as a result of complications of the condition. Richard Abbott’s presentation took as its starting point the clinical guidelines for bacterial keratitis that have been developed by the American Academy of Ophthalmology and the International Council of Ophthalmology.

These guidelines state that bacterial keratitis should be treated with topical antibiotic drops using a broad-spectrum agent. Initially, very high doses and frequency are used (a loading dose), with treatment modified after 48 hours, depending on the response and cultures. Topical steroids can be introduced in due course to control scar formation in the cornea. Abbott pointed out that the most effective antibiotic is one which balances high, sustained levels at the site of infection with minimal associated toxicity. A broad-spectrum antibiotic is required until etiology is confirmed and, he noted, fluoroquinolones are the only antibiotic class that is recommended for all causes of bacterial keratitis. Of these, the most effective later-generation fluoroquinolone antibiotic is levofloxacin: it kills a wide range of bacterial targets rapidly; it readily penetrates the cornea, where it reaches high concentration, and it has minimal tissue toxicity.

Bacterial resistance is a major concern and Abbott summarized actions aimed at preventing its development. These include:

- Using high concentrations
- Using a bactericidal drug
- Using a high dosing frequency
- Using a maximum time course (of two weeks)
- Never tapering the dose
- Limiting the duration of the dose

**Conclusion**

The panel agreed that levofloxacin is as close to the ideal antibiotic as you can get for the conditions discussed in the symposium. Levofloxacin has the following qualities:

- Effective against a wide range of ocular pathogens
- Low level of bacterial resistance
- Excellent tissue-penetration
- Excellent solubility profile
- Rapid onset of action
- Low toxicity
- Compatible with other drugs

**References**


With Diabetic Macular Edema (DME) increasing in prevalence, a major question facing ophthalmologists today is how to manage insufficiently responsive, long-term cases. There are treatment options, but when should a patient be considered unresponsive? What diagnostic criteria provide useful categorization of the patient population? What readouts of responsiveness to therapy are most reliable?

To help stimulate discussion of best practice within the community, The Ophthalmologist is organizing a competition for Case Study reports that address DME management.

The five leading entries will be published as part of a feature in the print edition The Ophthalmologist, and the authors will be invited to attend the 2014 Annual Meeting of the American Academy of Ophthalmology, to be held in Chicago, October 18–21, as our guests. Flights, accommodation and delegate fees will be covered.

The ten best submissions will be published online at: www.theophthalmologist.com.

Case reports should include relevant positive and negative findings from history, examination and investigation, and should include clinical photographs.

The closing date for submission is March 31, 2014.

Full information on how to submit your entry can be found at www.theophthalmologist.com/travel-award

Submit your Case Study today and help the ophthalmology community to identify and manage patients with DME.

Enter online at: theophthalmologist.com/travel-award

Sponsorship for these travel awards, including funding for travel, accommodation, and registration, is kindly provided by Alimera Sciences Limited.
Stem cells are unspecialized cells that can, given the appropriate stimulation, give rise to differentiated cells of various kinds. Therapies based on stem cell treatments are considered to have tremendous potential in medicine. Ocular diseases are at the forefront of stem cell medicine, in part because the eye is a relatively simple, accessible and easily-monitored organ and also because stem cells in the eye are protected from potentially devastating immune attack by the organ’s immune privilege status.

Despite decades of research, stem cell therapies have yet to be licensed for ophthalmic use. Where does the field currently stand? On the following pages we present a graphical representation of all currently ongoing clinical trials in this therapeutic area.
**Stem cell type**

- Autologous bone marrow derived mesenchymal stem cells - 3%
- Autologous bone marrow derived stem cells - 17%
- Adult Stem Cells (HotCNS-Sc derived from purified human neural stem cells) - 3%
- Allogenic or autologous limbal stem cells - 3%
- Autologous blood stem cells - 3%
- Autologous cultured limbal stem cells - 3%
- Autologous hematopoietic stem cells - 3%
- Autologous mucosal stem cells - 3%
- Encapsulated RPE (CNTF) - 17%
- RPE-derivated human-derived embryonic stem cells - 18%
- RPE sheets derived from human embryonic stem cells - 3%
- Oral mucosa epithelial stem cells - 9%
- Unknown - 15%

**Disease states in which stem cells are being trialled**

- Retinitis Pigmentosa/ Dry AMD - 3%
- Cornea - 6%
- Devic’s Disease - 3%
- Eye Injury - 3%
- Glaucoma - 3%
- Idiopathic Juxtafoveal Telangiectasia - 3%
- Limbal Stem Cell Deficiency - 6%
- Macular Telangiectasia - 3%
- Multiple - 3%
- Neuromyelitis Optica - 6%
- Ocular Surface Disease - 3%
- Optic nerve - 3%
- Retinoblastoma - 3%

Academic - 43%
Biotech - 33%
Government - 14%
Private Practice - 5%
Pharma/Academic collaboration - 5%
The various clinical trials covered here are being conducted in the United States, South America, Europe, Iran, India, South Korea, Taiwan, Japan and China. To date, more than 300 patients worldwide have received stem cell/cell therapy treatments.

