Supplement to
Australian Optometry

2013 Contact Lens Prescribing Trends Survey

pharma

DECEMBER 2013

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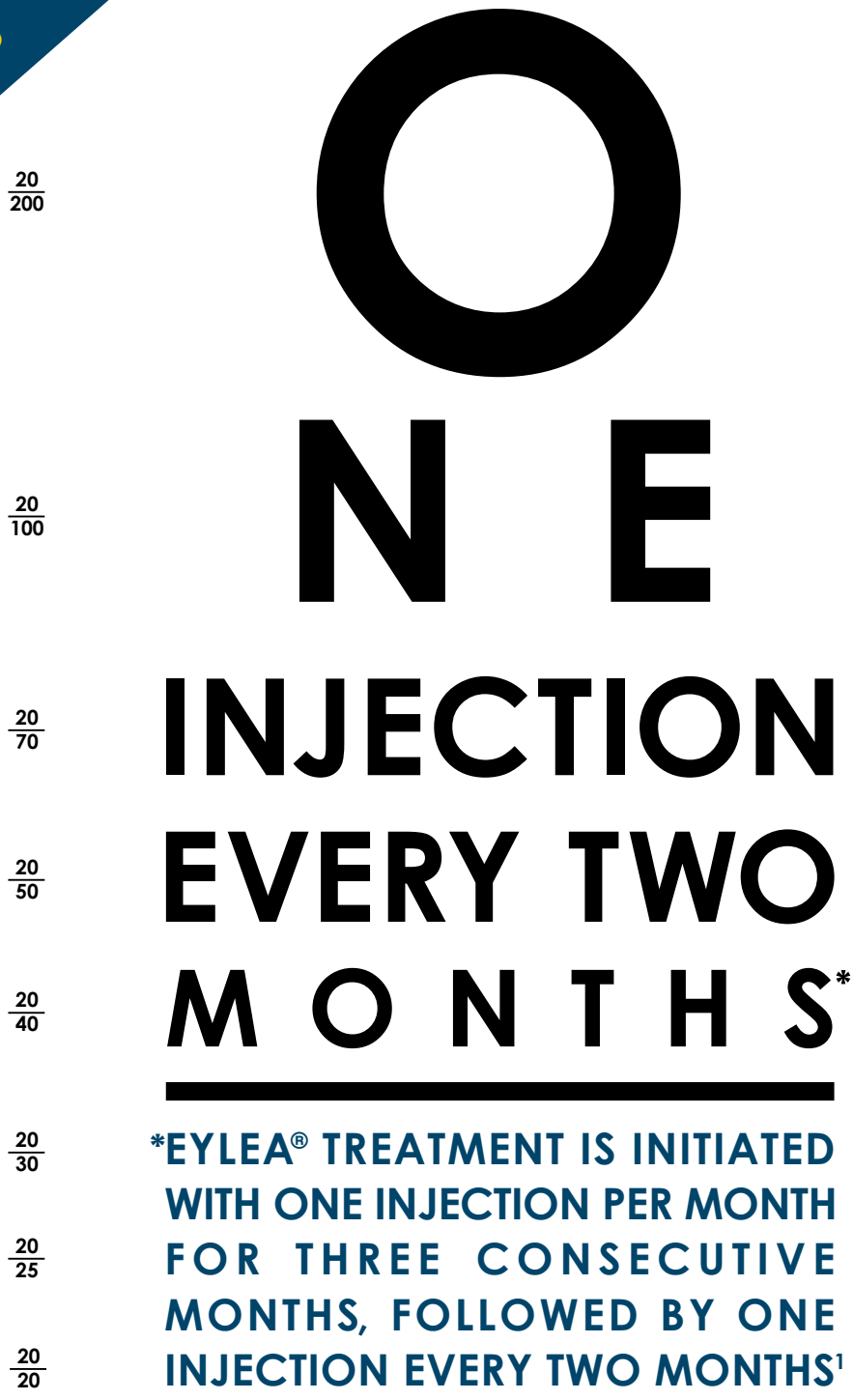

***EYLEA® TREATMENT IS INITIATED WITH ONE INJECTION PER MONTH FOR THREE CONSECUTIVE MONTHS, FOLLOWED BY ONE INJECTION EVERY TWO MONTHS[1]**

PBS Information: Authority Required for the treatment of subfoveal choroidal neovascularisation (CNV) due to age-related macular degeneration (AMD). Refer to PBS Schedule for full Authority Information.

PLEASE REVIEW APPROVED PRODUCT INFORMATION BEFORE PRESCRIBING. APPROVED PRODUCT INFORMATION AVAILABLE ON REQUEST. FOR THE MOST UP TO DATE PRODUCT INFORMATION go to http://www.bayerresources.com.au/resources/uploads/PI/file10294.pdf.

MINIMUM PRODUCT INFORMATION EYLEA [aflibercept (rch)] INDICATIONS: EYLEA (aflibercept) is indicated for the treatment of neovascular (wet) age-related macular degeneration (wet AMD). **DOSAGE AND ADMINISTRATION:** Injection volume of 50 µL EYLEA (equivalent to 2 mg aflibercept). Treatment is initiated with one intravitreal injection per month for three consecutive months, followed by one injection every two months. **CONTRAINDICATIONS:** Known hypersensitivity to aflibercept or excipients; ocular or periocular infection; active severe intraocular inflammation. **PRECAUTIONS:** Endophthalmitis, increase in intraocular pressure; see full PI for effects on fertility, pregnancy, lactation, effects on ability to drive or use machines. **ADVERSE EFFECTS:** Cataract, conjunctival haemorrhage, eye pain, retinal detachment, retinal pigment epithelium tear, detachment of retinal pigment epithelium, corneal erosion, intraocular pressure increased, vision blurred, vitreous floaters, corneal oedema, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, conjunctival hyperaemia. Others: see full Product Information. Date of most recent amendment: December 2012.
References: 1. EYLEA Product Information.

EYLEA®
aflibercept (rch)
solution for intravitreal injection

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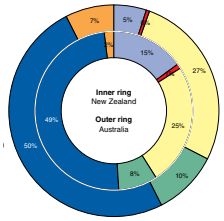

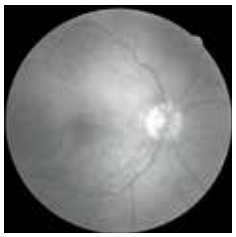

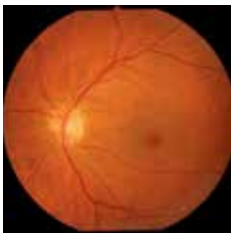

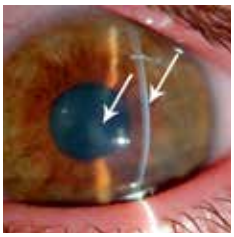

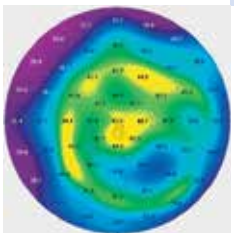

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Contact lens prescribing

Efron, Morgan and Woods's 14th annual

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The 14th annual survey of Australian contact lens prescribing was conducted between January and April 2013. The same format as in previous years was employed. About 3,000 practising members of Optometrists Association Australia were sent an e-mail message with a link to a downloadable questionnaire and a request that this be accessed, printed and completed to provide details of the first 10 patients fitted with contact lenses after receipt of the questionnaire.

The questionnaire was designed to be straightforward while capturing key information about the patients' prescribed contact lenses. Practitioners were asked general questions about themselves, and for each contact lens fitting, they were requested to complete the following details: date of fitting, new fitting or refitting, age and sex of patient, lens material, lens design, frequency of replacement, times per week of wear, modality (daily or extended wear) and care system. Practitioners were asked to return the questionnaire by fax or post.

Completed questionnaires relating to 459 contact lens fittings were received. Each fitting was given a rating based on the number of lenses fitted per year by the practitioner (based on the date information on the form). This means that data generated by practitioners who conducted many contact lens fittings were afforded a higher rating than those performing fewer fittings.

The discussion below will concentrate primarily on data relating to new lens fittings, as opposed to refittings. We believe that new fittings are a more sensitive barometer of current patterns and future trends, whereas refittings are more indicative of previous fitting behaviours.

Demographics

As in previous years and in keeping with other markets around the world, a majority of lenses in Australia (66 per cent) were fitted to females. The average age of contact lens wearers continues to edge upwards. This year, the mean ± standard deviation age at fitting was 38.2 ± 15.9 years, varying from nine to 76 years.

Soft lenses

As has been the case for the past 30 years, soft lenses accounted for the majority of new fittings (96 per cent). Figure 1 is a composite of pie charts detailing the key findings of the 2013 survey in relation to soft lenses. Silicone hydrogels represented 77 per cent and 67 per cent of materials prescribed as new fittings and refittings, respectively—an increase over the 2012 data[1] (68 per cent and 62 per cent). The balance of lens materials comprises largely mid-water content hydrogel materials. Low and high water content lenses accounted for only three per cent and four per cent of new fittings, respectively, although these lenses were fitted at a higher rate for lens refittings (seven per cent and 10 per cent, respectively).

Figure 2 shows fitting trends in relation to soft lens materials in Australia between 2000 and 2013. It is evident that the extent of silicone hydrogel lens fitting rapidly expanded between 2000 and 2007 and stabilised thereafter, although there appears to have been a further slight increase in fitting this material over the past three years.

The four major categories of lens designs are spherical, toric, multifocal and anti-myopia. Monovision is an alternative fitting strategy, but such fittings are generally performed using spherical lens designs. Grouping monovision fittings in the spherical design category, we find that the majority of soft lens designs prescribed are spheres, which represent 54 per cent and 58 per cent of new fittings and refittings, respectively.

There has been a slight decrease in the prescribing of soft lenses for the correction of astigmatism in 2013, with 32 per cent of soft lens new fittings being toric designs, versus 39 per cent 2012.[1] The current level of toric lens prescribing in Australia suggests that nearly all 'clinically significant'

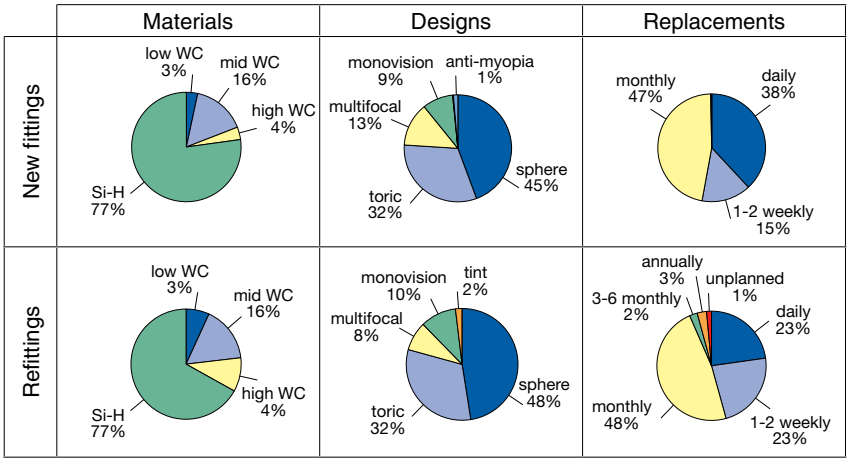

Figure 1. Detailed results for soft lens prescribing in the 2013 Australian survey. Si-H: silicone hydrogel, WC: water content

trends

survey of Australian contact lens prescribing habits

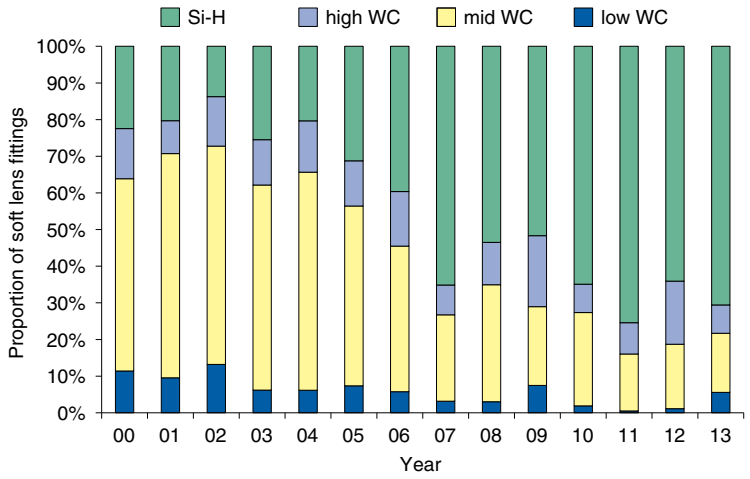

Figure 2. Percentage of soft lens fittings prescribed for silicone hydrogel (Si-H), high-, mid- and low-water content (WC) lenses in Australia between 2000 and 2013

astigmatism (> 0.75 D) is being corrected (the accepted target in this regard is about 35 per cent of lenses[2]).

Multifocal lenses appear to be favoured by practitioners over monovision around the world in recent years,[3] and presbyopia fitting practices in Australia are generally consistent with this trend. There were more presbyopic new fittings with multifocal lenses (13 per cent) compared with monovision lenses (nine per cent). There were no recorded new fittings with coloured (tinted) soft lenses in this survey.

Over the past five years, there has been a great deal of interest in anti-myopia lenses. These are specially-designed soft lenses that alter the image profile in the lens periphery to arrest the progression of myopia. Preliminary research suggests that these lens designs do seem to have some efficacy in arresting myopia progression, albeit limited and somewhat unpredictable.[4] Despite these promising advances, only one per cent of new fittings at the present time are with this form of lens.

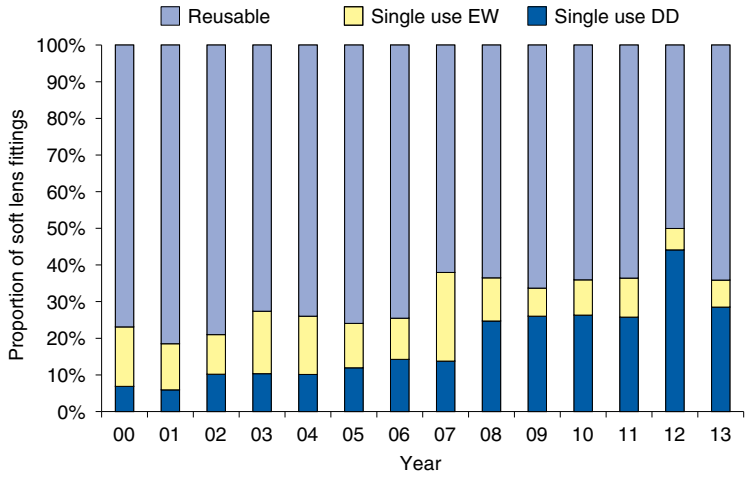

Figure 3. Percentage of soft lens fittings prescribed as reusable, single use extended wear (EW) and single use daily disposable (DD) lenses between 2000 and 2013

This is probably a result of a combination of initial practitioner resistance or caution, and the fact that these products are not readily available currently in Australia.

Daily disposable lenses continue to be popular in Australia, although the proportion of daily disposable lens new fittings decreased from 42 per cent of all soft lens fittings in 2012 to 38 per cent in 2013.

The fitting of monthly replacement lenses as new fittings increased sharply from 32 per cent in 2012 to 47 per cent in 2013. This dramatic change appears to have been at the expense of one-to-two week replacement lenses, which dropped from 24 per cent of new fittings in 2012 to 15 per cent in 2013. The practice of replacing lenses less frequently than monthly has been in steady decline since we began surveying the Australian market in 2000. It has now reached the point where there were no such lenses were prescribed for new fittings in 2013; that is, we now have a market that is exclusively frequent lens replacement (in other words, at least monthly).

The extent to which the Australian market has shifted to single use lenses is illustrated in Figure 3. 'Single use' simply means that the lens is inserted and removed once only before being discarded and as such, this means daily disposable and extended wear lenses. Although extended wear has often been touted in the past as the ultimate form of convenient lens wear, this modality has rarely exceeded a 'glass ceiling' of about 15 per cent of soft lenses prescribed anywhere in the world.[5]

Extended wear lenses represented seven per cent of soft lens fittings in 2013, and all single use lenses (in other words, extended wear and daily disposable lenses combined) represented 36 per cent of all soft lens fittings in 2013. This overall level of single use fittings has remained fairly constant since 2007.

Multi-purpose solutions account for 92 per cent of prescribed care regimens, with the balance comprising peroxide systems.

Continued page 4

Contact lens prescribing trends

From page 3

Rigid lenses

Non-orthokeratology and orthokeratology rigid contact lenses represented five per cent and zero per cent, respectively, of all contact lens fittings. As has been the case in recent years, our data set for non-orthokeratology rigid lens fitting is so sparse that it is statistically untenable to break the data down into sub-categories of materials, designs and replacement frequencies. The level of orthokeratology fitting is apparently nonexistent at present, although orthokeratology did represent four per cent of fittings in 2012. This apparent volatility in orthokeratology fitting may in part be attributed to the wide confidence intervals (and thus lack of precision) inherent in surveying such rare fitting behaviours.

Australia versus New Zealand

We started conducting contact lens prescribing surveys in the UK in 1996 and have progressively included more countries over the years to the point where we now survey about 40 countries annually.[5] This provides an opportunity to benchmark Australian trends against international colleagues, and this year we compare Australian contact lens prescribing with that of our neighbour, New Zealand. The current pattern of contact lens fitting in these two countries in shown in Figure 4. Six key categories of lens type are represented. The outer and inner rings show the Australian and New Zealand data, respectively.

Overall, Figure 4 reveals that contact lens prescribing patterns are remarkably similar between the two nations. This is perhaps unsurprising, as the two nations are in the same geographical region and have similar demographics, social and political systems and economic profiles. As well, some of the major contact lens companies have joint or shared trans-Tasman management and distribution arrangements. Therefore, there are commonalities in the promotion, marketing and distribution of contact lenses in the two countries. In addition, the trend towards true globalisation of the contact lens market over the past decade means that the vast majority of soft lenses sold worldwide rests in the hands of a small group of companies that operate in virtually all countries.