Positive results have been reported in both Stargardt’s disease and dry AMD trials (1). Transplanted human embryonic stem cell (hESC)-derived retinal pigment epithelial cells have resulted in engraftment and visual acuity gains (2); one dry AMD patient improved from 20/400 vision to 20/40 vision (3), which is good enough to obtain a driver’s license in most US states!

Stephen Rose, Chief Research Officer at The Foundation Fighting Blindness, wrote, “Of course, it would be nice if all the parts of our bodies, including our retinas, came with extended warranties so you could just swap them out when they go bad. But now that I think about it, that’s what stem cells might do for us someday” (4).

References
3. ACT Confirms Clinical Trial Participant Showed Improvement in Vision from 20/400 to 20/40 Following Treatment, Press Release, May 16, 2013.
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DIY Market Research
Market research requires that you examine three things: customers, the competition and the environment. We tell you how to do it yourself.

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Does the Patient Know Who You Are?
Patients need to know what their ophthalmologist actually ‘does’, and what to expect when they are referred.
DIY Market Research

Market research tells you what you’re doing well and what needs to improve, enabling you to direct your efforts to the right places. You can do it yourself, successfully: here’s how.

By Kristine A. Morrill

When marketing people talk marketing, we use phrases like ‘marketing mix’ and the ‘7 Ps’ to describe the activities and tools that we’ll use to market a business, device, drug, and so on.

The phrase ‘marketing mix’ pretty much does what it says – it’s the mix of tools that you use to market your practice, while the 7Ps (Figure 1) refer to the tools, customers, and methods by which we carry out marketing. Of these 7Ps, four – Place, Price, People and Physical evidence – require a good understanding of the market environment and dynamics of where you operate. Of course, you can speculate and base your understanding on your own opinion, but this approach can lead to mistakes and waste if you target your marketing budget in the wrong direction.

To get the right information and answers, what you need is market research. This gives the information that you need about your market by delving into the behaviors and buying habits of the consumer segments that you’ve decided to target. Ultimately, market research can save you money by helping you avoid costly marketing mistakes, but often it’s the last item on the list when it comes to prioritizing spending. While it’s best to seek the help of an expert in this area, there are things that you and your team can do to inform your marketing efforts.

Types of market research

Market research requires that you examine three things: customers (in this case, patients and would-be patients), the competition and the environment. Activities can be divided into two categories: primary, which includes focus groups, patient surveys and open-practice evenings; and secondary, which comprises information and data gathered by others, such as newspapers, Google and local publications.

Customer information

A patient (customer) satisfaction survey is the most valuable, and easiest, marketing tool that you can put in place. Unfortunately, it is also the most expensive.

For current patients, the survey can take the form of a paper questionnaire handed out at the end of a visit – ideally with a stamped, addressed envelope that makes it easy for the patient to get it back to you. This may, however, result in the patient walking out with the survey and never returning it. To avoid this, consider implementing tablet computers with the survey on it and handing it to patients at the end of their examination; just remember to tell them to return it with their paperwork as they check out.

Alternatively, consider developing an online survey that will allow you to e-mail a link to the patient following his or her visit. Online survey tools such as Survey Monkey (www.surveymonkey.com) and Survey Gizmo (www.surveygizmo.com) are easy to use, inexpensive, and have the added bonus that the software will analyze the results for you.

Tips for the survey:

• Keep it short – 10 questions is a reasonable rule-of-thumb and use a mix of closed (that is, Yes/No) and open questions. An example of an open question is, “What could we do to improve the waiting area?”

• As a matter of practice, every patient should receive a survey. By doing this, the survey becomes part of the routine of the patient visit.

• Analyze the results at least twice per year; quarterly is better. Once you’ve digested the results, share the information - both good and bad - with your staff.

• Take note of the feedback and make changes accordingly – don’t just stuff it in your desk drawer for later!

Former patients – those that haven’t returned to your practice in a year or more - should also be sent a survey. This can be done by either sending a paper survey mailed to a home address (complete with a stamped, addressed return envelope) or, if an e-mail address is available, by sending a link to an online survey. Take the opportunity to remind them about the importance of regular eye exams and try to understand why they haven’t been back.

For prospective patients, that is, those that have enquired through your website or a phone call but haven’t followed through, follow a similar approach to the former patients: send an email to discuss the next steps towards surgery or to determine if they have gone elsewhere for a procedure.
Other options for patient market research include focus groups, which can be done on an informal basis by inviting a handful of patients for breakfast or lunch for a discussion about their views on your practice. Alternatively, host a practice open evening, inviting current patients to hear an update on your practice along with a chance to give their views over a glass of wine or champagne. If you go this route, make certain to give plenty of notice and send reminders once they’ve accepted your invitation.

The competition
To understand what your competitors are offering and charging for services, my favorite method is to do some ‘secret shopping.’ Here, you enlist the help of a trusted friend or family member to call or even visit a practice to ask about procedures and pricing. You can find out a great deal about the philosophy of a practice by how the phone is answered and how much knowledge the person answering the phone has.

Have your ‘secret shopper’ take note of:

- How quickly the phone was answered
- Whether the person was knowledgeable about the different services offered
- If they disclose pricing for the services
- Whether they request contact information from the caller
- If contact details were requested, did they receive a follow-up email with additional information?

Ideally, you should secret shop at least five practices in your area to benchmark what is being offered and how these practices perform when it comes to a prospective patient. Once done, it’s also a good idea to enlist some friends to secret shop your practice in order to see how your team stacks up – the results may surprise you!

The environment
For market research on your environment – the economic, social and political forces that shape a business – most of the information can be gleaned via your local chamber of commerce/business organizations, web searches, as well as local publications. Here, it’s important to take note of things like hiring trends and local economic data. Membership of organizations like your local chamber of commerce or trade association can serve as great networking opportunities that provide insight into how local business owners perceive the environment.

Marketing is crucial when it comes to gaining the attention of prospective consumers/patients. You can develop new products or services confident that they are in demand, and turn those prospective consumers into satisfied patients. What drives successful marketing is having a strong knowledge base – this is where market research is critical.

Market research doesn’t have to be expensive or complex. Simple tools and some homework will provide the answers that you need to create a winning marketing strategy.

Kristine Morrill is a founding partner of medeعونнт, a Strasbourg-based medical device strategic marketing company. This article is based on a presentation given at the ESCRS 2013 Congress Practice Development Workshop.
Does the Patient Know Who You Are?

Clearing up “image discrepancies” maximizes health care delivery and can save time and money.

By Sophia Ktori

“My clients get to see me at their allotted appointment time, so why have I been kept waiting for an hour?” was the opening statement made by one banking executive to his ophthalmologist on entering her office recently. It’s probably a greeting that many clinicians will recognise as an opening gambit: busy ophthalmology practices with full appointment lists are normal, running late is par for the course. It may seem obvious that every patient should be given the amount of time they need, rather than the amount of time written on the appointment list, but do patients understand why?

Perhaps it’s even more relevant to ask whether patients actually know what their ophthalmologist ‘does’, and what to expect when they are referred? The issue of job misconceptions was highlighted in a recent study (1) which found that many professionals, from architects to accountants, commonly say their clients misunderstand them and what they do, and that “image discrepancies” have a real impact on how they perform their jobs.

For an ophthalmologist, patient misconceptions might mean that you’ll have to go back to basics and explain why they’ve been kept waiting for their appointment, and this can get a consultation off to a rocky start. “Ophthalmologists can’t necessarily stick to rigid timetables,” Corbett continues. “Patients need to be treated as individuals, not time-slots, and emergencies will have to take precedence over routine appointments. This means that for many clinics, running late is a normal part of everyday practice. Patients are generally fine once they are given the reasons, but they may need a nudge to understand that an appointment at the ophthalmology clinic isn’t the same as an appointment at the bank.”

Expectations once they are in the system also vary greatly. In the UK, for example, patients may not realise that their eye surgery is free of charge. And while some individuals will put complete trust in any decisions their consultant ophthalmologist makes, others – often the more highly educated people – will expect to have every minutiae of their diagnosis, disease or condition explained, and every treatment or surgical option and potential outcome outlined to them.

Does the doctor always know best? “People living with a chronic and stable, but possibly fluctuating ophthalmic disorder may be better placed than I am to know whether their treatment needs to be modified when they are experiencing ‘down’ periods,” Corbett says. “I can monitor for side effects of treatment, assess the severity of their condition and make decisions if therapy needs to be changed because the condition is worsening, but I can’t presume that I will always know better than patients who have years of first-hand experience managing their own disorder.”

It’s a case of managing the patient, as well as each clinical diagnosis, on an individual basis to ensure they understand why they have been referred, who you are, what you can do for them and what their diagnosis and treatment options are. “The more we can explain to our patients, the more likely they are to stick to treatment programs prescribed, maximizing the chances of successful treatment, and ultimately saving time and money.”

Reference
The Ophthalmologist × Alimera

ILUVIEN® is an intravitreally-administered fluocinolone acetonide implant that, once administered, delivers therapeutic corticosteroid concentrations for a 36-month period. The National Institute for Health and Care Excellence (NICE), the organization that decides which drugs and treatments are available on the UK National Health Service (NHS), recently approved ILUVIEN® for “the treatment of vision impairment associated with chronic diabetic macular edema (DME) considered insufficiently responsive to available therapies,” (1). This means that ILUVIEN® will soon be available for use in clinical practices across the UK.

“Available therapies” include ranibizumab for patients with DME and a central foveal thickness (CFT) ≥400 μm, and laser photocoagulation for those with a CFT <400 μm. However, NICE’s approval wording does not define what either “chronic DME” or “insufficiently responsive to available therapies” actually means. To address these issues, Alimera Sciences organized an expert roundtable meeting on September 27, 2013 at the Marriott Courtyard Hotel, Hamburg, during the XIIIth EURETINA congress. This article summarizes that event.