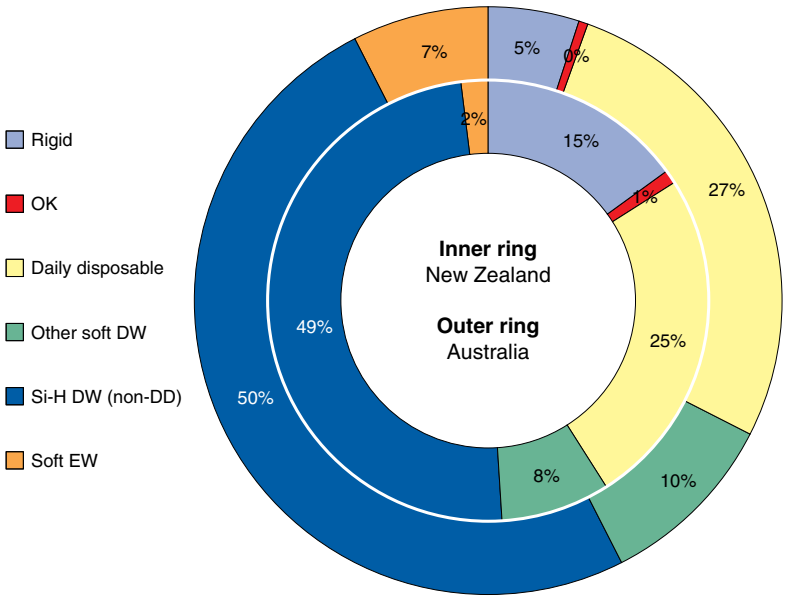

Figure 4. Percentage of all contact lenses prescribed in Australia (outer ring) compared with New Zealand (inner ring). OK: orthokeratology, DW: daily wear, Si-H: silicone hydrogel, EW: extended wear.

The only real differences between Australia and New Zealand are in the fitting of rigid lenses and the prescribing of soft lenses for extended wear. The extent of rigid lens fitting is apparently three times greater in New Zealand compared with Australia. This may reflect the traditional approach to contact lens fitting in New Zealand, fuelled by loyalty to the remaining active rigid lens laboratories—Contact Lens Corporation and Precision Contact Lenses, both of which are in Christchurch.[6]

There has been a progressive merging and/or closing down of rigid lens companies in Australia. Eycon, CooperVision-Hydron and NuContacts have ceased operation in the past five to 10 years. Only three Australian rigid lens laboratories remain in business: Australian Contact Lenses (Melbourne), Gelflex (Perth) and Capricornia (Brisbane). The fact that three rigid lens laboratories operate in Australia and two in New Zealand—although Australia has more than five times the population—reflects the relative dearth of rigid lens fitting by Australian practitioners.

The level of orthokeratology fitting is very low in New Zealand (one per cent) and as noted above, is apparently non-existent in Australia at present. At best, orthokeratology remains a niche market in both countries, as is indeed the case in the vast majority of countries we survey.

In contrast to rigid lens fitting, 3.5 times more soft extended wear lenses are fitted in Australia compared with in New Zealand. The reason for this is unclear but again may relate to the more conservative approach adopted by New Zealand practitioners.

Conclusions

Perhaps the most notable finding of our 2013 survey of Australian contact lens prescribing is the increasing dominance of silicone hydrogel lenses. It is remarkable to observe that a specific product innovation—which was introduced to the world market only at the turn of the century—could have such a huge impact on a global retail market valued at approximately $8 billion annually.

The other significant change this year has been the decline in one-to-two weekly lens replacement to only 15 per cent. This indicates that Australia is rapidly moving towards a two-modality market of daily or monthly disposable lens replacement.

Full correction of astigmatism remains to be the norm, with continuing high levels of practitioner confidence in toric lens fitting. Multifocal soft lenses are still the preferred form of correction for presbyopes over monovision. Rigid lens prescribing continues to be low and there is little current interest in orthokeratology. The contact lens demographic continues to trend towards older age, typically female wearers. ■

References are available from j.megahan@optometrists.asn.au, subject: Contact lens trends, Pharma *December 2013.*

Suboptimal responders

Treating anti-VEGF tachyphylaxis

Switching to aflibercept may help patients for whom treatment with bevacizumab and ranibizumab is not effective

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Intravitreal anti-vascular endothelial growth factor (VEGF) drugs have revolutionised the treatment of the neovascular form of age-related macular degeneration (AMD) and are the current standard of care for the condition. These agents work by blocking the actions of VEGF, a substance important in the pathogenesis of neovascular AMD due to its ability to stimulate the growth of abnormal blood vessels underneath the retina.

Anti-VEGF drugs used to treat neovascular AMD

There are three anti-VEGF agents currently available in Australia, all of which have been shown to be safe and effective for the treatment of neovascular AMD in numerous high-quality, large randomised multicentre clinical trials.

Bevacizumab

Bevacizumab (Avastin) is a full-length antibody against VEGF and was the first anti-VEGF agent to become available in Australia in 2006. It was designed for intravenous use in the treatment of colon cancer and is not licensed for intraocular use; its use for the treatment of neovascular AMD is off-label. The efficacy and safety of intravitreal bevacizumab has been confirmed in the IVAN and CATT trials.[1-2]

Ranibizumab

Ranibizumab (Lucentis) is an anti-VEGF antibody fragment, which was designed for ocular use. It was first listed on the Pharmaceutical Benefits Scheme (PBS) in 2007 for the treatment of subfoveal choroidal neovascularisation (CNV) due to AMD. The efficacy and safety of monthly ranibizumab was demonstrated in the MARINA and ANCHOR trials.[3-4]

Aflibercept

Aflibercept (Eylea) is a decoy receptor produced by fusing DNA sequences from VEGF receptors onto a human antibody backbone, known as the Fc region. This is the most recent addition to our treatment armamentarium against neovascular AMD and was first listed on the PBS in November 2012. The efficacy and safety to aflibercept was proven in the VIEW 1 and VIEW 2 trials.[5]

The visual results reported for each of the three anti-VEGF agents after one year of treatment are impressive and broadly comparable, with all drugs maintaining visual acuity (VA), defined as losing less than 15 ETDRS letters, in approximately 95 per cent of patients, and leading to a marked improvement in VA, defined as gaining at least 15 ETDRS letters, in 30 per cent to 40 per cent of patients.

There is ongoing debate among experts regarding subtle differences between the agents in relation to duration of efficacy, effectiveness in reducing subretinal fluid, the frequency of injections required, ocular side-effects such as uveitis and progression of geographic atrophy, as well as concerns about systemic cardiovascular risks. It is currently uncertain how much of the observed differences are genuine drug effects or simply due to random chance.

With the increasing numbers of patients with neovascular AMD needing regular anti-VEGF injections in Australia, the issue of frequency of injections is important. More frequent injections impose a psychological, financial and logistic burden on patients and their carers, expose patients to the risks of endophthalmitis and retinal detachment associated with injections, and are expensive for the health-care system.

The VIEW 1 and 2 trials demonstrated that aflibercept injected every eight weeks is clinically equivalent to ranibizumab injected every four weeks for maintaining VA over one year.[5] The potential advantage of aflibercept to achieve similar efficacy and safety results with fewer intravitreal injections than required with ranibizumab has led it to become one of the fastest-growing medicines in the history of biotechnology.

Suboptimal responders to anti-VEGF treatment

Despite the excellent results reported in clinical trials and routinely seen in clinical practice, many patients require continued monthly anti-VEGF injections on a long-term basis because of persistent fluid exudation in the macula from leaking CNV. In the CATT trial, persistent fluid was demonstrated on ocular coherence tomography (OCT) at one year in 56 per cent of patients receiving monthly injections of ranibizumab.[2] It is possible that resolution of this fluid might result in improved visual outcomes.

Some patients have a good initial response to treatment with resolution of fluid exudation, but then later become resistant to further treatment and develop recurrent exudation with vision loss. The mechanism of this resistance to treatment is not well understood but tachyphylaxis, that is, a diminishing response to repeated doses of a drug, may be an important factor.[6]

Patients who develop persistent or recurrent macular fluid exudation following anti-VEGF treatment can be termed 'suboptimal responders'. Potential strategies employed to treat suboptimal responders include increasing the frequency of treatment, increasing the dose of the anti-VEGF agent

Continued page 6

Anti-VEGF

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used, or using a drug with a higher VEGF-binding affinity.

Recent data on switching therapy to aflibercept

Anecdotally, retinal specialists commonly find that individual patients respond better to one anti-VEGF agent than to another (Figures 1 and 2). Following the introduction of aflibercept, there has been a plethora of recently published studies from the United States, each reporting a beneficial response from switching treatment to aflibercept in patients who are suboptimal responders to bevacizumab or ranibizumab.

Five of these studies are retrospective case series reports from different research groups spread throughout the USA.[7-11] Each report describes the treatment results for a group of between 28 to 94 patients (with a collective total of 296 eyes of 272 patients) who had been classified as suboptimal responders to an average of 17 to 29 bevacizumab or ranibizumab injections. All patients had their anti-VEGF treatment switched to aflibercept and received a minimum of three aflibercept injections with subsequent follow-up ranging from three to six months.

All of the published papers demonstrated a statistically significant anatomical improvement, with a reduction or elimination of macular fluid exudation demonstrable on OCT scanning occurring in 50 per cent to 91 per cent of patients.

A switch study by Kumar and colleagues involving 34 eyes of 33 patients showed no improvement in VA after switching to aflibercept at three months, but did demonstrate a significant improvement in VA at six months after initiating aflibercept treatment.[10]

The authors suggest that in suboptimal responders to previous anti-VEGF agents, the response to treatment with aflibercept may be different from the treatment to naïve eyes evaluated in clinical trials, such that an improvement in VA requires more time and a greater number of injections to become apparent. The other recently published switch studies demonstrated no change in VA despite the anatomical improvements, although two of the studies had follow up of less than six months.[7,9]

A study by Yonekawa and colleagues of 102 eyes of 94 patients who were switched to aflibercept after a suboptimal response to multiple bevacizumab or ranibizumab injections reported that switching to aflibercept reduced the injection burden by enabling an increase in the interval between injections from 7.2 weeks prior to switching, to 9.5 weeks after initiating aflibercept treatment.[11]

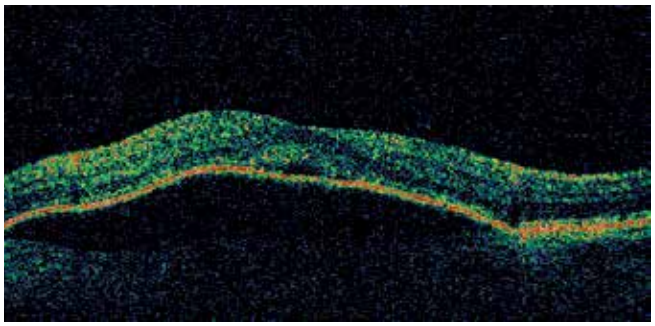

Figure 1. OCT scan of an 84-year-old patient with neovascular AMD showing persistent subretinal fluid and pigment epithelial detachment despite eight intravitreal ranibizumab injections. VA is 6/6.

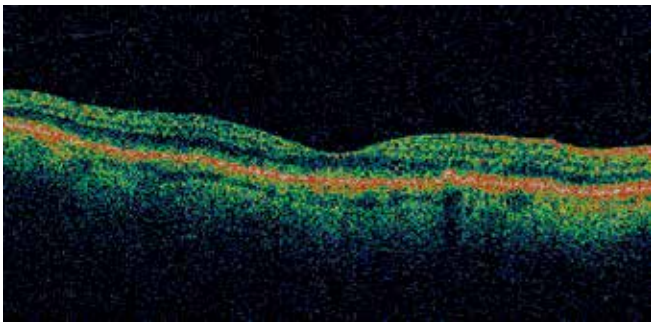

Figure 2. OCT scan of the same patient as in Figure 1 showing complete resolution of subretinal fluid and pigment epithelial detachment four weeks after a single intravitreal aflibercept injection. VA had improved to 6/24.

Mechanism of action of aflibercept in suboptimal responders

There are various potential mechanisms that may explain the improved anatomic changes seen after switching suboptimal responders to aflibercept.

Aflibercept has a significantly higher binding affinity *in vitro* to VEGF compared with bevacizumab and ranibizumab.[12] The intravitreal half-life of aflibercept is 4.7 days in rabbit eyes, which is longer than ranibizumab (2.9 days) and bevacizumab (4.3 days). The combination of a higher binding affinity and longer half-life has led to a calculated duration of effect of an intravitreal injection of aflibercept of six to 12 weeks in human eyes compared to four weeks for ranibizumab.[13]

In contrast to bevacizumab and ranibizumab, which bind only to the VEGF-A isoform of VEGF, aflibercept has additional mechanisms of action by also blocking the effects of the VEGF-B isoform as well as a substance related to VEGF called placental growth factor.[14] VEGF-B and placental growth factor have been implicated in pathogenesis of neovascular AMD.

Tachyphylaxis may develop following repeated anti-VEGF injections possibly due to the formation of neutralising antibodies to bevacizumab or ranibizumab.[15] By switching to a new anti-VEGF such as aflibercept, tachyphylaxis to the previous agents is avoided.

Conclusion

The use of aflibercept by Australian retinal specialists to treat neovascular AMD has increased rapidly since it was listed on the PBS in December 2012. Many patients have been switched from ranibizumab to aflibercept with the goal of extending treatment intervals or achieving better responses for refractory cases.

With increasing clinical experience, published data is rapidly accumulating to indicate that switching to aflibercept is effective in producing anatomical improvements in the macula while maintaining VA in patients who are suboptimal responders to bevacizumab or ranibizumab. ■

References are available from j.megahan@optometrists.asn.au, subject: Suboptimal responders, Pharma *December 2013.*

Nutrition and eye health

A clearer view

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At a time when patients are becoming more proactive about their own health issues and enjoy internet access to myriad nutritional tips, optometrists are facing the same challenge encountered by all health practitioners: sorting the fact from the fiction to provide their patients with clear and accurate nutrition messages.

I have compiled a few of the most common eye health issues below and offer a brief discussion on their relation to the current understanding of nutrition management. As anyone committed to staying informed of the rapidly-changing field of nutrition knows, certainty is often elusive. The aim of this article is to inspire discussion on the topic of ocular nutrition, not to offer a list of final, irrevocable pronouncements.

Diabetes

It is estimated that about 150,000 Australians suffer from diabetic retinopathy.[1] Vascular damage puts a further 850,000 diabetic patients at risk of glaucoma. Dietary advice for diabetes is a broad topic that extends beyond the scope of the optometrist. While the key messages of regular, low-GI food choices can be reinforced, the most effective message that can be given to patients with questions about nutrition is for them to seek advice from a dietitian.

Hypertension

Due to increases in vascular pressure and damage, hypertension increases risk of retinopathy and glaucoma. A reduction in salt intake can improve blood pressure.[2] While patients are often conscious of the need to limit added salts, they may be unaware of hidden salts in processed foods.

Encouraging patients to avoid added salt and to limit their intake of processed foods, particularly high-salt savoury snacks, takeaway foods and processed meats, is sound advice for optometrists to pass on to patients.

Alcohol excess

In addition to contributing to overall dietary calories, long-term excessive alcohol intake results in the body's reliance on its microsomal ethanol oxidising system (MEOS) for alcohol breakdown. The resultant by-products of this system prevent vitamin A utilisation, leading to night blindness and xerophthalmia. How much alcohol is too much? The National Health and Medical Research Council recommends limiting intake to one or two standard drinks a day.

AMD

Australian supermarket margarines are generally not high in trans fats due to the interesterification processing which does not result in trans fat production. Although butter is considered more 'natural' by some, it is high in saturated fat which is associated with coronary heart disease[3] and increased progression to advanced AMD.[4] The suggestion to choose margarine and use all added fats sparingly is the most sound advice to give to your patients.

A higher intake of omega-3 fatty acids, particularly from oily fish, combined with a lower omega-6 intake may reduce the risk of progression of AMD.[4,5,6] The safest message to give to your patients may be to limit overall fat intake, enjoy oily fish regularly and consider the possibly detrimental effects of high omega-6 supplements—including evening primrose oil, black current oil and spirulina.

Clear messages from AMD research indicate that high intake of processed baked goods is associated with a worsening progression, and that fish and nuts in the diet may be protective.[5,7] Ginkgo biloba has shown promise in reducing progression in small trials but there is not yet enough evidence for recommendation to patients.[8]

In 2001, the National Eye Institute's AREDS study showed significant benefits in specific supplements in slowing the progression of AMD.[9] As others have shown in this issue of *Pharma*, the results of the AREDS2 trial, published this year, were surprising and often contentious, leaving room for future studies to provide greater clarification and guidance for the use of ocular nutrition supplements for the prevention of AMD.

Dry eye syndrome (DES)

Omega-3 supplementation has been proposed to reduce symptoms of dry eye, with results of one trial noting improvement in tear production and symptoms in patients.[10] These participants received the equivalent of three standard 1,000 mg fish oil capsules, and one standard 1,000 mg flaxseed oil capsule daily.

Higher dietary omega-3 intake has been shown to decrease DES incidence in women and increased risks associated with a high ratio of omega-6 to omega-3.[11,12]

Cataracts

Currently, there is no good evidence to support any specific nutritional supplements to assist with cataract risk or progression. As well, there are no trials successfully demonstrating improvements in cataracts in either high dose antioxidant supplements or multivitamin supplements.

Conclusion

The evidence is limited on regular supplement use for eye health. Advising the inclusion of dietary omega-3 and nuts, in line with the recommendations of the Heart Foundation may be the most beneficial guidance the optometrist can offer the patient.

The NHMRC's 'Australian Guide to Healthy Eating' can easily be accessed by patients on www.eatforhealth.gov.au. Directing patients towards these simple messages is a way for optometrists to feel confident that they are providing sound advice.

In the final analysis, advice on overall healthy eating, with an aim to limit dietary fats, salt and processed items will yield the greatest benefits for your patients. ■

References are available from j.megahan@optometrists.asn.au, subject: Nutrition and eye health, Pharma *December 2013.*

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Claims don't match results

Primarily, AREDS2 was designed to determine whether adding oral supplements (lutein and zeaxanthin) and/or long-chain omega-3 fatty acids (DHA and EPA) to the AREDS cocktail of vitamins and minerals decreases the risk of progression to advanced AMD for those with intermediate disease. Its secondary aim was to evaluate the effect of eliminating beta carotene, lowering zinc doses, or both in the AREDS formulation.

The results of AREDS2 were eagerly anticipated by patients, eye-care practitioners, researchers and the purveyors of dietary supplements. But what did the study chairwoman, Dr Emily Chew, present at the Association for Research in Vision and Ophthalmology conference in May, and how does it compare to what is contained within the *JAMA* article published online at the same time, and how does that measure up to what has been claimed by various third-party commentators?

As with many oral presentations, Dr Chew's discussion of the AREDS2 results was nuanced, and can be used to support a number of different positions when taken in isolation from the published results. Despite the possible differences in interpretation, there seems little disagreement with her conclusion that the addition of lutein and zeaxanthin, DHA and EPA, or both, did not significantly reduce risk of progression to advanced AMD.

The apparent contradiction with her conclusion that the addition of lutein and zeaxanthin showed a significant additional decrease in risk of progression to advanced AMD is explained by the difference between primary and secondary analyses. Put simply, the small positive result for adding lutein and zeaxanthin was found only through lower-order exploratory analyses and cannot be used as the basis for a clinical recommendation.

> **Put simply, the small positive result for adding lutein and zeaxanthin was found only through lower-order exploratory analyses and cannot be used as the basis for a clinical recommendation.**

Dr Chew also stated that there was no effect due to eliminating beta carotene or lowering zinc dose. Although used by some to argue for the retention of high-dose zinc, the application of Ockham's razor would suggest the opposite: that beta-carotene could be removed and the zinc dose lowered without a loss of benefit.