Achieving Consensus on the Treatment of DME with ILUVIEN®

The UK body that performs health technology appraisals (NICE) has approved ILUVIEN® for the treatment of chronic DME-associated vision impairment that is considered insufficiently responsive to available therapies. Who, exactly, should receive it?

Roundtable participants

Chair: Yit Yang

Expert panel members:
Peter Addison
Frank Ahfat
Tariq Aslam
Somnath Banerjee
Mandeep Bindra
Helen Cook
Louise Downey
Haralabos Eleftheriadis

Martin Harris
Simon Horgan
Roland Ling
Luke Membrey
Arijit Mehta
Tree Richardson
Maria Teresa Sandinha
Sandy Taylor

Plus representation from Alimera Sciences & Visions4Health

Royal Wolverhampton Hospital
Moorfields Eye Hospital, London

Maidstone Hospital, Kent; Manchester Royal Eye Hospital; University Hospitals of Leicester NHS Trust; Stoke Mandeville Hospital, Aylesbury; Hull and East Yorkshire Eye Hospital; King’s College Hospital, London; The Royal Free Hospital, London; St George’s Hospital, Tooting; Royal Devon & Exeter Hospital; Birmingham & Midland Eye Centre; Croydon University Hospital; Sunderland Eye Infirmary; St Paul’s Eye Research Centre, Liverpool.

*All are UK-based Consultant Ophthalmologists/Consultant Ophthalmic Surgeons, unless indicated; †Nurse Manager/AMD Research Study Coordinator.
Defining chronic DME

The discussions were led by Professor Yit Yang, Consultant Ophthalmic Surgeon at the Royal Wolverhampton Hospital.

“To tackle chronic DME, you need to understand why NICE used that term,” he explained, “and so we go back to the Fluocinolone Acetonide in Diabetic Macular Edema (FAME) trial (sidebar) and examine why a median time period of three years was used to define chronic DME”.

“Chronic” was defined by the median DME duration among patients at enrolment into the FAME trial; this was found to be three years. Philip Ashman of Alimera Sciences noted that a conservative method was used to calculate the median duration of DME (sidebar on page 45); as one year was added to all calculated durations of DME. “Why plus one? Some patients have only the year of diagnosis recorded, not the exact date,” he explained. “So the median of three years is only according to this strict algorithm. If we pick midpoints of years, and look at the median again, it’s 1.73 years. This needs to be clear to CCG (Clinical Commissioning Group) commissioners” (Figure 2).

On the basis of the strict algorithm definition of three years for chronic DME, Yit asked: “So if you have a patient with chronic DME, they had their first laser nine months ago, their CFT is already >400 μm, and you’re about to start ranibizumab, Are you happy to have to wait three years before you can use ILUVIEN®?” The absolute consensus was no.

Tariq Aslam pointed out that the situation facing clinicians today is a “different ballgame” to 2007 when the first patients were recruited into FAME. “For that population laser therapy was three years away. Now, they may have had multiple ranibizumab injections and still shows edema. There is a clear rationale for reducing the time period from three years.” Peter Addison agreed – to general consensus – “there is no reason to use that definition of three years”, and added, “I think we need to clarify the term ‘chronic edema’ – are we thinking of the term timespan, or are we talking about anatomical change?”

To explore Peter Addison’s question, Yit reviewed the natural history of the morphology of DME. “It starts with a spongiform morphology, which later becomes cystoid,” he noted. “Can edema be termed ‘chronic’ when it is so bad that the fluid becomes extracellular – meaning that the swelling is destroying cells?” he asked, adding, “cystoid morphology is evaluable with optical coherence tomography (OCT).” This concept was well received. Simon Horgan expressed his enthusiasm for an anatomical definition of chronic DME. “It gives the capacity to cope with a change in the rate of DME. We all know that it can change at a disproportionate rate. For instance, we can have a very innocuous-looking DME, then the patient has a cataract removed, and the DME accelerates; the macula thickens, and you’re straight away into a chronic DME picture that we would recognize.” This prompted Yit to state, “So you can have a patient that you’ve just operated on, they’ve gone cystoid, but they’ve only had DME for one year,” leading him to ask the expert panel, “Are the 1.73-year and the three-year cutoffs ridiculous in terms of clinical management of the patient?” Simon Horgan said that these time limits, “made things artificial”. Tree Richardson took a more pragmatic approach: “You could just add ‘or’ to the chronic DME definition – cystoid morphology or 1.73 years,” before suggesting that 18 months be used instead of 1.73 years – for ease of calculation. She noted that although OCT confirmation of cystoid morphology was desirable, some patients may be unable to undergo OCT due to mobility or morbidity reasons. A short discussion between panel members led to agreement that clinical assessment or biomicroscopy can be used if OCT was unavailable.