Dr Chew did suggest in her presentation that removal of beta carotene from the AREDS formulation could reduce the risk of lung cancer in smokers and former smokers, but it should be noted that AREDS2 did not randomise any smoker to receive beta carotene, and her suggestion is based on exploratory analyses of lung cancer rates among former and non-smokers taking all formulations without beta carotene versus all formulations including beta carotene.

Once again, the conclusion is based not on primary analyses but exploratory lower-order analyses of the AREDS2 data and combined with evidence from other sources. Nonetheless, it is a reasonable suggestion based on minimising potential harm. Overstating Dr Chew's conclusion as a clear recommendation to remove beta carotene and replace it with lutein zeaxanthin is not what was presented and is not supported by the evidence from AREDS2.

Diet

One could argue that it would be better to counsel individuals to increase their dietary uptake of lutein and zeaxanthin, something Dr Chew hinted at in her ARVO presentation: '[AREDS2] confirms the basic recommendation that people should have good diets; first of all, eat a healthy diet of vegetables'.

For those who have not yet read the *JAMA* article the language is unequivocal: 'addition of lutein and zeaxanthin, DHA and EPA, or both, to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD' and 'there was no apparent effect of beta carotene elimination or lower–dose zinc on progression to advance AMD'.[1] Essentially, there is strong evidence of no benefit in adding to the formulation and less evidence of no (loss of) effect by removing beta carotene or reducing the zinc dose.

It is instructive to note that the authors also stated that 'exploratory analyses demonstrated results that suggest the role of lutein and zeaxanthin needs to be examined further' and that 'lutein and zeaxanthin may play a role for reducing risk of progression to advanced AMD when given without beta carotene' but 'this hypothesis requires further study'.[1] Hardly a clear recommendation.

Finally, it is interesting to note that all four primary randomisation groups in AREDS2 (each receiving a variation of the AREDS formulation) progressed to advanced AMD at rates higher than the placebo (no treatment, natural history, high risk categories 3 and 4) sub-group in the original AREDS clinical trial (29 to 31 per cent compared to 28 per cent) and much higher than the same high risk category receiving the AREDS formulation (20 per cent) in the original AREDS.

It has been stated that the AREDS2 study population was older, with a median age being five years older than the full AREDS study population, but that does not compare the median age for participants in the same high risk group (categories 3 and 4) across the two studies.

Whatever the median age, it does demonstrate the importance of comparing similarly aged groups when making sense of risk of progression to advanced AMD, and in combination with the absence of a true placebo group in AREDS2, disallows the claim that AREDS2 confirms the benefits of dietary supplements found in AREDS.

Unfortunately, as Emily Chew said in her ARVO presentation, AREDS and AREDS2 will never be repeated, so a number of outstanding questions will never be answered, but no doubt we will read more about this and interesting exploratory analyses of the data in future AREDS2 reports. ■

A video of Dr Chew's ARVO presentation is available for OAA members on the *Pharma* webpage.
Log in: australianoptometry.com.au > Pharma

1. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomised clinical trial. *JAMA* 2013; 309: 19: 2005-2015.

review

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Gains were modest but real

The results of the AREDS2 study are finally in. What do the data reveal? Let's take a quick look at the details and the recommendations. The National Eye Institute's (NEI) recommendation adds 10 mg lutein and 2 mg zeaxanthin and eliminates beta carotene that was in the original AREDS supplement. Results from AREDS2 report an 18 per cent reduction in progression to advanced AMD in subjects who received 10 mg lutein and 2 mg zeaxanthin in addition to an AREDS supplement without beta carotene compared to the original AREDS supplement with beta carotene.

This reduction in progression to advanced AMD is even greater in study subjects with the lowest intake of lutein and zeaxanthin in their diet, which is more representative of the general population. In the USA, the dietary intake of lutein and zeaxanthin is typically less than 1 mg per day. This amount is well below the level that science has shown to be needed to be effective in prevention of AMD.

The NEI also recommends improving the safety and efficacy of the AREDS supplement by removing beta carotene and replacing it with 10 mg lutein and 2 mg zeaxanthin. This recommendation is due to potential safety concerns of former smokers who received beta carotene in the original AREDS supplement. About 50 per cent of people with AMD are former smokers.

In summary, the lutein and zeaxanthin made a small change in late-stage disease.

> **In summary, the lutein and zeaxanthin made a small change in late-stage disease.**

Surprises, observations

Dr Emily Chew, the lead investigator, mentioned during her presentation of the AREDS2 results that lutein supplementation of more than 10 mg per day may be toxic. There are more than 10 peer-reviewed published studies that have supplemented subjects with more than 10 mg of lutein per day, none of which has demonstrated any toxicity.

To the surprise of many, there was no effect of omega-3 essential fatty acids (EPA/DHA). There are speculations why this occurred, ranging from a 'well-nourished' study population who took fish oil on their own, to those reaching a saturation point of serum levels of these acids. Considering that the highest levels of fatty acids in the retina are DHA, more evaluation of these results are warranted.

AREDS2 subjects were at a more advanced stage of AMD and were on average five years older (average age 74) than the participants in the original AREDS study (average age 69). The AREDS2 subjects also had double the incidence of diabetes. The authors note that these differences could impact the ability to detect a more significant reduction in the progression to advanced AMD.

Other concerns regarding the study

- The AREDS2 study design (similar to the original study) was to determine progression to the late stages of AMD—not prevention, reversal or stopping of the disease.
- In the primary prevention aspect of the study, there were no positive results of any of the intervention nutrients (L/Z or EPA+DHA). Only when secondary outcomes were reviewed were there any significant results.
- The participants in the AREDS2 study were considered 'well-nourished' which is not representative of the US population in general.
- Evaluations of progression to advanced AMD were based solely on visual acuity and retinal photography. No tests for functional vision (contrast sensitivity, glare recovery, dark adaptation and so on) were performed.
- Genetic evaluations were conducted on only one-fourth of the study population and those statistics have not been released yet.
- Macular pigment optical density was measured on only one-fourth of the study population and those statistics have not been released yet.
- The placebo arm had high intakes of EPA + DHA in their diet that confounded the statistical analysis. Otherwise, it is unclear why this dosage of EFAs did not make a difference. Perhaps a higher intake was needed but a Holman RBC index was not obtained. Perhaps more DHA was required as found within the NAT2 study.[1] Folate is required to enhance DHA absorption. Perhaps the participants were taking systemic pharmaceuticals that depleted the B vitamins.
- Cataracts are a part of a slow developing process and other studies have shown that high levels of certain antioxidants, such as lutein/zeaxanthin, in patients with low habitual dietary intake, can be effective in reducing the incidence and/or progression of cataracts.[2,3]
- The amount of zinc recommended in the AREDS2 formula is over twice the recommended daily intake set by the Institute of Medicine board. While this study did not show the negative effects, it might have been due to the type (oxide) of zinc used. Zinc oxide is not well absorbed into the cells. We look forward to more data and discussion.
- There was no true control group; all study participants received a supplement of some sort.
- Lutein and zeaxanthin are not a 'substitute' for beta-carotene because they are xanthophyll carotenoids and don't convert to vitamin A.
- In the original AREDS study, about 67 per cent of the participants took Centrum while the AREDS2 participants had about 89 per cent taking Centrum Silver. At the time of AREDS, Centrum did not yet contain lutein.
- It is unclear why the geographic atrophy patients fared poorer with supplements, compared with AREDS post-op analysis results. Could geographic atrophy be a separate AMD disease state dependent on additional nutrient factors? ■

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2. Christen WG, Liu S et al. Dietary carotenoids, vitamins C and E, and risk of cataract in women: a prospective study. *Archives of Ophthalmology* 2008; 126: 1: 102-109.
3. Lyle BJ, Mares-Perlman JA et al. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. *Am J Epidemiol* 1999; 149: 9: 801-809.

After AREDS

Translating research evidence

Many of the important questions relating to the role of nutrition in halting the progression of AMD remain.

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There continues to be significant interest in the potential role that antioxidant therapy may have in preventing the development and/or progression of age-related macular degeneration (AMD). Early interest in this area began in the 1990s, when several epidemiologic studies published data to suggest that antioxidants may reduce the risk of cancer, cardiovascular disease and age-related ocular disease.[1-3]

At that time, there were limited management options for AMD and as is still the case now, a lack of effective prophylactic treatment. The findings from these studies,[1-3] in combination with extensive advertising by the manufacturers of dietary supplements, resulted in the widespread consumption of high-dose vitamin and mineral formulations containing antioxidants and zinc.[4] This was despite the lack of compelling evidence to support the efficacy or safety of such interventions.

Enter AREDS

The AMD clinical trial within the original Age Related Eye Disease Study (AREDS) was designed, in part, to evaluate whether pharmacologic doses of antioxidant vitamins and zinc were effective and safe in reducing the onset and/or progression of AMD. Post hoc analyses of the data suggested that daily, long-term oral supplementation with a formulation containing vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80 mg as zinc oxide) and copper (2 mg as cupric oxide) reduced the risk of progression to late AMD from 28 per cent to 20 per cent at five years, in subjects with at least intermediate AMD.

These findings come with some important provisos.

First, it is important to understand the currently-accepted clinical classification of AMD.[5] 'Intermediate AMD' is defined by the presence of large drusen (>125 micron in diameter) and/or any definite hyper- and hypo-pigmentary abnormalities with at least one medium drusen (more than 63 microns but no more than 125 microns in size) located within two disc diameters of the fovea. Late disease constitutes 'neovascular AMD' or 'geographic atrophy'.

Essentially, patients with less than intermediate disease (in other words, early AMD) did not show any significant reduction in progression to late AMD.

Second, AREDS considered only one formulation, which contained the specific combination of nutrients, as detailed. AREDS therefore does not contribute to understanding whether a single component or a combination of components is required to achieve a beneficial effect, or understanding what the minimum effective dose(s) are.

On further review

Two important systematic reviews, published by the Cochrane Collaboration in 2012, summarised available evidence from randomised controlled clinical trials (RCTs) regarding the benefit of nutritional interventions for attenuating both the development[6] and progression[7] of AMD.

With regard to the use of antioxidant supplements to prevent AMD onset, the Cochrane meta-analysis included four high-quality RCTs, conducted in Australia, Finland and the United States. This analysis indicated that there was no significant effect of antioxidant therapy for preventing the development of AMD.[6]

> **While it has been claimed that, based on the findings from AREDS2, replacing beta-carotene with lutein and zeaxanthin appears to be a safer and more effective form of antioxidant therapy,[11] it is imperative that these findings are not over-stated.**

It is important to emphasise that 'evidence for no benefit' is distinct from 'an absence of evidence' to support the benefit of antioxidant therapy. In relation to AMD progression, a total of 13 RCTs were included in the analyses; AREDS was described as one of the primary sources of evidence for the benefit of antioxidant supplementation in reducing the risk of progression to late AMD.[7]

In relation to the safety of antioxidant supplements, while AREDS was underway evidence became available to indicate that high-dose beta-carotene supplementation was associated with an increased risk of lung-cancer related mortality among patients who were heavy smokers.[8,9] As a result, caution has been urged regarding the use of dietary supplements containing beta-carotene for smokers. The high daily dose of zinc in the AREDS formula was also associated with a significant number of participants reporting gastro-intestinal disturbances.

Could the AREDS formulation be improved to enhance both its safety and efficacy?

into clinical practice

Enter AREDS2

The eagerly anticipated results from AREDS2, also co-ordinated by the National Eye Institute in the United States, were published earlier this year.[10] AREDS2 sought to examine the effect of daily nutritional supplementation with lutein + zeaxanthin and/or omega-3 essential fatty acids (EFAs) on AMD progression, in subjects with at least intermediate disease.

The major finding was that there was no additional benefit in adding lutein + zeaxanthin and/or omega-3 EFAs to the original AREDS formulation; there was also no significant effect on mortality.

A sub-group analysis demonstrated that participants who had the lowest natural (dietary) intake of lutein and zeaxanthin (≤ 0.823 mg/day) but who took the AREDS formulation plus lutein + zeaxanthin, had their risk of developing late AMD reduced from 35 per cent to 27 per cent, compared with participants with a similar dietary intake who were not supplemented with the xanthophyll carotenoids.

While it has been claimed that based on the findings from AREDS2, replacing beta-carotene with lutein and zeaxanthin 'appears to be a safer and more effective form of antioxidant therapy',[11] it is imperative that these findings are not over-stated. The AREDS2 exploratory analyses found that when sub-groups of participants from secondary randomisation were considered overall, there was the suggestion of a further reduction in the rate of progression of AMD when beta-carotene was replaced by lutein + zeaxanthin.

That said, the merit of replacing lutein + zeaxanthin for beta-carotene was not a predefined outcome of AREDS2. In fact, the AREDS study group emphasised the need for further investigation of this hypothesis.

AREDS2 in practice

What does AREDS2 mean for clinical practice? Adding lutein + zeaxanthin and/or omega-3 EFAs does not enhance the antioxidant protective effect. Formulations with these additional components are not supported by evidence as being more effective than the original AREDS formulation.

It is less clear whether AREDS2 supports the finding from the original AREDS clinical trial that specific combination(s) of antioxidant vitamins and minerals, including the original AREDS formulation, are of any benefit in reducing the risk of progression to late AMD in 'at risk' patients, that is, patients with intermediate AMD.

This position requires further consideration and is based on an observation that the probability of progression to advanced AMD was found, for all primary randomisation treatment groups in AREDS2, to be higher (29 to 31 per cent) than those with category 3 or 4 AMD who received placebo (no treatment) in AREDS (28 per cent).

The AREDS2 findings do suggest that there could be benefit in clinicians surveying the dietary intake of lutein and zeaxanthin in high-risk AMD patients, in order to recommend appropriate dietary changes to boost their consumption of these carotenoids and thus reduce the risk of progression to late AMD. Obtaining essential nutrients from food sources is preferred to supplementation, as it is considered to be sustainable, less costly and has significantly lower risk of side-effects.[12]

The question of whether beta-carotene should be replaced by lutein + zeaxanthin in the AREDS formulation has not yet been answered definitively. Given the potential for an increased risk of lung cancer in current and former smokers who take beta-carotene supplements, it may well be reasonable for one carotenoid (beta-carotene) to be replaced by another set of carotenoids (lutein + zeaxanthin) to enhance the safety profile of the formulation. However, clinicians need to be aware that this is not a recommendation that can be made based solely on the data provided in AREDS2.

Many important questions relating to the role of nutrition and AMD still remain to be answered. For instance, is optimising diet alone actually safer and more effective than dietary supplements? It is already established that when beta-carotene is consumed from dietary sources it does not confer the same risk of lung cancer to current or former smokers as when sourced from dietary supplements.

It is also unclear which specific components of the AREDS and AREDS2 formulations are actually providing the therapeutic effect. What is the minimum dose of the particular component or combination of components that provides protection against progressive AMD?

It is vital that clinicians understand the available evidence and can reconcile this evidence to assess the merit of claims by third parties. Providing individualised patient care that is based on the most recent available evidence, that is, the adoption of evidence-based practice, is essential for delivering the highest standards of clinical care to our AMD patients. ■

References are available from j.megahan@optometrists.asn.au, subject: Translating evidence, Pharma *December 2013.*

Nutritional supplements survey

Dr Laura Downie and Dr Peter Keller are conducting a survey on behalf of the University of Melbourne to assess the use of nutritional supplements by Australian optometrists and the recommendations they make to patients about nutrition.

To participate in the survey, visit www.surveymonkey.com/s/OptometryNutrition.
The questionnaire is anonymous and will take about seven minutes to complete.

Abstracts

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The link between mothers' nutrition and the eyes of their newborn infants

Study findings suggest that maternal zeaxanthin status may play a more important role than lutein status in macular pigment deposition *in utero*.

Measurements were taken for mother and infant skin carotenoids using resonance raman spectroscopy (RRS) for serum and mother breast milk carotenoids using high performance liquid chromatography (HPLC) and for infant macular pigment levels using non-invasive blue light reflectometry.

Thirty healthy term infants and their mothers were enrolled in the study. A subset of infants (n = 16) were also assessed for macular pigment optical density (MPOD). Both infant and mother serum zeaxanthin levels correlated with infant MPOD (r = 0.68 and r = 0.59, respectively). Infant and mother serum lutein levels did not correlate MPOD. Mother-infant correlations were also evident for total serum (r = 0.42) and skin (r = 0.48) carotenoids.

The authors agree that further controlled clinical trials are required to determine whether maternal zeaxanthin prenatal supplementation can raise infant macular pigment levels and/or improve ocular function.

Invest Ophthalmol Vis Sci 2013; 54: 8: 5568-5578

Advising patients at risk of AMD

A cross-sectional survey of eye-care professionals in the United Kingdom, predominantly optometrists, has shown that there is a need to raise awareness of the evidence underpinning the use of nutritional supplements. It was also found that optometrists should have an increased involvement in targeted smoking cessation.

The study invited optometrists and ophthalmologists on membership databases of professional organisations for each profession to participate in an online survey. A total of 1,468 responses were received (96.3 per cent from optometrists, 3.7 per cent from ophthalmologists).

The majority of respondents indicated that they routinely provide dietary advice to patients with established AMD (67.9 per cent) and those considered at risk of AMD (53.6 per cent). Typical advice consisted of a recommendation to eat plenty of leafy green vegetables and more oily fish.

The decision to recommend nutritional supplements was based on the practitioner's assessment of risk of progression to advanced AMD. For most responses, the type of supplement recommended was not consistent with current best-research evidence. Only one in three optometrists regularly assessed smoking status and advised the patient to stop smoking.

BMC Public Health 2013; 13: 564

Patients could benefit from pharmacogenomic management

Following genetic analysis of a randomised, prospective clinical trial evaluating the interaction between genetics and the type or nutritional supplement that subjects received in the Age-Related Eye Disease Study (AREDS), the authors of the study have concluded that patients with intermediate AMD could benefit from pharmacogenomic selection of nutritional supplements.

Subjects (n = 995) were patients with intermediate AMD in one eye and any AMD in the fellow eye, enrolled in AREDS, with available peripheral blood-derived DNA. Participants were evaluated for known AMD genetic risk markers and treatment category.

The progression rate to late AMD was analysed by genotypes and AREDS treatment group using regression analysis. The primary outcome was the effect of inherited gene polymorphisms on treatment group-specific rate of progression to late AMD.

It was found that individuals with one or two complement factor H (CFH) risk alleles derived maximum benefit from antioxidants alone. In these patients, the addition of zinc negated the benefits of antioxidants. Subjects with age-related maculopathy sensitivity 2 (ARMS2) risk alleles derived maximum benefit from zinc-containing supplements, with negative responses to antioxidants.