Yit summarized the consensus (Figure 2):

- Waiting for three, or even 1.73 years to treat chronic DME is unacceptable
- Chronic DME should be defined primarily by its natural history, then by duration: if it is cystoid, it is chronic; if it is non-cystoid, it needs to have been present for over 18 months to be considered chronic
- Assessment should be made by OCT where available, but clinical assessment is acceptable where OCT is unavailable

Defining “insufficiently responsive”

In patients that can receive ranibizumab

“In the current DME pathway, we have patients with CFT >400 μm; patients who, according to current guidelines, we are supposed to treat with intravitreal ranibizumab,” noted Yit. “The number of ranibizumab
injections will vary from person to person, but what we don’t know: what does ‘insufficiently responsive to ranibizumab’ mean in these patients?"

To Yit’s question, “How many injections would you go for before deciding on insufficient response? When do you start looking at the response?” Roland Ling replied that, “In practice you give the patient three or four injections as a loading dose. So within four. That’s when I would do the OCT comparison with baseline CFT measurements.”

Yit posed the questions: “If OCT showed that edema was worse after the fourth ranibizumab injection than at baseline (or after earlier injections), is that ‘insufficient response’?” The panel agreed.

Yit asked the panel if they thought that using visual improvement to assess treatment response was a valid method in this patient group. The response was unanimous: “Vision is unreliable”. Nevertheless, Yit noted that he was “happy to use declining vision as a trigger to investigate whether the patient is insufficiently responsive to ranibizumab.”

Mandeep Bindra posed a question about patients that have improved with ranibizumab, but aren’t completely dry. Martin Harris advised that in these cases, “You wait until six injections – only after then you can say you have insufficient response.”

Mandeep then discussed “frequent flyers” – patients that need to continue monthly ranibizumab injections, as dropping bi-monthly injections results in vision degradation. Yit suggested, “If patients required more injections than in the DRCR.net protocol, that is, more than three in the second year of treatment, then that should also be considered ‘insufficient response’.” Arijit Mehta felt that “we should give patients the choice at that point”, which Yit acknowledged, modifying the recommendation to: “Static, but greater than three injections, in the second year; consider patient factors.”

Simon Harris made a popular observation: “Isn’t that micromanaging things?” His thoughts were that “there needs to be a bit more discretion with the treating ophthalmologist. I think we’re perfectly bang to rights

**ILUVIEN®’s UK indication is based on data from the FAME trial**

- FAME consisted of two parallel trials with identical designs that compared two ILUVIEN® doses with “best standard of care” for the treatment of DME (4)
- The trials were presented together as a merged dataset comprising data from 953 patients with CFT ≥250 μm
- The primary efficacy endpoint was the difference between the treatment and control groups in the percentage of patients whose best corrected visual acuity (BCVA) improved by ≥15 letters at month 24 compared with baseline levels
- ILUVIEN® was significantly more efficacious than the best standard of care in patients with chronic DME (Figure 1)

**Before ILUVIEN®: the 400 μm ranibizumab DME divide**

- Before 2011, the standard of care for treating DME-associated visual impairment was laser photocoagulation therapy
- In 2011, NICE approved ranibizumab for the treatment of DME-induced visual impairment – but only for patients with CFT ≥400 μm at the start of treatment (2)
- This generated two DME patient populations, those that can receive ranibizumab, and those that cannot
- The ranibizumab summary of product characteristics states that if no visual acuity improvements are seen after “the first three injections, continued treatment is not recommended” (3)
Defining “chronic DME”

Revisit the FAME trial definition of “chronic DME”
Conservative definition of “chronic edema”: 3 years
True median duration of DME in chronic group: 1.73 years
Discussion: is a 1.73- or 3-year wait fair?
Defining the onset of DME is challenging
Should clinical and anatomic considerations be included?
How can these be assessed?

Many patients in FAME had only the year of DME onset in their records. To avoid patients that had diagnosis in Jan 2012 and trial entry in Dec 2012 having a DME duration of 0 years, +1 years was added to the calculation

True median duration of DME in chronic group: 1.73 years
Discussion: is a 1.73- or 3-year wait fair?
Defining the onset of DME is challenging
Should clinical and anatomic considerations be included?
How can these be assessed?

If OCT is impractical or unavailable, use clinical assessment or biomicroscopy

Waiting for three years to treat is unacceptable.
Define chronic DME primarily by its natural history.
DME is chronic if it is:
• Cystoid
• Non-cystoid, but ≥18 months since diagnosis
Assessment:
• By OCT where available
• Clinically where OCT is unavailable

Three years is an artificial and unacceptable wait. 1.73 years is is challenging to calculate in a busy clinic – use 18 months instead

Yes. This accounts for patients with rapidly worsening disease and comprises a fair assessment of disease state. The presence of cysts confers “chronic” status

Defining “insufficiently responsive”

In patients with CFT ≥400 μm:
• When do you assess ranibizumab response?
  • Partial response assessment
  • Static response/“frequent flyers”
  • Raised IOP
In patients with CFT <400 μm:
• Assess quality of prior laser therapy
• Anatomical factors: cysts, thickening
• Declining VA

After the initial four ranibizumab injections; if edema is thicker than baseline or a previous measurement, consider this “insufficient response”