Ophthalmology 2013; Epub ahead of print

Why do people take dietary supplements?

A cross-sectional, population-based study examined the motivation for adults in the USA to take dietary supplements and to characterise the types of products used for the most commonly-reported motivations.

On the whole, users of dietary supplements are motivated to take these products for their perceived benefit to overall health, rather than for supplementing for nutrients that may be lacking in their diet.

Data from adults aged 20 years or older (n = 11,956) were examined in the 2007-2010 National Health and Nutrition Examination Survey. The most commonly reported reasons for using dietary supplements were to 'improve' (45 per cent) or 'maintain' (33 per cent) overall health. Multivitamins were the most commonly reported type of supplement.

Older adults (60 years or older) were more likely than younger adults to report motivations related to site-specific reasons, such as heart, bone, joint or eye health. Less than one-quarter of individuals used products as a result of the recommendation of their health-care provider.

JAMA Intern Med 2013; 173: 5: 355-361

Blood plasma and lutein supplementation

Lutein supplementation has been found to be associated with a marked decrease in the circulating levels of complement factors D, C5a and C3d.

Oral supplementation with lutein had been proposed to be potentially a simple method to control this inflammatory pathway of the innate immune system.

The purpose of this study was to determine whether the ingestion of lutein, a retinal carotenoid, affects activation of the complement system. Complement factor D (CFD) is a rate-limiting component of the alternative pathway of complement activation and the complement activation products C5a and C3d.

Subjects (n = 72) with early age-related macular degeneration (AMD) were randomly assigned to receive either lutein (10 mg/day) or placebo for one year. Subjects supplemented with lutein had a significant (0.11 µg/ml monthly) decrease in plasma CFD concentration, resulting in a 51 per cent decrease over 12 months. The blood plasma concentrations of C5a and C3d were also significantly reduced in the lutein group compared with controls.

PLoS One 2013; 8: 8: e73387 ■

Channel surfing

Fundus photography in a new light

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Digital ocular fundus photography is a common and widely available imaging modality in optometric practice. While most practitioners are familiar with colour and red-free fundus photography for analysing vascular structures in the retina, a considerable amount of additional diagnostic information can be gleaned from exploring other ways of viewing the retinal photos captured by a fundus camera.

Monochromatic or split-channel viewing

Digital fundus cameras capture images of the fundus with a white light flash. Contained in that light are red, green and blue colour channels which when combined, render a full-colour image of the retina. With the use of standard image analysis software, practitioners can 'split' the RGB light channels and view fundus images with each colour. Essentially, this simulates a filter blocking the transmission of wavelength bandwidths corresponding to the other two colours. It's important to note that objects appear lighter (reduced contrast) when viewed through a light channel of the same colour.

Figure 1 shows a composite (white colour) fundus image and the same image viewed through individual red, green and blue channels. Note that different features of the fundus are accentuated in different light channels due to differing absorption spectra of retinal luteal pigment (most densely concentrated at the macula), haemoglobin and melanin. In other words, by eliminating channels, the visibility of various structures can be enhanced. Haemoglobin in blood vessels is best seen in the green channel. Melanin in RPE/choroid is best seen in the red channel. Features of the retinal architecture are best examined in the blue channel. Disregard a camera lens artefact at 2 o'clock position.

Blue channel

Blue channel (B) increases the visibility of more anterior retinal structures, for example, the internal limiting membrane and nerve fibre layer, which are virtually transparent in white light and likely to be 'drowned out' by the deeper layers of the retina and the RPE.

Therefore, this single channel (approximately 490-510 nm) is of particular benefit when viewing xanthophyll pigment concentrations in photoreceptor layer (lutein, zeaxanthin and meso-zeaxanthin), epiretinal membranes, macular holes or retinal nerve fibre layer defects in early glaucoma. While there are currently no established clinical protocols for correlating retinal pathology and xanthophyll appearance on fundus photography, the blue channel does allow a better view of the macula pigment compared to white light. Similarly, this channel would also be useful in differentiating small cotton wool spots (retinal nerve fibre layer infarct) from a druse.

It is worthwhile to note that since short-wavelength light is more prone to scatter, the quality of the blue channel is particularly susceptible to degradation due to cataract or corneal opacification.

Figure 2 compares full colour and blue channel view of the same fundus in a patient with moderately advanced glaucoma. Note the emphasised visualisation of the superior nerve fibre layer losses in the blue channel. A flash artefact is also present next to the disc.

Continued page 14

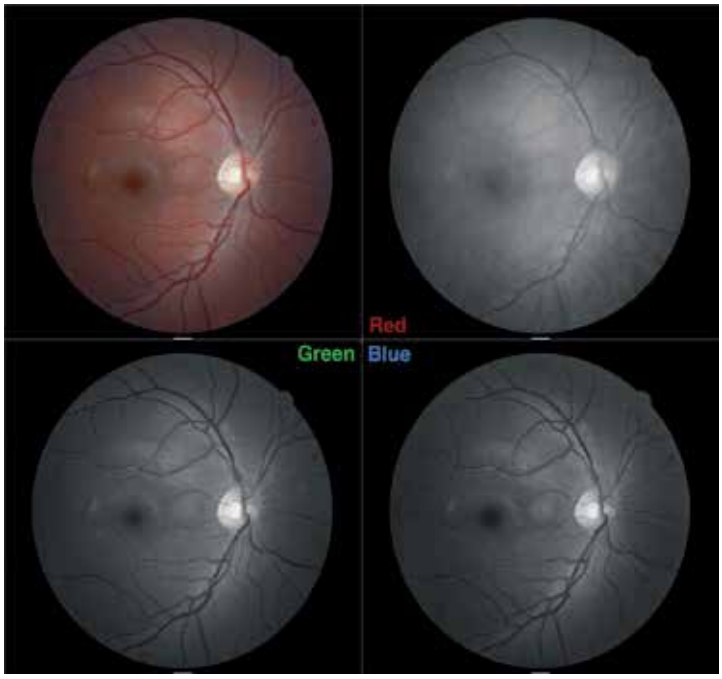

Figure 1. The composite fundus image (top left) and the same image viewed through the red, green and blue channels.

Photography

From page 13

Green channel

Green channel (G) bandwidth is in the middle of the visual spectrum (530-550 nm) and is less affected by cloudy media. The green channel provides great definition to the outer retinal architecture. Haemoglobin in the blood readily absorbs light in this wavelength region, depending on the level of oxygenation, so this channel is particularly useful for documenting retinopathy, anomalous blood vessel calibre changes and other subtle vasculopathies. Drusen and exudates will also appear enhanced in this view.

Isolating the green light channel produces an image similar to the familiar red-free fundus image; however, traditional red-free photography uses a broadband filter to block the longer wavelengths, while allowing mixed short (blue) and medium (green) wavelength bands to be viewed together.

Figure 3 shows the fundus of a patient with diabetic retinopathy. Note the enhanced contrast of haemorrhages in the green channel due to absorption by haemoglobin (arrows). Also note the evident venous dilation and some areas of beading (X).

Red channel

The red (R) channel uses longer wavelength light, with the peak around 590-620 nm. Blood components and retinal vessel walls look indistinct in this channel, as does the optic nerve head. However, retinal pigment epithelium (RPE), choroidal nevi and other pigmented features will stand out better against the paler fundus appearance, and subtle atrophic macular degenerative

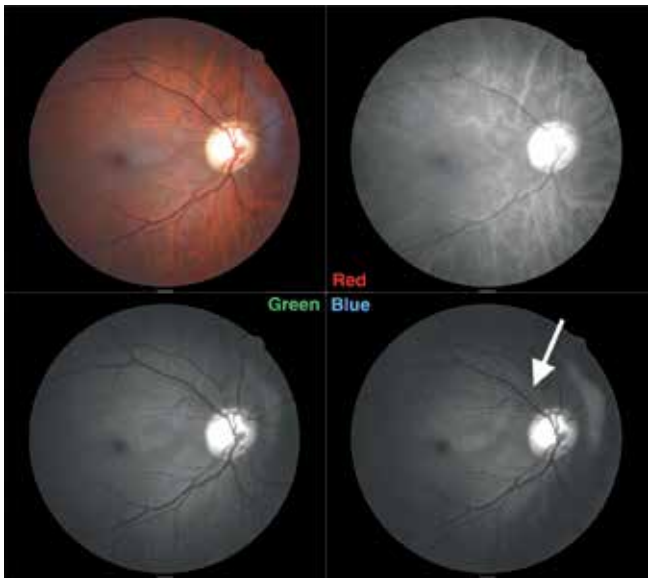

Figure 2. A patient with moderately advanced glaucoma. The blue channel emphasises superior nerve fibre layer losses.

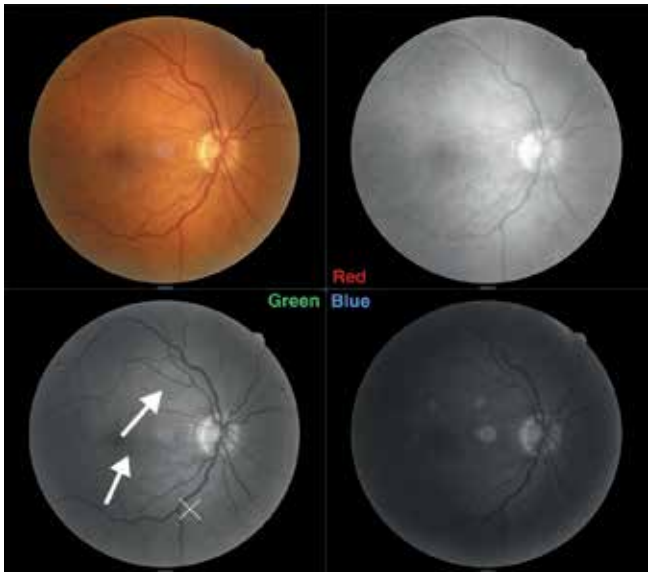

Figure 3. A patient with diabetic retinopathy: green channel enhances contrast of haemorrhages, venous dilation and beading

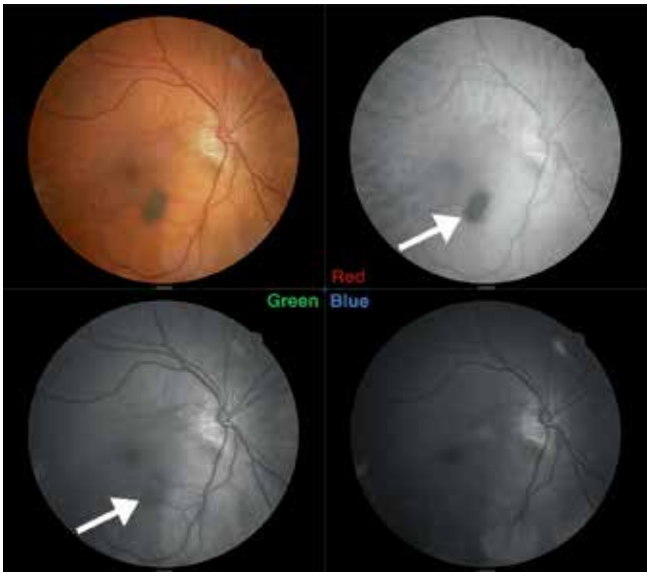

Figure 4. The choroidal nevus has the highest contrast in the red channel, but is invisible in the blue channel

changes or choroidal melanoma features may become more visible than they would be in white light.

The red channel highlights the layout of the choroidal layer. Finer details of the choroidal layer may be indistinct when viewed through the overlying retina in white light.

Figure 4 compares full colour, red channel, green channel and blue channel photography of a choroidal nevus. Note the nevus has the highest contrast in the red channel (due to the abundance of melanin). There is significantly less visibility in the green channel and none in the blue channel.

Additionally, the green channel highlights the presence of a microaneurysm at the superotemporal edge of the fovea, a feature absent in the red channel view.

The benefits of composite diagnoses

Single channel viewing can be particularly useful in observing multiple features of the fundus, which may be difficult or challenging to view together in an overlapping full colour image. In a particularly apt example (Figure 5), the patient's retina exhibits:

- Geographic atrophy due to atrophic macular degeneration–best appreciated in the red channel, which allows ready visualisation of choroidal vessels through the missing RPE
- Multiple small choroidal naevi and peripapillary atrophy–again, best viewed in the red channel
- A small intraretinal haemorrhage adjacent to the macula–best viewed in the green channel
- Disrupted macular pigmentation in the photoreceptors of the macula–seen best in the blue channel.

Thus a complex clinical presentation and image may be 'split' into composite diagnoses by the depth of pathology in the photographed tissue.

Figure 5 shows a case of multiple retinal pathologies, presented in both colour and individual red, green and blue channels.

It is important to remember that both normal and abnormal fundus colouration is highly variable in all patients and depends on many factors, such as the patient's age, ethnicity, media and refractive status, so that the appearance of retinal structures in the RGB channels may vary.

Fundus photography is a valuable imaging modality in clinical practice, and should be used alongside other diagnostic tools such as ocular coherence tomography and fundus autoflorescence (FAF) in the management of ocular disease. It is my hope that this brief article encourages the reader to look at retinal fundus photography in a new or at least not exclusively 'white' light in the management of their patients and ocular disease. ■

Acknowledgement

The author acknowledges the assistance of Dr Adrian Bruce in preparing this article.

All images were taken with a Canon CR-1 digital fundus camera.

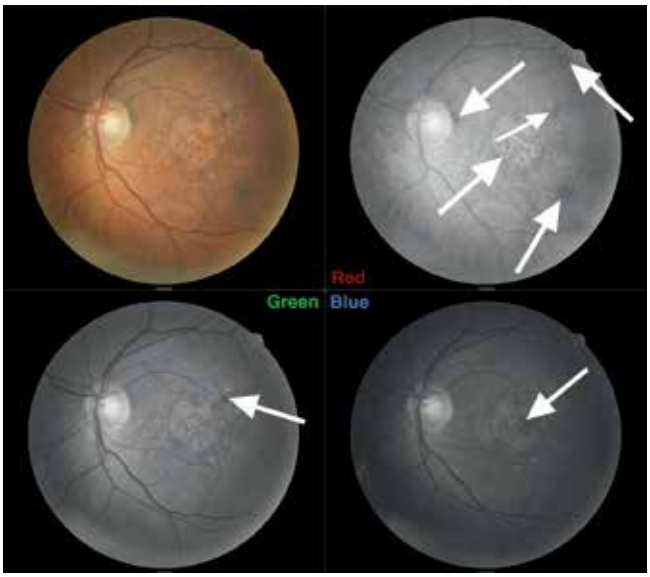

Figure 5. A case of multiple retinal pathologies, revealed through channel separation

Endothelial keratoplasty

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Over the past decade, endothelial keratoplasty (EK) has replaced penetrating keratoplasty (PK) as the treatment of choice for the surgical management of corneal endothelial failure.[1] In 2012, 42.6 per cent of all corneal transplants performed in Victoria were EKs. That number has been steadily increasing since 2008, when it represented only 10.3 per cent of treatments.[2]

Of the several advantages EK has over PK, perhaps the most important is the increased amount of intra- and post-operative safety it affords. In addition, visual results for EK patients are faster and better than for those undergoing PK. There is an absence of induced astigmatism, which is often seen after PK, and an absence of other suture-related complications.[1] Significantly, the incidence of rejection is reduced with EK[3] and this may have a positive impact on the long-term survival.

History

The concept of targeted replacement of the corneal endothelium was first published in 1956 by Charles Tillett,[4] but it was not until Gerrit Melles published in 1998 that this concept began to take hold.[5] Melles developed a technique called posterior lamellar keratoplasty (PLK) that was later refined by Mark Terry to be termed deep lamellar endothelial keratoplasty (DLEK).[6] DLEK was a promising procedure but the technique was somewhat difficult as it involved an intraocular trephination and an inlay of donor tissue.

In 2002, Melles again refined the technique to be an onlay procedure, in which additional tissue was added to the inner surface of the cornea.[7] This procedure was later named Descemet's stripping endothelial keratoplasty (DSEK), by Francis Price.[8] Corneal surgeons around the world adopted this technique rapidly, as early results were extremely promising.[9]

DSEK involved a manual preparation of donor tissue, such that just the endothelium, Descemet's membrane (DM) and posterior stroma could be transplanted. Mark Gorovoy in 2004[10] described the automated preparation of donor tissue, using a microkeratome, similar to the microkeratomes previously used during corneal refractive surgery. As a consequence, DSAEK was developed and it is this technique that forms the gold standard of EK today.

The procedure

The most common indications for EK are Fuchs' corneal endothelial dystrophy, pseudophakic bullous keratopathy, and failed PK, although the surgery is appropriate for any form of endothelial failure. For DSAEK, donor tissue is prepared by removing the anterior portion with the microkeratome, leaving a smooth surface that will later form the interface between the donor and the host.

Tissue may be 'precut' in the eyebank and provided to the surgeon, or may be prepared in the operating room by the surgeon just prior to the procedure. The surgery is most commonly performed under local anaesthesia, and involves removal of the diseased endothelium and DM from the host prior to insertion of the donor tissue. The eye is then filled with air, to provide tamponade and allow the smooth surfaces of the donor and host cornea to stick together without sutures. (Figure 1)

Results of DSAEK have consistently been

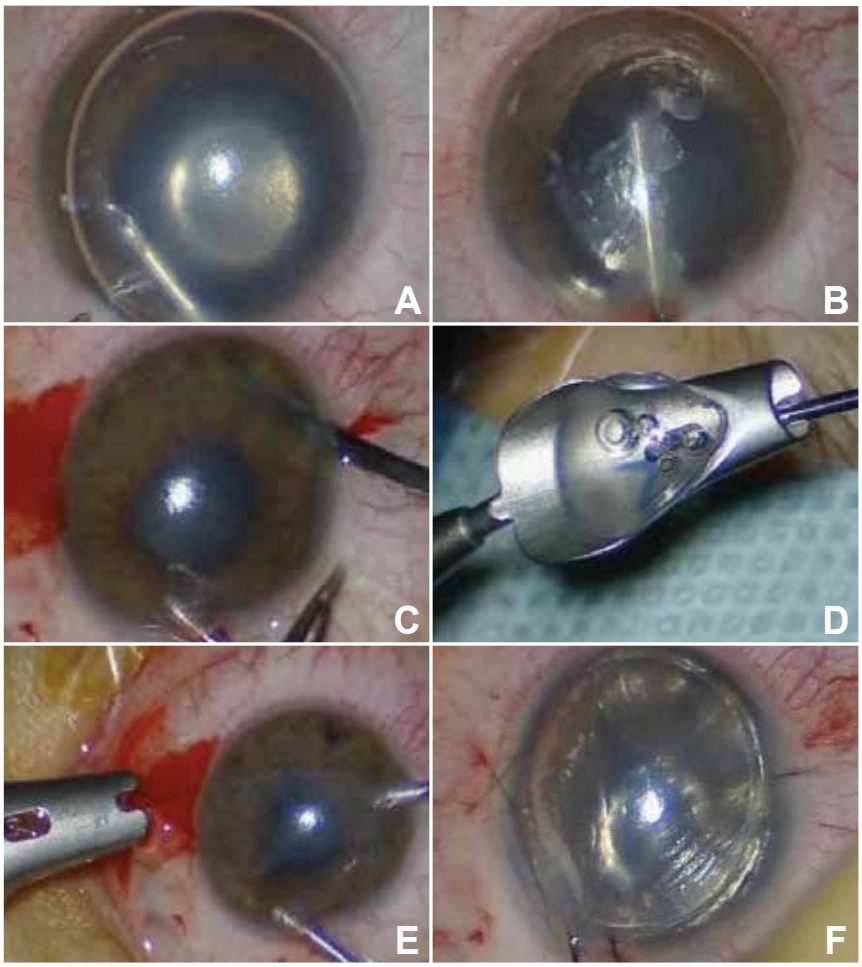

Figure 1. Surgical steps of DSAEK. A: Descemet membrane (DM) is scored under air. B: DM is 'stripped' or removed. C: Inferior iridotomy is created to avoid pupil block glaucoma. D: Prepared donor tissue is loaded onto a Busin Glide. E: Donor tissue is pulled into the eye. F: Air is injected underneath the donor tissue and surgical wounds are sutured.