If patients need >3 injections in the second year, this is “insufficient response.” Consider patient factors and use clinical judgment regarding switching to Iluvien

Patients that experience persistently raised IOP do extremely well with trabeculectomy/trabeculoplasty

VA is an unreliable surrogate marker for the status of DME. Vision decline should definitely be used as a trigger to investigate DME status

For patients with CFT ≥400 μm, receiving ranibizumab, insufficient response is:
• Worsening or static CFT by OCT
• Partially dry DME
• After initiation ranibizumab, assess after 4–6 injections; consider Iluvien unless patient or clinician discretion says otherwise
• For patients with CFT <400 μm, insufficient response is:
• Any thickening or decrease in VA that, in the opinion of the clinician, is unlikely to respond to laser

Assess the quality of prior laser with FFA or fundus autofluorescence imaging, if available

Cyst presence or foveal thickening suggest an insufficient response to laser photoacoagulation

Figure 2. Defining “chronic DME”.

Figure 3. Defining “insufficiently responsive”.
to say: a measurable clinical response. And that can be interpreted by the treating physician." This was backed up by Louise Downey, who described patients that have achieved only partial response with ranibizumab – but who were very happy with their improvement in vision, who you would “have a hard time convincing to switch therapies”. Accordingly, Yit suggested that the pathway be: “after the four-to-six injections, convert to ILUVIEN®, unless your clinician’s discretion comes up with some reason not to switch.”

In patients that can’t receive ranibizumab

The panel then turned to what constitutes “insufficient response” in patients with CFT <400 μm. Such patients have already undergone laser photocoagulation therapy, but their CFT is too thin to receive ranibizumab. Yit asked: “What do you do? How do you define insufficiently responsive in these patients?”

Simon Horgan replied that, “The first thing I’d do is make sure they’ve had adequate laser therapy,” observing that, “Just because someone’s documented that they’ve had macular laser, it doesn’t mean that it has been done well.” He said that it was a matter of “performing fluorescein angiography and fundus imaging to assess that.” This immediately raised the question: should another laser treatment be performed? Louise Downey stated that she thought that “OCT is more important in this category, as the visual acuity response is such a slow effect,” leading Yit to summarize the following options:

1. A CFT cutoff without it being cystoid or non-cystoid. For example, a CFT >300 μm would define “insufficient response” to laser.

2. Apply at OCT/CFT cutoff.

Simon Horgan interjected: “Why does it have to be one?” which resulted in Yit changing the statement to “Cystoid, or thickening above 300 μm”. Helen Cook asked: “Why can’t you have thickening that’s not improved or is worsening, despite laser? Rather than having to put a number on it.”

This led to Yit proposing a final scenario for patients with CFT <400 μm on which consensus was finally achieved: “We have a patient who has had five lasers over the past few years; their CFT is still under 400 μm, and they still have thickened macula – we may see spongiform or cystoid thickening, and you say that they have reduced visual acuity – 6/18 or 6/12, say – purely due to edema, not cataract or anything else. In your opinion, further laser is not going to help. You eyeball that patient and you say, look, they’ve got laser scars there, they haven’t got any leaking micro-anneurysms that you can see, let’s go for that definition for an ‘insufficient response’ to laser” (Figure 3).

Conclusion

The roundtable meeting addressed some issues of substantial importance. ILUVIEN® has the potential to preserve and improve the vision in many patients with chronic DMO – patients whom NICE described as being “insufficiently responsive to available therapies”. The expert panel achieved consensus on what “chronic DMO” actually meant, by examining the clinical trial data that underpinned NICE’s decision to approve ILUVIEN® for that indication, and bringing to it their front-line clinical experience of managing these patients today, determining that anatomical – not chronological – is the best place to start when diagnosing chronic DMO.

NICE did not describe what was meant by “insufficient response to available therapies” in their approval, which meant that the interpretation of that statement might vary. The expert panel formed consensus guidance on what they believe “insufficient response” to mean, based not only on careful study of the clinical trial data that supported NICE’s approval of ranibizumab for treating DMO in patients with CFT ≥400 μm, but also based on their experience of treating patients with ranibizumab, including important patient types such as partial ranibizumab responders, and “frequent flyers.” Furthermore, for patients with chronic DMO and a CFT <400 μm, they established an algorithm for defining who these patients were, what was meant by insufficient response to laser therapy, and when ILUVIEN® should be administered.

References


During the DOC 2013 in Nürnberg/Germany the new Geuder MACH2 Double-Blade Vitreous Cutter was introduced.

For the first time, the technology of two active blades has been realized in a sterile product. Currently there are two main trends in ophthalmic-surgical technology: Cutting rates constantly getting higher respectively innovative aspiration pumps. With these two characteristics, manufacturers try to provide a fast core vitrectomy as well as a safe vitreous base shaving. With the cutting window being closed, original vitrectors cannot aspirate or cut tissue. This aspiration stop inevitably leads to a pulsation of the tissue in front of the cutting window. Due to the effect of a high cutting rate the flow at the vitreous cutter is reduced, which results in less tractions at the tissues and less pulsation. At the same time the aspiration quantity is also reduced. Other systems try to avoid this behaviour by means of new pump systems, but nevertheless, there is also no flow when the vitreous body window is closed.