Faster, better and safer, EK is achieving excellent results with promising new techniques

reported as excellent (Figure 2); 75 per cent of eyes without comorbidities have achieved spectacle-corrected acuity of 6/9 or better at one year, increasing to 90.7 per cent by three years.[11]

In a quest to further improve visual outcomes, Gerrit Melles again developed a new technique. Descemet's membrane endothelial keratoplasty (DMEK) was described in 2006[12] and involves the insertion of just DM and endothelium of the host cornea.

Visual results of DMEK were found to be even better than DSAEK, with 98 per cent reported to achieve 6/9 or better at one year.[13] However, DMEK is challenging surgery and the complication rate may be unacceptably high.[14] Tissue may be lost during the preparation phase, and unfolding the tissue inside the eye is perilous. The incidence of detachment requiring repeat air injection is much higher than for DSAEK, and tissue loss and primary failure occur more commonly.[14]

In attempt to achieve the visual results of DMEK, with the surgical ease of DSAEK, Massimo Busin developed ultrathin (UT) DSAEK.[15] UT DSAEK involves the use of a very thin donor tissue, prepared by a double pass with the microkeratome (Figure 3). Results of UT-DSAEK were published this year,[15] with 95 per cent of patients without comorbidities achieving 6/9 vision by 12 months and 100 per cent by two years. The complication rate was much lower in the 280 cases reported, with a detachment rate of less than four per cent, compared to as much as 68 per cent reported for DMEK.[15]

It has been reported that the incidence of endothelial rejection is much less in DSAEK than PK,[3] occurring in about 12 per cent of cases by year two. The incidence of rejection after DMEK is just one per cent at two years,[3] and UT-DSAEK, perhaps as expected, falls between at three per cent.[15] While it is too early in the development of these new techniques to comment on the comparative survival, the initial endothelial cell loss is similar across all three groups[15] and is likely to be the most important predictor.

As we await the long-term data on all of these forms of EK, new techniques are in development. Stem cell culture of endothelial cells and medical treatments for endothelial failure may well be a reality in the future. Hopefully, there will be many more exciting developments to come in this field but the one consistent message is that PK is no longer indicated for the treatment of corneal endothelial failure. ■

References available on request. Email j.megahan@optometrists.asn.au, Subject: Beltz Endothelial keratoplasty

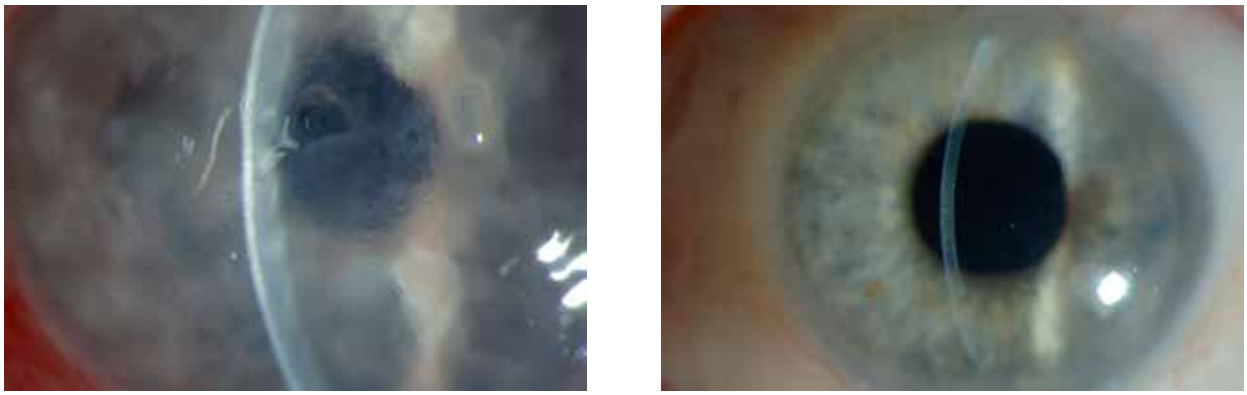

Figure 2. (Left) Preoperative appearance of an eye with marked endothelial failure secondary to Fuchs' endothelial dystrophy. (Right) Three months postoperatively, the patient already has 6/9 visual acuity.

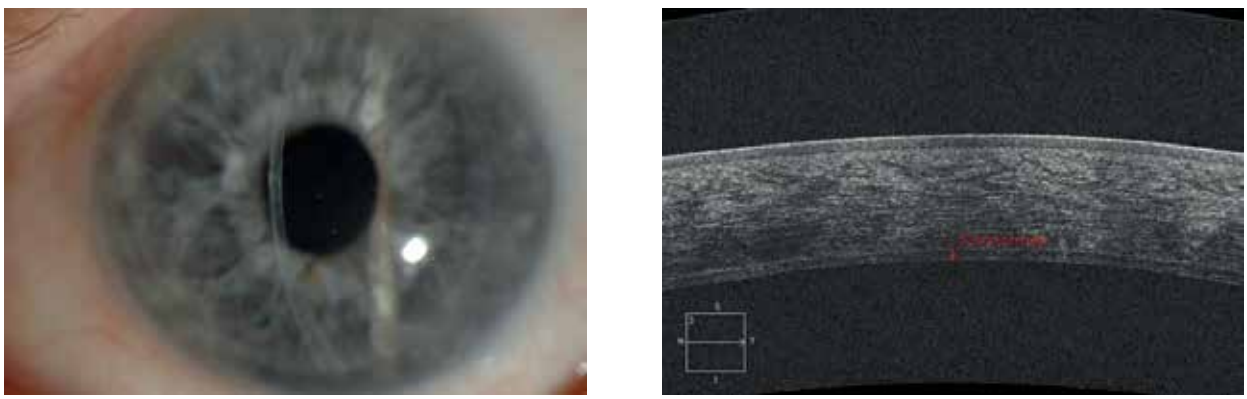

Figure 3. (Left) Postoperative appearance of an eye three months post ultrathin DSAEK. The relative thickness of the donor compared to the host cornea can be seen in the slit. (Right) Anterior segment ocular coherence tomography may be used to ensure attachment of the donor and measure the central thickness, in this case just 52 µm.

Plaquenil screening

HCQ/CQ retinopathy

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Hydroxychloroquine (HCQ) and chloroquine (CQ) are anti-malarial drugs commonly used in the treatment of rheumatoid arthritis, lupus and several other inflammatory conditions.[1] Hydroxychloroquine has largely replaced chloroquine in the treatment of these diseases, as it has fewer side-effects and is therefore better tolerated by patients.[1] However, patients who use these medications run the risk of developing an uncommon but serious complication known as HCQ/CQ retinopathy.[1] It has also been referred to as 'bull's-eye maculopathy'.

This condition results from the affinity of these medications for the retinal pigment epithelium (RPE), causing RPE depigmentation and additional damage to surrounding retinal tissue.[1] The drugs also have a predilection for the rod and cone receptors within the macula.[2] Once visible damage is seen on funduscopy, an irreversible loss of vision will typically occur.[3] Even with prompt discontinuation of therapy, vision often deteriorates further for several years.[2,4] Therefore, early detection of any retinal change is fundamental in preserving vision.

Toxicity rates and dosage

The risk of retinopathy is low during the first five years of therapy but quickly increases to about one per cent after five to seven years of use.[5] The same is true with a cumulative dose of 1000 g HCQ, or 460 g CQ.[5] Those taking the drug for longer than seven years possess an even greater risk.[5] Studies have also shown that the risk of maculopathy stands independent of daily dose.[5] The typical daily dose of 400 mg HCQ or 250 mg CQ is acceptable.[5]

Caution must be used in patients of short stature, as these doses may be too great and will elevate the risk for maculopathy.[5] In these situations, the correct dose should be calculated based on height and ideal weight, with 6.5 mg/kg/day being the cut-off for HCQ, and 3.0 mg/kg/day for CQ.[5,6] This also applies to obese patients, as these drugs are not stored within fatty tissue and can accumulate elsewhere, for example, the retina.[5]

When to screen

A comprehensive baseline examination, including thorough funduscopy, is needed within the first year of therapy initiation.[4,5] It will serve as a comparison for future exams and screenings. After the baseline examination, it is recommended that patients receive yearly screenings after five years of use of these medications.[5] High-risk patients should be screened earlier and possibly more often.[1,5] High-risk criteria include older age, and pre-existing retinal disease.[3] Liver or kidney disease is also a high-risk factor, as both organ systems aid in removing these medications from the body.[3,7] Refer to Table 1 for a full list of high-risk factors.

Screening methods

In 2011, Marmor and colleagues[5] released new screening guidelines through the American Academy of Ophthalmology. This update indicates a shift towards more objective testing to help confirm or deny the presence of maculopathy. A thorough fundus examination is still essential at each visit to document any visible changes over time. It may also be wise to obtain fundus photos for future reference.[5]

The new guidelines urge clinicians to use 10-2 visual field testing, as it assesses the patient's macular function.[5] Any change, however subtle, should be taken seriously. Paracentral scotomas typically manifest first, affecting saccades in reading.[5] Central scotomas and a decrease in acuity can also result if toxicity spreads towards the fovea.[5,6] Spectral domain ocular coherence tomography (SD-OCT), multifocal electroretinogram (mf-ERG), or fundus autofluorescence (FAF) must be used in addition to 10-2 visual fields when possible.[5] These objective tests are highly sensitive and assist in detecting subtle retinal changes.[5]

It is worth noting that the mf-ERG was found to be a suitable alternative to 10-2 visual fields, as it too measures function.[5] This may prove useful when reliable fields cannot be obtained, for example, in poor responders. Regardless of which procedure is used to assess function, at least one of the other objective tests should be employed as well. Amsler grid is no longer recommended but can be used as an ancillary test to support other data.[5] Colour vision testing may also be performed but is not recommended as part of standard screening protocol, as colour vision changes are not always specific to anti-malarial therapy.

SD-OCT is likely to be the most accessible and widely used objective procedure. On these scans, the practitioner must look for a disruption of the photoreceptor integrity line (PIL), also known as the inner/outer segment layer.[5,8] This is first seen in the parafoveal retina. As this area is further damaged and begins to thin, the foveal depression becomes shallower and less distinct.[8] Additionally, a 'flying saucer' shape on the SD-OCT may develop at the fovea where the retinal structures are generally preserved.[8] It is important to understand that time domain OCTs are not sufficiently sensitive to detect these early retinal changes associated with HCQ/CQ therapy.[5,8]

Risk factor	Description
Dose	> 6.5 mg/kg/day HCQ > 3.0 mg/kg/day CQ
Duration	> 5 years
Age	> 60 years
Systemic conditions	Liver or kidney disease, resulting in increased blood medication levels
Pre-existing retinal disease	Any compromise of retinal tissue may render it more susceptible to toxicity. May also obscure early signs of toxicity.
Body habitus	High percentage body fat, or obese

Table 1. High-risk factors for HCQ/CQ retinopathy [3,5,7]

Case report

Detection of early HCQ retinopathy

A 53-year-old Caucasian woman with rheumatoid arthritis presented to the clinic for a complete vision examination. She had been taking the standard 400 mg dose of hydroxychloroquine for the previous five years and was being monitored for any vision changes indicative of early HCQ retinopathy. The patient had noticed some vision changes since her last examination, with best corrected visual acuity being 6/9 in the right eye (OD), and 6/7.5 in the left eye (OS). This demonstrated a decrease in acuity from her prior eye examination, when acuity was 6/6 in each eye.

Ocular motilities, confrontation fields and pupils were all normal. Macular cube SD-OCT scans of each eye revealed noticeable parafoveal thinning (Figure 1). The foveal depression also appeared relatively shallow in these scans. Fundus photos exhibited subtle parafoveal RPE pigment changes (Figure 2). These findings, in addition to visual field defects and nonspecific colour vision changes, raised our suspicion of early HCQ retinopathy. A decision to discontinue use of HCQ was then made in collaboration with the patient's prescribing rheumatologist.

On re-examination two years later, the patient's vision had returned to the baseline of 6/6 in each eye, and colour vision tested normal with the Farnsworth D-15 dichotomous colour blindness test. SD-OCT scans of the maculae still demonstrated residual parafoveal thinning but there was no additional progression. The patient will continue to be monitored for any further changes.

Summary

The new screening guidelines for patients taking HCQ/CQ recommend using 10-2 visual fields with additional objective testing, such as an SD-OCT, mf-ERG or FAF.[5] While the risk of a patient developing retinopathy secondary to these medications is relatively low, the potential visual consequences are significant and often permanent.[1,5,6] Careful screening must be conducted to ensure proper dosing, reveal any early retinal changes and hopefully, prevent any unnecessary loss of vision.

Patients should be advised to return before their regularly-scheduled examinations if they note any new changes in vision, especially reduced visual sensitivity, reading difficulty or blind spots.[5]

As always, any ocular or visual changes should be discussed at length with both the patient and their prescribing physician. This allows for a joint effort in deciding on the best course of action, whether it be continuing, stopping or changing the use of these medications. ■

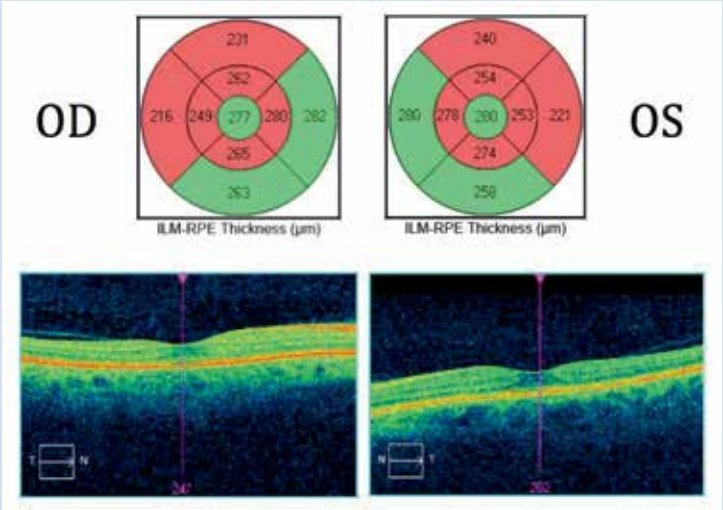

Figure 1. SD-OCT scans uncovered significant parafoveal thinning, with preservation of the central macula. Cross-sections of the maculae indicate a relatively shallow foveal depression. Image: Craig McCormick OD

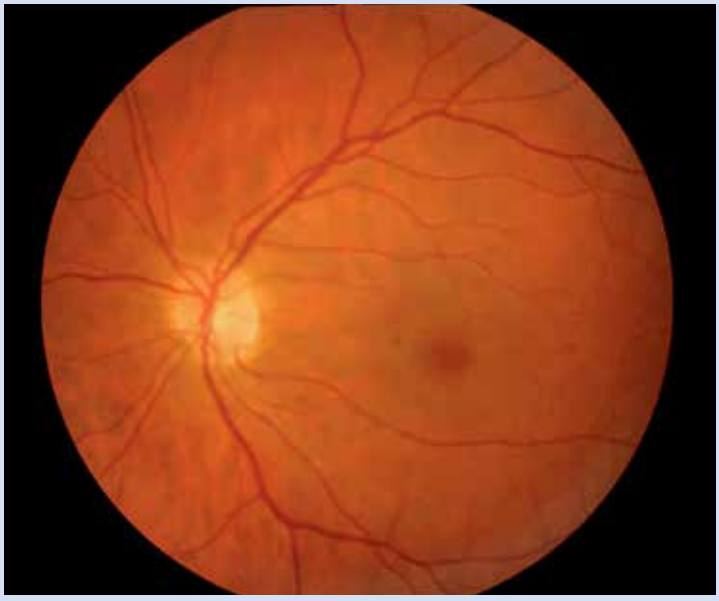

Figure 2. Fundus image of the left eye showing subtle parafoveal RPE changes consistent with HCQ retinopathy. Image: Craig McCormick OD

References available on request. Email j.megahan@optometrists.asn.au, Subject: Bull's-eye maculopathy.

Corneal collagen cross-linking in keratoconus:

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Keratoconus may be characterised as a disorder of young people.[1] There is a bimodal distribution of the age of onset with typical keratoconus beginning in the late teens or early twenties, and a later onset in middle age for the pellucid marginal corneal degeneration subtype. The earlier the onset of keratoconic keratectasia, the higher the chance of progression necessitating eventual corneal transplantation. Early onset keratoconus typically progresses for a decade or so before stabilising (relatively) in the early thirties. This is thought to be due to physiological collagen cross-linking that occurs with ageing.

What causes keratoconus?

Despite continuing research, the exact cause of keratoconus remains unknown. Research indicates that keratoconus may be caused by an excess of proteolytic enzymes that break down the proteins within the cornea, causing the cornea to become thin and stretched.

The genetic inheritance of keratoconus has not clearly been determined although sometimes it runs in families. It appears that it may involve a number of different genes – 27 at last count. Blood relatives of someone affected with keratoconus have minor changes in their corneas that may indicate that keratoconus probably varies both in the specific genetic cause as well as in its expression within a family.

Vigorous eye-rubbing can contribute to the disease process. People with keratoconus should absolutely avoid rubbing their eyes. This is sometimes difficult because atopy is commonly associated with keratoconus. Anti-allergy drops such as Patanol or Zaditen can help. Another association is sleep apnoea.