With the new MACH2 Vitreous Cutter Geuder has chosen a completely different way. I am fortunate to have tested the new product during surgery. Due to its special geometry the MACH2 has a permanently open cutting window. The result is a maximum high flow for a fast core vitrectomy as well as full control near the vitreous body base, with a constant and perfectly controllable flow. This has the advantage that the surgeon doesn’t need to take influence indirectly on the cutting rate but he can control the flow directly via the bi-directional footswitch of the Megatron S4. Furthermore, due to its two blades the MACH2 provides excellent cutting quality in comparison with a one-blade vitreous cutter.

From now on, in connection with the new double-blade MACH2, the Geuder vitrectomy systems dispose of a double cutting rate. The Megatron systems offer a cutting rate of 1,600 cpm, the Megatron S3 VIP and Megatron S4 a cutting rate of 5,000 cpm. In my opinion, the new MACH2 with its particular technology might become the new standard vitreous cutter in vitrectomy.
Results indicate that safety, efficiency, predictability and postoperative visual quality are extremely high with the new AMARIS excimer laser.

Current excimer laser technology uses sophisticated algorithms and optimised tools to plan surgery and improve surgical outcomes including visual acuity and night vision. Over the past year, we have assessed the efficacy, predictability, and safety of LASIK for the correction of low to moderate myopia and astigmatism using the SCHWIND AMARIS 1050RS excimer laser. This laser has a repetition rate of 1,050 Hz and an ablation time of 1.3 seconds per diopter. Its optical system is essentially identical to the SCHWIND AMARIS 750S, and other characteristics including online pachymetry (200 Hz), Intelligent Thermal Effect Control (ITEC), Automatic Fluence Level Adjustment, and particle aspiration are identical to the 750S. In contrast, the AMARIS 1050RS provides seven-dimensional active eye tracking for the first time. This pioneering seventh dimension concerns the time factor and ensures latency-free tracking. To date, 114 eyes with a manifest refraction spherical equivalent (MRSE) from -0.75 to -7.88 D (mean, -3.13 ±1.47 D) and up to 3.50 D of astigmatism (mean, 0.84 ±0.80 D) have been treated at our center. All eyes underwent treatment targeting emmetropia with the AMARIS 1050RS’s nonwavefront-guided aspheric algorithm.

Refractive outcomes and corneal HOAs were analyzed pre- and postoperatively. At 3 months, the average MRSE was -0.12 ±0.18 D. All but one eye was within ±0.50 D of intended correction, and all but two had astigmatism of 0.50 D or less. UCVA was 20/20 or better in 96% of eyes, and no eye lost 2 or more lines of BCVA. Additionally, the total corneal HOAs root-mean-square decreased by 0.157 μm, the change in spherical aberration was not statistically significant, and vertical and horizontal coma decreased by 0.049 μm and 0.045 μm, respectively. These results confirm that an aberration-free concept can correct sphere and cylinder and preserve corneal HOAs.

*Myopia, without astigmatism, 12.5 mm vertex distance, 6 mm optical zone.
When Physics is Your Friend

Sitting Down With Jim Taylor, President and CEO of Oraya Therapeutics
Why did you move from a big to a small company?
Some might say temporary insanity. Seriously, I had been at Zeiss for eight years and felt that a change was needed at the end of 2008. It has not been the optimal period for getting funding, but I saw the potential of Oraya technology to make a tremendous difference to patients with wet age-related macular degeneration (AMD).

What are Oraya’s origins?
It was founded in 2007 with the concept of delivering radiation to the back of the eye. It’s an invented-in-house technology, with two major innovations. One is the use of low-energy X-rays, which sounds like it should have been attempted before, but wasn’t. Once you have that, physics is your friend—you can deliver the X-ray dose with a high level of precision to a very small volume of tissue. The other is the ability to control and track eye motion, which allows the therapy to be delivered accurately.

Between 2007 and 2009 the company did the feasibility work, including animal and human studies. I joined in July of 2009 to replace the founder, and since then we’ve done a randomised, sham-controlled, double-masked study across five European countries. The two-year data have been very well received and we now have initial three-year safety data, which are really encouraging. In the target population, a single session of our stereotactic radiotherapy provided equal or better vision outcomes than anti-VEGF mono-therapy and significantly reduced the injection burden. The therapy provides a significant cost benefit to payers, and helps physician take on the flood of patients from the cumulative and ongoing growth in wet AMD, as well as new patients with diabetic macular edema now treatable with anti-VEGF.

How big is the problem—and market—that you are tackling?
Take Germany; there are around 70,000 new eyes affected by wet AMD per year and approximately 400,000 patients living with the disease. Twelve centers are probably needed to provide coverage. Across Europe, the available market size is of the order of $1 billion, of which we could expect to target a 20 percent slice. The markets in Asia and North America are roughly the same, so it’s a $500-600 million annual market.