Until recently, the only option for a keratoconus patient who was intolerant of a rigid contact lens was a corneal transplant, lamellar or full-thickness. About 20 per cent of keratoconus patients need corneal transplants during their life-times;[2] however, pioneering work by a group in Dresden, Germany, under the direction of Theo Seiler MD PhD has provided a new treatment option to significantly delay or prevent the need for transplants in these patients.[3]

Corneal collagen crosslinking

When Professor Seiler originally introduced corneal collagen crosslinking (CXL) in 2003 as a therapeutic option to delay or prevent the progression of keratoconus, it was viewed with a healthy degree of scepticism but preclinical experiments and a large body of literature supporting its efficacy have since convinced us that this is a safe and effective treatment.[4]

The first randomised trial of this treatment, which was conducted in Melbourne at the Royal Victorian Eye and Ear Hospital, showed definite benefits[5] (Figure 1). These results have been replicated many times and CXL has now become solidly established as a therapy. A minority of treated corneas also show significant flattening and improved best spectacle corrected visual acuity. (Figure 2)

In a clinical trial, Rabinowitz and colleagues have followed 300 cases done to date with three-year follow-up. They have noted minimal progression in only two per cent of patients. They have also treated 43 patients younger than 18 years of age using CXL. In these 51 eyes, even though keratoconus progression was rapid preoperatively, they have not seen any progression to date. Long-term follow-up studies suggest that the effect of CXL lasts at least eight years.[6]

Based on Seiler's recommendations,[7]

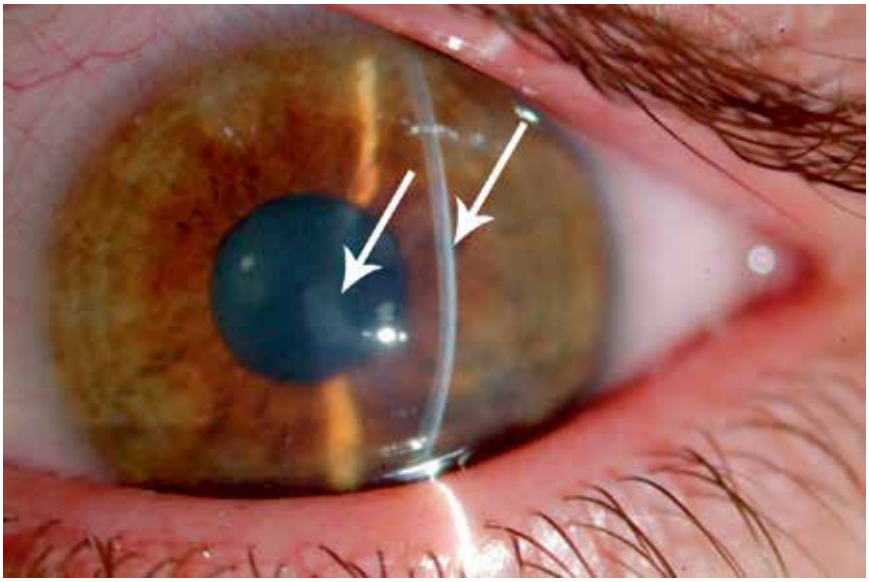

Figure 1. Week 1 postoperative. Left arrow indicates residual scar from removal of apical nodule, right arrow indicates anterior one-third corneal haze.

how young is too young?

CXL is a well-established therapy to delay or prevent the progression of keratoconus. The growing consensus is that it should be performed earlier rather than later.

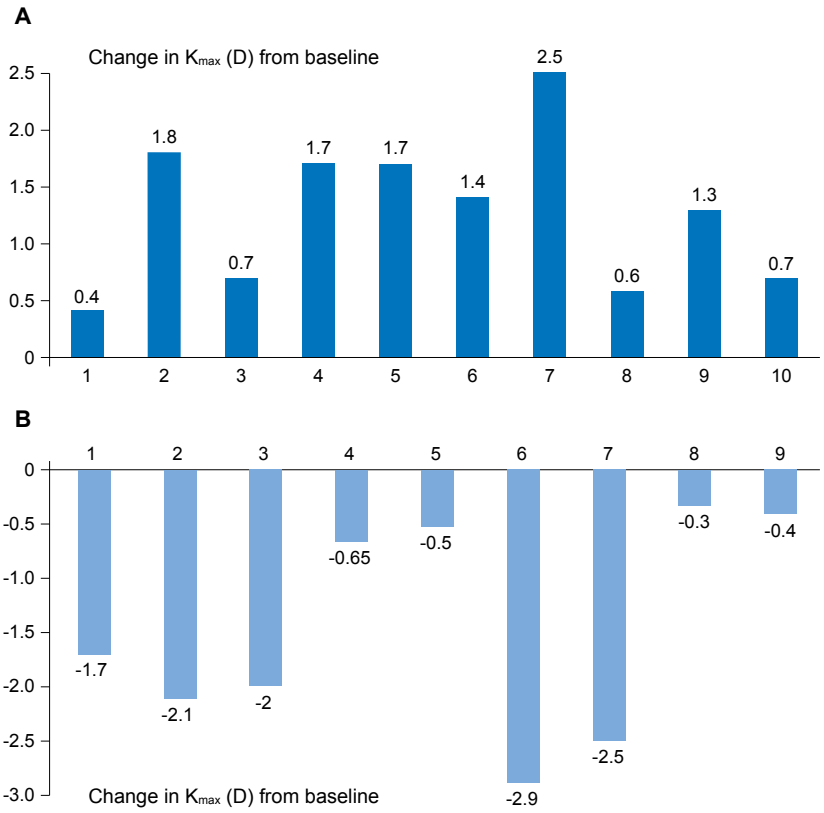

Figure 2. Results of the Melbourne trial. Untreated eyes (A) deteriorated while treated eyes (B) stabilised or improved.

we have adopted the following inclusion criteria for CXL:

- Progression of astigmatism by refraction of at least 1.00 D and confirmed by topographic evidence of progressive keratoconus in the year preceding treatment
- Corneal thickness, as measured by ultrasound, of no less than 400 µm
- Central K readings not exceeding 58 D
- No central or paracentral corneal scarring.

In selected eyes in which corneal thickness is between 350 and 400 µm, we have started performing CXL after using hypotonic solution to swell the cornea. Treating without epithelial removal has also been studied and seems to have about 30 per cent of the effect of treatment with removal of epithelium.[8-10]

If we believe that outcomes will be less than optimal because of severe central corneal irregularity, we recommend penetrating keratoplasty or deep anterior lamellar keratoplasty instead of CXL to avoid performing an additional procedure prior to proceeding to a transplant.

How young?

Young age is not now thought of as an exclusion criterion for CXL. Recent publications with paediatric patients have shown significant and rapid functional improvement in these young patients with progressive keratoconus who underwent CXL.[11-19]

Caporossi and colleagues found a good functional response and stability of the keratoconus with three years of follow-up.[14] Vinciguerra and colleagues reported improved UCVA and BSCVA in patients up to 18 years of age with progressive keratoconus who underwent CXL.[15] They felt that this improvement was most likely to be due to significant reduction of corneal asymmetry, and corneal as well as total wavefront aberrations. Gaster and colleagues reported in 2012 on 31 eyes of teenagers who underwent CXL and found significant improvement in UCVA and BSCVA and decreased pachymetry along with no significant complications.[16] They concluded that CXL in young patients is safe and efficacious, and should be performed earlier rather than later.

A large Swiss study reported by Chatzis and Hafezi followed 59 eyes of children and adolescents aged nine to 19 years.[17] They found significant corneal flattening up to two years post-treatment but observed some possible loss of effect at three years. Other recent papers[18,19] suggest a similar positive response in younger patients as is seen in adults.

Treating children can introduce logistical and other difficulties. In adults the procedure is usually performed under topical anaesthesia, with 30 minutes of soaking with riboflavin solution followed by 30 minutes of focused UVA irradiation. This is not always well tolerated in children. We have treated a number of uncooperative patients at the RVEEH under general anaesthesia.

Conclusion

The future for keratoconus patients looks good and hopefully, in the not too distant future, the need for corneal transplantation will be significantly reduced. Unfortunately, this relatively new procedure is not yet covered by the Australian Medicare Benefits Schedule. ■

References available on request. Email j.megahan@optometrists.asn.au, Subject: Sullivan Corneal crosslinking

Idiopathic macular holes

OCT has transformed the way we understand the formation and progression of macular holes. In the modern vitreoretinal era, surgical repair is now a viable option.

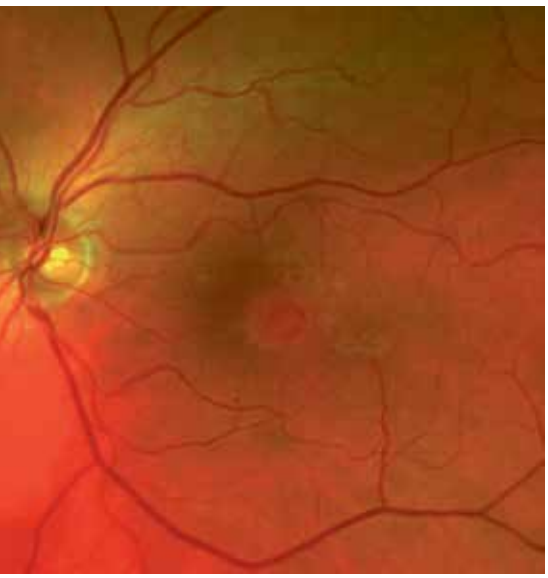

Figure 1A. Fundus image of a macular hole

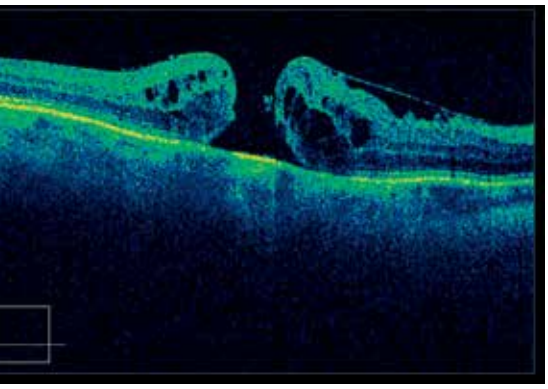

Figure 1B. OCT of a macular hole

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Macular hole is a condition in which a defect develops at the fovea, resulting in central vision impairment (Figures 1A, 1B).

Pathogenesis

The most common type of macular hole is the so-called 'idiopathic' variety, which occurs in older patients, but it may also develop following retinal detachment and as a consequence of blunt ocular trauma.

Idiopathic holes occur in the ageing eye as a result of an abnormally firm adhesion between the cortical vitreous and the fovea, leading to incomplete detachment of the posterior vitreous from the retina (PVD). The current theory of macular hole pathogenesis is that shrinkage of the prefoveal cortical vitreous causes traction on the fovea and dehiscence at the umbo, the point at which the retina is thinnest (Figure 2). Once there is a breach in the inner limiting membrane (ILM), fluid is able to enter the surrounding neuroretina, creating the cystic cavities often found around the margins of a macular hole.

The four stages

In the Gass classification[1,2] there are four stages of idiopathic macular hole, which are readily differentiated on ocular coherence tomography (OCT), an imaging modality that has enhanced our understanding of the formation, progression and staging of this condition.

Stage 1

Also known as an 'impending hole', stage 1 is characterised initially by a yellow spot at the fovea, (stage 1A, Figure 3) and later by a central yellow ring (stage 1B, Figure 4). On OCT there is persistent attachment of the vitreous to the fovea, creating vitreo-foveal traction, loss of the foveal depression with separation of the photoreceptors from the pigment epithelium (RPE) and progressive dehiscence of the outer retina. In about 50 per cent of stage 1 holes, the vitreous detaches completely from the fovea, leading to spontaneous reversal of the macular changes.

Stage 2

An enlarging defect develops in the innermost layer of the retina and very fine radiating traction striae, as well as intraretinal cystic cavities, may become visible around the hole, which typically has a diameter of less than 400 μ (Figure 5). The vitreous is still attached to the edge of the hole. Most stage 2 holes progress but a few are capable of spontaneous closure (Figures 6A, 6B, 6C).

Stage 3

There is further enlargement of the hole to exceed 400 μ in diameter and the vitreous separates completely from the macula. In many cases this results in a small 'operculum' suspended anterior to the hole (Figure 7), which may be visualised by the patient as a tiny translucent floater. This 'operculum' is made up of glial elements but sometimes contains photoreceptor fragments. Many stage 3 holes do not progress to stage 4,

Figure 2. Histological cross-section of macula

and with the passage of time develop small white deposits of RPE proliferation in the base (Figures 8A, 8B).

Stage 4

The vitreous detaches from the optic disc (complete PVD), sometimes creating a Weiss ring, but the macular hole may not enlarge much more from this point.

Epidemiology

The peak incidence of idiopathic macular holes is in the sixth and seventh decades of life, whereas traumatic holes generally affect younger people. Numerous epidemiological studies[3-7] have reported a prevalence of around 1.5 to 3.3 cases per 1,000 head of population, with the highest rate occurring in Caucasians. In a retrospective study conducted over 10 years at the Mayo Clinic,[7] researchers found an incidence of eight per 100,000 per year in a predominantly white population. Macular holes are three times more common in females than males and approximately 12 per cent are bilateral.[7]

Presentation

Macular holes generally present in one of three ways:

- The patient becomes aware of metamorphopsia or a change of vision in the affected eye.
- The patient realises they have a problem with one eye when they cover the other one.
- Some patients, particularly the elderly, are not aware of a problem until they undergo a routine eye examination and the diagnosis is made by an optometrist.

A retinal detachment developing as a result of a macular hole generally occurs only in highly myopic eyes with chorioretinal atrophy at the posterior pole (Figure 9).

Continued page 24

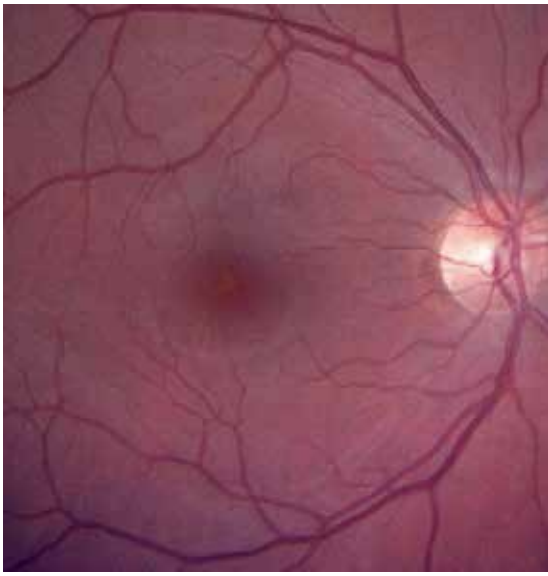

Figure 3A. Fundus image of stage 1A macular hole

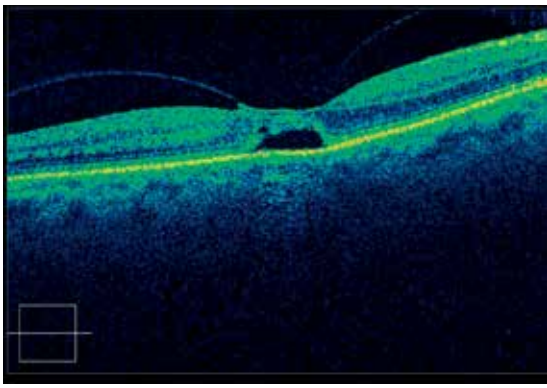

Figure 3B. OCT of stage 1A macular hole

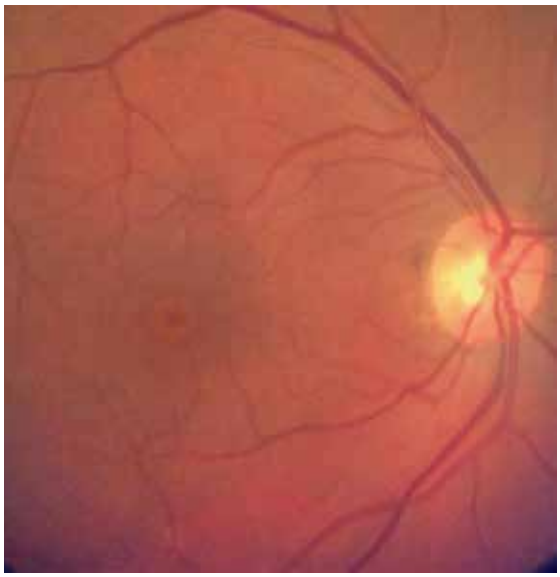

Figure 4A. Fundus image of stage 1B macular hole

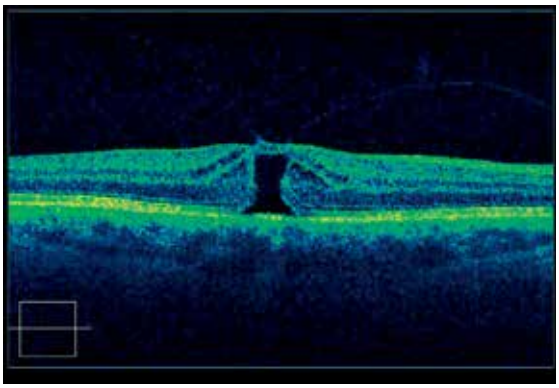

Figure 4B. OCT image of stage 1B macular hole

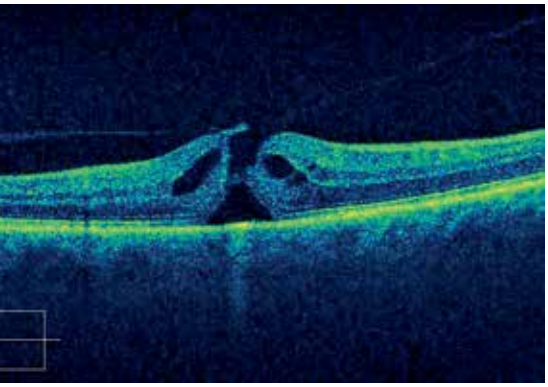

Figure 5. OCT of stage 2 macular hole

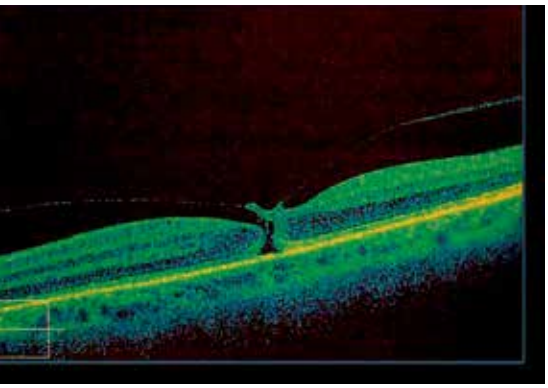

Figure 6A. May: VA 6/12

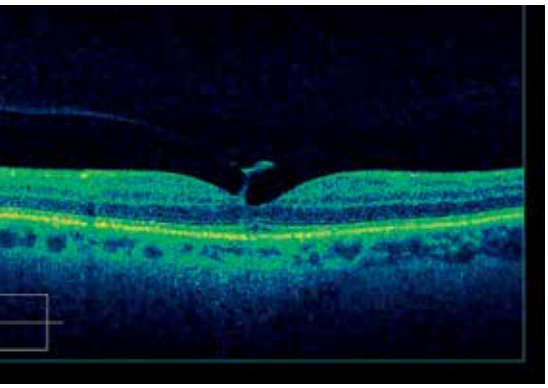

Figure 6B. August: VA 6/6

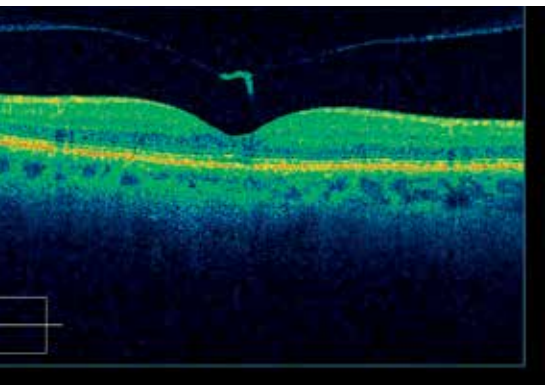

Figure 6C. December: VA 6/5

Figure 6. OCT of spontaneous resolution of stage 2 macular hole

Idiopathic macular holes

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Examination

The visual acuity is typically in the range of 6/12 to 6/60 and Amsler grid testing reveals a central scotoma with distortion of the surrounding lines. Macular holes do not generally affect the pupil reactions. Slitlamp biomicroscopy reveals a round central neuroretinal defect, which in larger holes is darker red due to exposure of the underlying RPE and choroid. There is usually a cuff of subretinal fluid surrounding larger holes and a number of tiny white deposits are often present in the base of holes of longer duration.

Investigation

OCT has become the key investigation in macular diseases in general and is very useful in the staging of macular holes.

Prior to the advent of OCT, the Watzke-Allen test was useful in the diagnosis of macular holes. A positive result is obtained when the patient is able to detect a gap in a vertical slit of light as it crosses the hole during biomicroscopy, but this test has become obsolete in centres in which OCT is available.

Autofluorescence photography reveals a focus of hyperfluorescence corresponding to the macular hole (Figure 10), but in most cases adds nothing to the information provided by OCT and rarely has a role to play in the diagnosis of this condition.

History of treatment

Stage 1 holes may simply be monitored, as they frequently resolve spontaneously but treatment is indicated for stages 3 and 4, as well as most stage 2 holes. It is questionable whether surgery should be offered to patients with chronic holes, in other words, of longer duration than a year, as the closure rate is lower and the visual benefit uncertain.

Prior to 1991, it was not appreciated that macular holes could be cured. In that year, Kelly and Wendel[8] published a small series on 52 eyes in which they were able to close. Using vitrectomy surgery and gas tamponade, they achieved success with 30 eyes

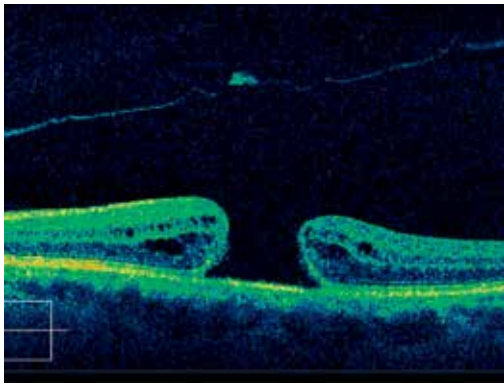

Figure 7. OCT of stage 3 macular hole with operculum

Figure 8A. Macular hole with white deposits in base

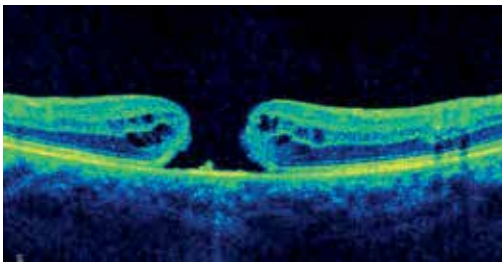

Figure 8B. Macular hole with white deposits in base

(58 per cent). The success rate was modest but their study demonstrated that something could be done for this condition and the era of macular hole surgery had begun.

The early technique consisted of 20-gauge vitrectomy, separation of the posterior hyaloid face from the optic disc and macula, fluid/air exchange, then replacement of the air with a slightly expansile concentration (15-16 per cent) of perfluoropropane gas (C_3F_8). The patient was then instructed to posture face-down as much as possible for the next two weeks to ensure the gas was tamponading the hole.

This was a challenging ordeal for frail, elderly patients, so special chairs and bed cushions were developed to facilitate prone positioning, but despite these aids many people found it difficult or impossible for extended periods. In addition, there are problems associated with the prolonged intraocular presence of C_3F_8 gas. For example, patients are not permitted to fly in an aircraft until the gas has been reabsorbed, which may take up to 10 weeks, and vision is impaired in the operated eye until the gas-fill is less than 50 per cent.

A key advance in macular hole surgery was the idea of peeling the ILM, first introduced by Park and Sipperley[9] in 1999, based on the theory that a taut ILM may produce radial traction on the hole, preventing it from closing. They reported a closure rate of 91 per cent in 58 eyes in which the ILM was peeled.

Initially the ILM was peeled without staining, which is technically challenging, but there are now several vital dyes, which make the exercise much easier. Indocyanine Green (ICG) is used in many centres, particularly in Japan and the United States, but concerns have been raised about possible retinal toxicity, so most retinal surgeons in Australia employ one of two blue stains: Trypan Blue (Membrane Blue) or Brilliant Blue G (ILM-Blue, Brilliant Peel). Early concerns that ILM peeling may have an adverse effect on the visual outcome have not been confirmed.

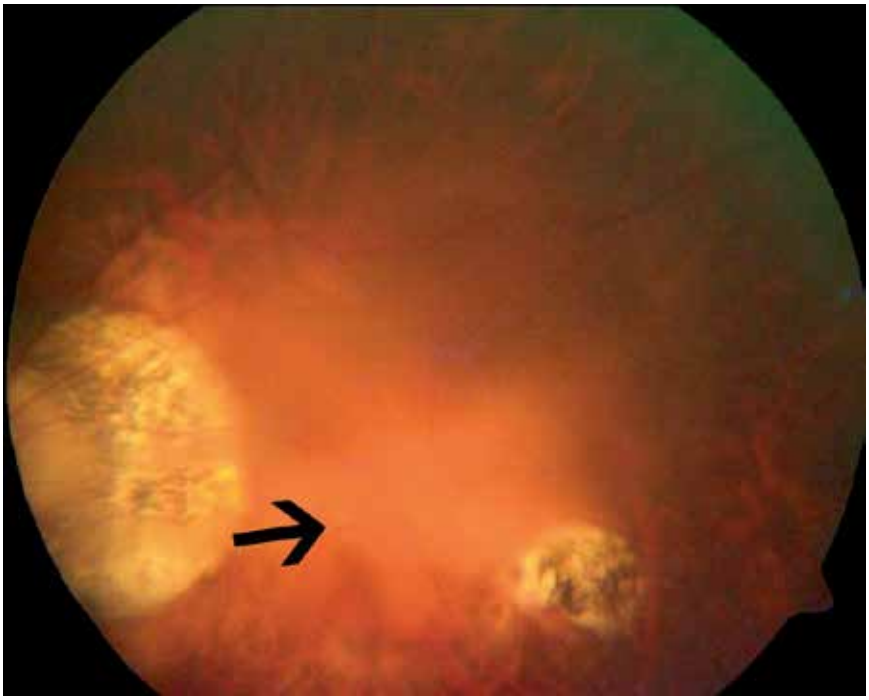

Figure 9. Myopic eye with detachment from macular hole (arrow)

Which approach?

There are four key points to consider when deciding on the best approach to macular hole surgery.

How quickly do macular holes close after surgery?

It is possible to obtain an OCT scan in many gas-filled eyes, particularly in the presence of pseudophakia, by selecting the maximum myopic correction on the instrument. There has been a number of recent studies[10-14] using this technique to demonstrate high closure rates within even the first 24 hours after surgery (Table 1). Figures 11A and 11B depict complete closure of a stage 3 hole on the first post-operative day.

Is it necessary to peel the ILM in every case?

As shown in Table 2, most studies[15-19] report a higher success rate following ILM peeling, although Tadayoni and colleagues[16] found it made no difference in holes smaller than 400 µ. Interestingly, Brooks[15] recorded a 25 per cent reopening rate within six months in eyes in which the ILM had not been peeled.

Continued page 26

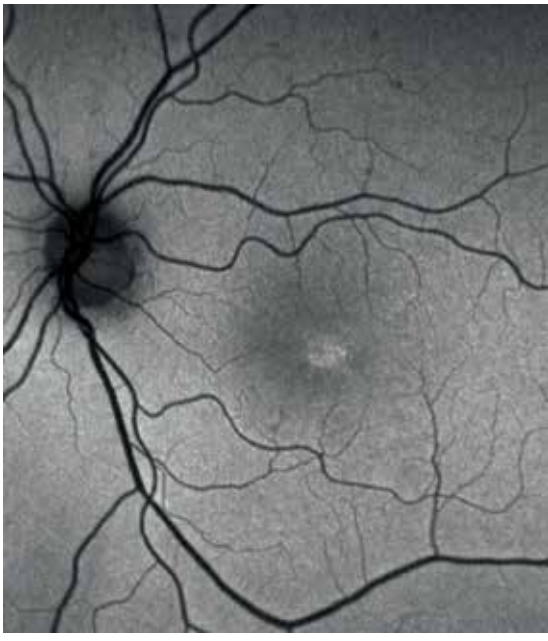

Figure 10. Autofluorescence

Idiopathic macular holes

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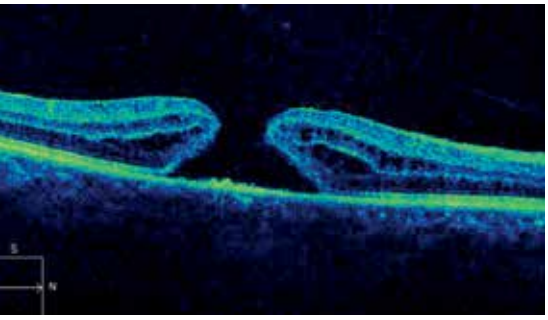

Figure 11A. OCT scan of macular hole preoperative

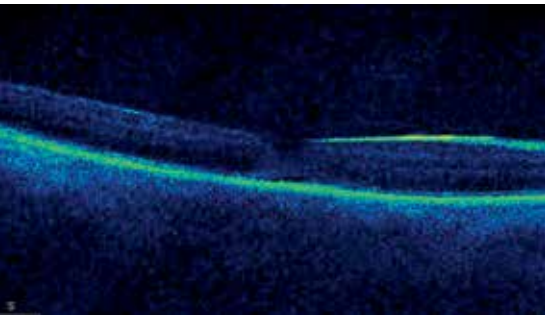

Figure 11B. OCT scan demonstrating closure of same macular hole as 11A, one day postoperative

Year	Author	Place	Cases	Interval	Closure
2008	Eckardt et al[10]	Frankfurt	33	72 hours	91%
2010	Gesser et al[11]	Frankfurt	112	72 hours	79%
2011	Sano et al[12]	Tokyo	24	24 hours	96%
2012	Goto et al[13]	Okayama	23	48 hours	96%
2013	Yamashita et al[14]	Kagoshima	21	24 hours	57%
				48 hours	76%

Table 1. Rate of closure of macular holes

Year	Author	Place	Cases	Peel	No peel
2000	Brooks[15]	Florida	160	100%	82% (25% reopened)
2006	Tadayoni et al[16]	Paris	84	> 400 µ 100% < 400 µ 100%	> 400 µ 73% < 400 µ 100%
2006	Tognetto et al[17]	Trieste	1,627	94%	89%
2009	Christensen et al[18]	Denmark	78	Stage 2 100% Stage 3 90%	Stage 2 55% Stage 3 36%
2011	FILMS Group[19]	Scotland	127	84%	48%

Table 2. Effect of ILM peeling on macular hole closure

Year	Author	Place	Cases	SF6	C2F6	C3F8
2008	Kim et al [20]	S Korea	79	90%	–	91%
2012	Rahman et al [21]	Halifax	78	87%	90%	–
2013	National database [22]	UK	1,078	No difference	No difference	No difference

Table 3. Comparison of gas tamponade

Is long-term gas tamponade with C_3F_8 required?

The three recent studies[20-22] summarised in Table 3, one of which included 1,074 cases, demonstrate that the duration of gas tamponade does not appear to influence the closure rate.

Is prone posturing necessary?

No issue in macular hole surgery has aroused as much controversy as this one. In the early days, prone positioning was universally thought to be mandatory and many retinal surgeons still believe it provides a more effective tamponade of the hole.

However, basic physics dictates that the pressure must be equal at any point on the surface of a bubble, which suggests that provided the gas is in full contact with the macula, the position of the eye is irrelevant (Figure 12).

Given that most holes close quickly after surgery, prone positioning is theoretically unnecessary and this has been confirmed by several studies[23-28] reporting closure rates of greater than 90 per cent without it (Table 4).

Based on these principles and reported results, the principal author's technique consists of the following steps:

- Fine gauge (25 g) three port pars plana vitrectomy.
- Detachment of posterior vitreous face from surface of retina using vitrectomy cutter.
- ILM peeling after staining with Trypan Blue or Brilliant Blue G.
- Internal fluid: air exchange with soft-tipped cannula on linear aspiration.
- Replacement of air with 25 per cent SF_6 in most cases; C_3F_8 (15 per cent) is reserved for chronic or larger (> 400 µ) holes.

Patients are instructed to posture upright by day and to sleep on either side at night,

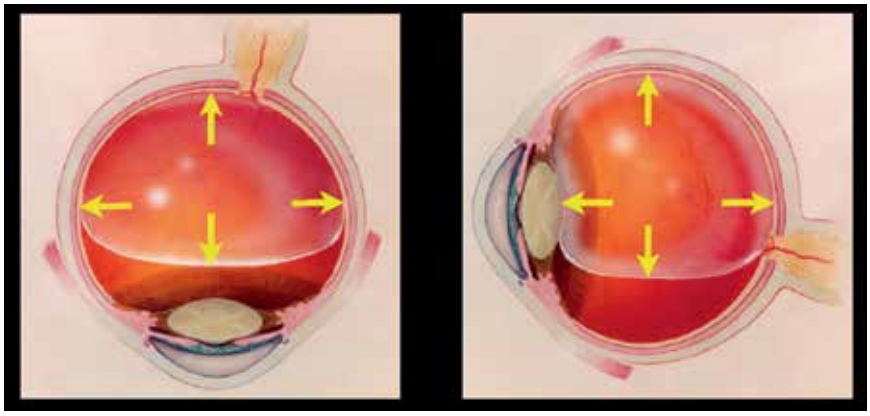

Figure 12. Diagram showing equal pressure effect of a gas bubble on the macula in the prone and upright positions

Year	Author	Place	Cases	NSP	FDP
2009	Yagi et al[23]	Tokyo	21	90.5%	–
2010	Heath et al[24]	West Yorkshire	40	92.5%	–
2011	Tadayoni et al[25]	Paris	69	91%	94%
2012	Yagi et al[26]	Tokyo	42	95%	–
2012	Forsaa et al[27]	Norway	67	91% (33 patients)	91% (34 patients)

NSP: Non-supine posturing. FDP: Face-down posturing

Table 4. Effect of posturing on macular hole closure

not supine. Since the Australian and New Zealand Audit of Surgical Intervention for Macular Hole (a database of the results of surgery in which all Australian and NZ retinal surgeons are invited to enrol) was established in November 2008, the principal author has contributed 53 cases in which the above technique was used.

The closure rate is 98 per cent, which compares favourably with the success rate in published series in which the patients were postured prone. The single case in which the hole did not close after SF_6 tamponade then did so following a regassing procedure with C_3F_8, but still no face-down positioning (Figures 13A, 13B, 13C).

Conclusion

Idiopathic macular holes generally affect older patients and are the result of an abnormality in the common ageing process of vitreomacular separation. Surgical repair has become a possibility in the modern vitreoretinal era and has an extremely high success rate. The technique involves pars plana vitrectomy, ILM peeling and gas tamponade.

The majority of macular holes close within a day or two of surgery, so that in most cases a short-acting gas tamponade is adequate and there is clear evidence that face-down positioning is an unnecessary ordeal for patients in the postoperative period. ■

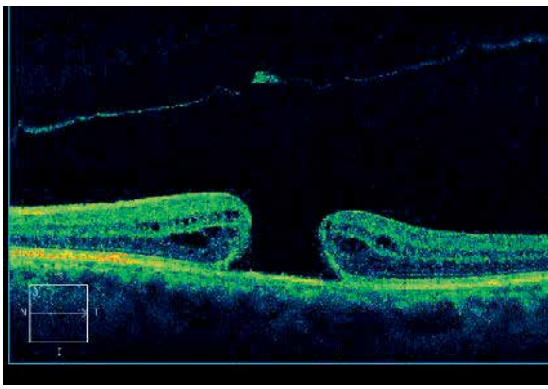

Figure 13A. OCT scan preoperative

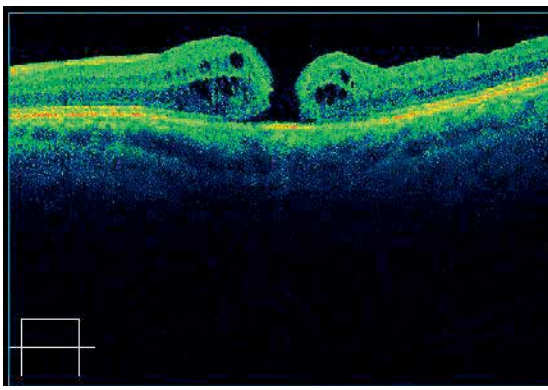

Figure 13B. OCT scan postoperative, SF_6 used

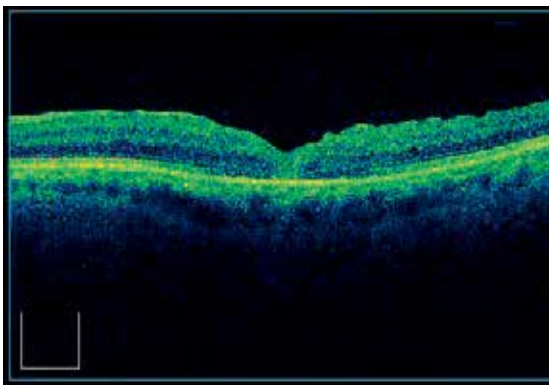

Figure 13C. OCT scan postoperative, C_3F_8 used

Figure 13. Successful closure of stage 3 macular hole with C_3F_8 after initial failure using SF_6

Monocular diplopia after a routine optometric examination

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Case report

A 53-year-old healthy man presented for a second opinion. Immediately following a routine consultation with his regular optometrist four weeks prior, he developed symptoms of vertical monocular (R > L) diplopia. His condition worsened, leading the optometrist to refer him to a neuro-ophthalmologist for a battery of clinical and costly diagnostic tests. The patient was anxious and concerned as apart from requiring reading glasses, he had never experienced any form of serious eye problems. The patient was convinced his symptoms started after his eye examination.