What is your background?
I went to our United States Naval Academy and drove nuclear submarines for a while. My first position in business was in the medical technology field working with the first CAT (computerized axial tomography) scanner company. Many years and several positions later I joined Carl Zeiss Ophthalmic as mentioned earlier, where I was CEO and board member for seven years.

How would you characterize your leadership style?
Find the best and brightest people that I can, make sure they know what they are talking about, identify obstacles that keep them from doing the best job possible, and provide the tools and support to overcome those obstacles.

The best lesson I ever got in leadership was the first time I walked onto a submarine as an officer—a 22 years old novice officer. The chief in charge of the divisions I was going to be responsible for said to me, “Mr Taylor, we can do this two ways. You can tell us what to do and how you want us to do it and we’ll work as hard as we can for you. Or, we can tell you what we think we ought to be doing and how we ought to be doing it, and you can help us by providing the tools and support that we need.” I thought that Plan B made a lot of sense, and I’ve used it my throughout my career.

An authoritative or ego-driven leadership style works in the short-term, and can get your picture on the cover of magazines. Ultimately, though, a serving leadership style works best for me. It’s not about having no ego or no personal ambition, it simply works better.

Does your approach change in a crisis?
Sure, there are times to go to the alternative plan: we may lack time, or I may not agree, or there are reasons that aren’t immediately apparent. If you have built up trust by showing support, when you step in and change things the staff will trust and follow you.

Thirty employees seems small for what you are trying to achieve. How are you organized?
Now, with the trial primarily done, around 40-50 percent of our resources are in technology and 25 percent in commercial. We outsource manufacturing to a partner that’s been involved right through design and development, and our first commercial system just got shipped.

At this stage, the company has successfully negotiated five out of the six big risks—the technology works, the clinical trial results are positive, the data hold up after two years, there’s been no shake-up in the marketplace to make us irrelevant (in fact, just the opposite). We can build the machine and we have the KOLs in target countries on board. The remaining unknown is in the timeline for adoption of the therapy. We would benefit from broader commercial resources, whether by an acquisition, partnership or an investment, and that’s my focus at the moment. This business is my passion—that’s how it gets you when you get to work on something that makes a difference in people’s lives.
Abbreviated Prescribing Information TAFLOTAN® (tafluprost 0.0015% eye drops, solution, single-dose container).

Presentation: Low-density polyethylene single-dose containers packed in foil pouch. Each single-dose container has a fill volume of 0.3 ml and there are 10 containers in each foil pouch. The following pack sizes are available: 30 x 0.3 ml and 90 x 0.3 ml. One ml of eye drops contains 15 micrograms of tafluprost. Indication: Reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension in patients who would benefit from preservative-free eye drops or who are insufficiently responsive or intolerant or contra-indicated to first line therapy, as monotherapy or as adjunctive therapy to beta-blockers. Dosage and Administration: The recommended dose is one drop of TAFLOTAN® in the conjunctival sac of the affected eye(s) once daily in the evening. Not recommended in children or adolescents (under the age of 18). In renal or hepatic impairment use with caution.

Contraindications: Hypersensitivity to tafluprost or to any of the excipients.

Precautions: Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. Some of these changes may be permanent, and may lead to differences in appearance between the eyes when only one eye is treated. Caution is recommended when using tafluprost in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema or iritis/uveitis. There is no experience in patients with severe asthma. Such patients should therefore be treated with caution. Interactions: Specific interaction studies with other medicinal products have not been performed with tafluprost. Pregnancy: Do not use in women of childbearing age/potential unless adequate contraceptive measures are in place. Driving: Tafluprost has no influence on the ability to drive. Undesirable Effects: The most frequently reported treatment-related adverse event was ocular hyperaemia. It occurred in approximately 13% of the patients treated with preserved tafluprost and 4.1% of the patients treated with preservative-free tafluprost. Other side effects include: Common (1% to 10%): eye pruritus, eye irritation, eye pain, changes in eyelashes, dry eye, eyelash discoloration, foreign body sensation in eyes, erythema of eye lid, blurred vision, increased lacrimation, blepharal pigmentation, eye discharge, reduced visual acuity, photophobia, eyelid oedema and increased iris pigmentation and headache. Uncommon (0.1% to <1%): superficial punctate keratitis (SPK), cataract, conjunctival oedema, blepharitis, ocular discomfort, anterior chamber flare, conjunctival follicles, allergic conjunctivitis, anterior chamber cell, conjunctival pigmentation and abnormal sensation in eye, hyperthermia of eyelid. Overdose: If overdose occurs, treatment should be symptomatic. Special Precautions for Storaget Store in a refrigerator (2°C - 8°C). After opening the foil pouch keep the single-dose containers in the original foil pouch, do not store above 25°C, discard an opened single-dose container with any remaining solution immediately after use. MA Holdert Santen Oy, Nittyhakaantie 20, 33720 Tampere, Finland. Date of Preparation: 11/2012.