Clinical details

Unaided acuities were RE 6/7.5 (ghosty) and LE 6/6 part, pinhole testing gave 6/6 in each eye. A small cylindrical refraction in each eye when trial-framed made no difference to his diplopia. The results of his topography depicted centrally swollen areas of epithelial islands (R > L) in the anterior corneas (Figures 1 and 2).

The patient's posterior corneas were normal with no ectasia. Pressures were RE 21 and LE 23 (iCare rebound tonometer). When a hard contact lens was trialed in each eye, his double vision resolved instantly.

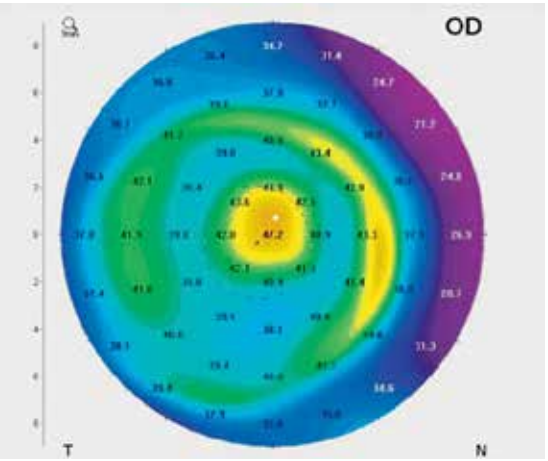
Slitlamp examination revealed a number of subepithelial whorls located centrally within the right cornea and to a lesser extent, in the left. A high-resolution Scheimpflug image revealed bilateral anterior corneal haze consistent with these examination findings (Figure 3). There was negative staining over these areas, suggesting that the likely diagnosis is early anterior basement membrane dystrophy (EBMD) or map-dot-fingerprint (MDF) dystrophy.

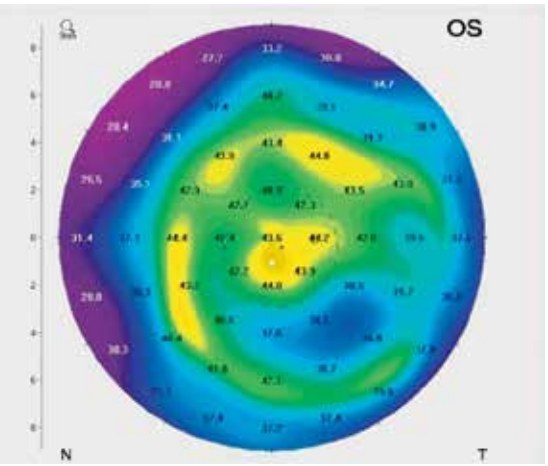
Discussion

Epithelial basement membrane corneal dystrophy, also known as map-dot-fingerprint corneal dystrophy, is an inherited congenital disorder affecting the corneal epithelium and basement membrane. Characteristic clinical expression is typically exhibited after the fourth decade of life.

Secondary corneal effects include epithelial microcystic oedema, recurrent corneal erosion and visual axis involvement.[1] Although this patient did not experience corneal erosions, he did present with diplopia and astigmatism. The fragility of the corneal epithelium is to be noted in these types of patients. Any form of ocular manipulation—anaesthetic eye-drops, applanation tonometry or even residual alcohol on the tonometer probe—can be enough to start the degenerative process. This is the most likely explanation for his rapid onset of symptoms.

With respect to EBMD, a progressive pathology occurs at the level of the epithelium





Figures 1 and 2. Oculus Pentacam tangential maps depict swollen areas in the anterior cornea

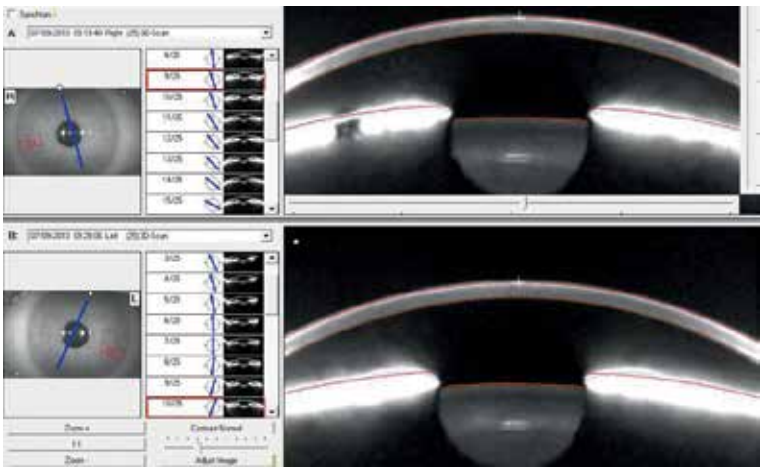


Figure 3. High resolution Scheimpflug image reveal bilateral anterior corneal haze

and its corresponding basement membrane, producing an interruption of cellular integrity and tissue function.[2] Resultant fluctuation or reduction in visual acuity, minimal to severe ocular discomfort or pain, epithelial oedema or more rarely, ruptured epithelial bullae, may end up becoming part of the clinical picture.

Treatment options

Treatment considerations will vary depending on the extent of corneal involvement and patient symptoms. The main strategy is to educate and reassure the patient that most cases of basement membrane dystrophy are asymptomatic and to reassure them that observation is the only necessary long-term approach.

In the event of progressive keratopathy with frequent recurrent corneal erosion, ocular surface pain or a reduction in VA, more aggressive medical or surgical treatment options may be indicated.

Non-invasive medical therapies are usually recommended initially with regular reviews to monitor and gauge the response to therapy. In this case, a topical anti-inflammatory eye-drop was prescribed along with a gel lubricant at night to help settle some of the metabolic side-effects of the dystrophy. The patient was scheduled for ongoing reviews.

This cases demonstrates many important messages such as a probing history to deduce the initial onset of symptoms, a careful biomicroscopic examination, in particular close observation of every layer of the cornea and appropriate anterior eye imaging complemented by simple optometric tests such as an RGP trial to help confirm an effective diagnosis. In many cases, a comprehensive ophthalmic work-up can reassure the patient and potentially avoid unnecessary diagnostic imaging like MRIs and expensive neurological work-ups. ■

1. Ramamurthi S, Rahman MQ, Dutton GN, Ramaesh K. Pathogenesis, clinical features and management of recurrent corneal erosions. *Eye* 2006; 20: 6: 635-644.
2. Arun Verma. Recurrent Corneal Erosion emedicine (accessed September 2013) http://emedicine.medscape.com/article/1195183-overview.

Herpes simplex keratitis and cataracts

The use of anti-viral drugs at the time of surgery will reduce the risk of HSK

Dr Michael Loughnan
MBBS PhD FRANZCO

The herpes viruses are a group of DNA viruses. The two main ocular pathogens are the herpes simplex virus (HSV) and varicella zoster virus (VZV), also commonly referred to as the herpes zoster virus. HSV is the most common human infection with greater than 95 per cent of people exhibiting antibodies to the virus. HSV is also the most common corneal pathogen, with about one in 650 people experiencing herpes simplex keratitis (HSK) at some time in their life.

After the initial infection with both HSV and VZX–either a sub-clinical vesicular skin rash or a follicular blepharoconjunctivitis with HSV, or chicken pox with VZX–the virus becomes latent within the neural cell body. For the cornea, this is within the ganglion of the trigeminal nerve, the fifth cranial nerve.

HSK manifests a wide spectrum of disease, ranging from primarily viral replicative disease such as an epithelial dendrite through to disease primarily due to the host's immune reaction to viral particles, as occurs with stromal necrotic keratitis.

VZV is the cause of herpes zoster ophthalmicus (HZO) shingles involving the second branch of the trigeminal nerve. While the cornea is commonly spared in HZO, a chronic kerato-uveitis can occur, often requiring years of topical steroid use to control the host immune reaction to residual viral antigen. Recent evidence also supports the idea that VZV may continue to replicate at a low level in such patients.[1]

One concern with the now common usage of varicella virus vaccines, such as Varivax, is that the normal exposure of adults with latent virus to VZV in the community will decrease as a result of the immunisation of younger people and as such, their immunity to VZV will fall and the prevalence of shingles within this group will increase.

A vaccine against VZV to prevent shingles is available. It is marketed in Australia by CSL Biotherapies and sold as Zostavax. It significantly reduces the risk of developing shingles as well as reducing the associated morbidity. In the USA, it is now recommended for standard use for people over the age of 55 years.

When to perform surgery

Chronic anterior segment inflammation, especially uveitis, commonly leads to an acceleration of nuclear sclerosis development. The long-term usage of topical corticosteroids can also lead to the development of a posterior subcapsular cataract (PSCC). As a consequence, patients with chronic kerato-uveitis requiring long-term topical steroids frequently develop visually significant cataract.

The timing of cataract surgery for people with VZV/HZO keratitis or HSV stromal keratitis, typically stromal necrotic disease or keratouveitis, is important. Most surgeons prefer to defer surgery until the cornea is not inflamed and easily controlled with minimal topical medication, usually one drop a day or less of corticosteroid; however, it is also preferable to remove the cataract before it becomes too dense and removal requires more phacoemulsification power.

Special considerations for surgery

Both HSV and VZV keratitis can lead to scarring and flattening of the cornea, resulting

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Herpes simplex keratitis and cataracts

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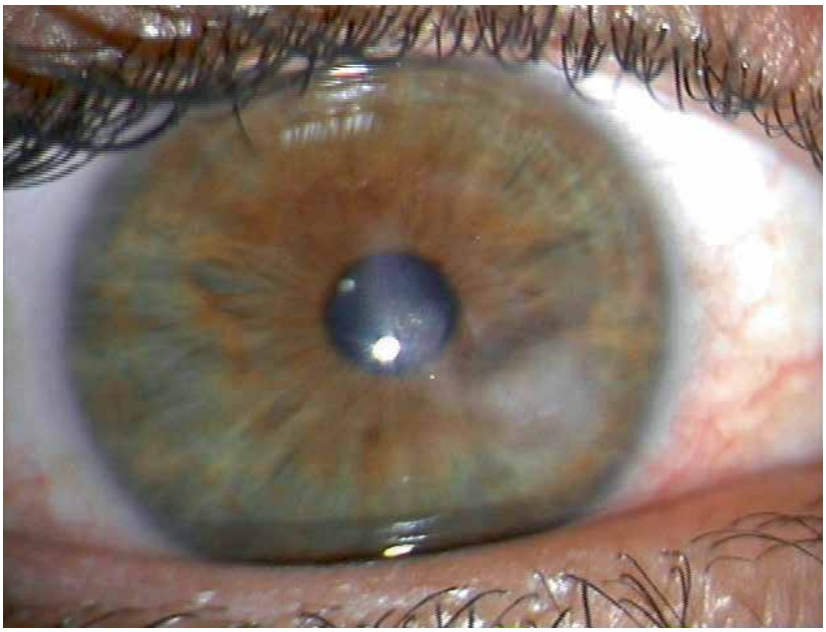

Figure 1. Central diffuse and focal peripheral corneal scarring secondary to stromal herpes simplex keratitis

in lower keratometry readings. Standard keratometry may be inaccurate due to the focal nature of both the scarring and the resultant flattening. Topography and the use of simulated keratometry readings may be a more accurate measure of the true corneal anterior surface power.

Chronic uveitis can also lead to weakening of the zonules and scarring of the trabecular meshwork predisposing to glaucoma. Extra care should be taken during the surgery not to stress the zonules, one of the indications for femtosecond laser-assisted cataract surgery, and peri-operative anti-glaucoma medication is indicated.

Preventing recurrences around time of surgery

The recurrence of both inflammation (keratitis and anterior uveitis) and reactivation of viral replication are a concern around the time of surgery. Thankfully, modern cataract surgery is so non-traumatic to the eye that this is probably less of a concern now than it was with previous more invasive and pro-inflammatory techniques.

The Herpetic Eye Disease Studies (HEDS) were a series of prospective, randomised, multi-centre eye studies from the early 1990s that looked at several aspects of HSV keratitis and uveitis. One of the studies in HEDS was the acyclovir prevention trial (APT). This trial found that in people with HSK that taking 400 mg of the anti-viral agent acyclovir orally twice a day reduced their risk of recurrent HSK to about 50 per cent of the control group who took a placebo. However, acyclovir has a short serum half-life of approximately four hours and as such, standard treatment for an active infection is 800 mg five times daily.[2]

The concern with respect to viral recurrence around the time of surgery is reactivation of latent tissue or nerve cell body virus secondary to localised tissue damage. This would occur after the surgery. Treatment with acyclovir is needed immediately post-surgery and for a period afterwards until the tissue has recovered. For this reason, typical treatment is with 800 mg orally five times daily for seven days, commencing immediately following surgery.

Acycolvir is not approved by the PBS for this indication, so it needs to be bought as a private script. It is now off patent and can commonly be purchased for about $100. The alternative is to use another anti-viral drug with a longer serum half-life, such as valaciclovir or famciclovir; however, both of these are significantly more expensive than acyclovir, although they require only twice or three times daily dosing.

There is no good evidence of which patients will benefit from peri-operative oral acyclovir. As a rule of thumb, it tends to be used in those patients who are at higher risk of recurrence. That is, patients with recent (within the past year) stromal keratitis or uveitis secondary to either HSV or VZV.

In addition to oral acyclovir, topical corticosteroids may have to be used longer than usual post-operatively to reduce the risk of a flare-up of inflammation. A common approach is to use a topical corticosteroid such as prednisolone acetate (Prednefrin Forte) four times a day for one week, followed by three times a day for two weeks then two times daily for six weeks, then either ceasing or, if the patient requires topical corticosteroids prior to surgery, a return to the usual maintenance dose.

Summary

Modern uncomplicated cataract surgery is generally safe even with a history of HSV or HZO. Surgery is best performed when the eye is quiet, and topical corticosteroids and oral acyclovir can be used around the time of surgery to reduce the risk of viral reactivation or an increase in ocular inflammation. ■

1. Hu AY et al. Late varicella-zoster virus dendriform keratitis in patients with histories of herpes zoster ophthalmicus. *Am J Ophthalmol* 2010; 149: 214-220.
2. Herpetic Eye Disease Study Group. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. *N Engl J Med* 1998; 339: 300-306.

PBS list of medicines for optometrists

Revised 1 November 2013

By writing a PBS prescription for an antiglaucoma agent, the prescriber is certifying that the criteria set out in the PBS guidelines are satisfied

		Product	Max qty	Repeats
Antiglaucoma preparations				
Betaxolol eye-drops, suspension, 2.5 mg (as hydrochloride)/mL, 5 mL		Betoptic S	1	5
Betaxolol eye-drops, solution, 5 mg (as hydrochloride)/mL, 5 mL		Betoptic, BetoQuin	1	5
Bimatoprost eye-drops 300 micrograms/mL, 3 mL		Lumigan	1	5
Bimatoprost with timolol eye-drops containing 300 micrograms bimatoprost with timolol 5 mg (as maleate)/mL, 3 mL		Ganfort 0.3/5	1	5
Brimonidine eye-drops containing brimonidine tartrate 2 mg/mL, 5 mL		Alphagan, Enidin	1	5
Brimonidine Tartrate eye-drops 1.5 mg per mL (0.15%), 5 mL		Alphagan P 1.5	1	5
Brimonidine with timolol eye-drops containing brimonidine tartrate 2 mg with timolol 5 mg (as maleate)/mL, 5 mL		Combigan	1	5
Brinzolamide eye-drops 10 mg/mL, 5 mL		Azopt, BrinzoQuin	1	5
Brinzolamide with timolol eye-drops containing brinzolamide 10mg/mL with timolol 5mg (as maleate)/mL, 5mL		Azarga	1	5
Dorzolamide eye-drops 20 mg (as hydrochloride)/mL, 5 mL		Trusopt	1	5
Dorzolamide with timolol eye-drops containing dorzolamide 20 mg (as hydrochloride) with timolol 5 mg (as maleate)/mL, 5 mL		Cosopt	1	5
Latanoprost 0.005% eye-drops 50 micrograms/mL, 2.5 mL	Restricted: reduction intraocular pressure	APO-Latanaprost, Chem Mart Latanoprost Latanaprost Pfizer, Latanaprost Sandoz, Terry White Chemist Latanaprost, Xalatan	1	5
Latanoprost with timolol eye-drops 50 micrograms latanoprost with timolol 5 mg (as maleate)/mL, 2.5 mL		Xalacom, Latanocom	1	5
Pilocarpine eye-drops containing pilocarpine hydrochloride 1% 10 mg/mL, 15 mL		Isopto Carpine	1	5
Pilocarpine eye-drops containing pilocarpine hydrochloride 2% 20 mg/mL, 15 mL		Isopto Carpine	1	5
Pilocarpine eye-drops containing pilocarpine hydrochloride 4% 40 mg/mL, 15 mL		Isopto Carpine	1	5
Tafluprost 0.0015% eye-drops, 30 x 0.3 mL unit doses		Saflutan	1	5
Tafluprost OP 0.0015% eye-drops, 30 x 0.3 mL unit doses		Saflutan	1	5
Timolol eye-drops 2.5 mg (as maleate)/mL, 5 mL		Tenopt	1	5
Timolol eye-drops 5 mg (as maleate)/mL, 5 mL		Tenopt, Timoptol	1	5
Timolol eye-drops (gellan gum solution) 2.5 mg (as maleate)/mL, 2.5 mL		Timoptol XE	1	5
Timolol eye-drops (gellan gum solution) 5 mg (as maleate)/mL, 2.5 mL		Timoptol XE	1	5
Timolol eye gel 1 mg (as maleate)/g, 5 g		Nyogel	1	5
Travoprost eye-drops 40 micrograms/mL, 2.5 mL		Travatan	1	5
Travoprost with timolol eye-drops 40 micrograms travoprost with timolol 5 mg (as maleate)/mL, 2.5 mL	Restricted: open-angle glaucoma	Duotrav	1	5

	Product	Restriction	Max qty	Repeats
Anti-viral eye preparations		Restricted:		
Aciclovir eye ointment 30 mg per g (3%), 4.5 g	Zovirax	Herpes simplex keratitis	1	0
Antibiotics		Unrestricted		
Chloramphenicol eye-drops 5 mg/mL (0.5%), 10 mL	Chlorsig, Chloromycetin		1	2
Chloramphenicol eye ointment 10 mg/g (1%), 4 g	Chlorsig, Chloromycetin		1	0
Ciprofloxacin eye-drops 3 mg per mL (0.3%), 5 mL	CiloQuin, Ciloxan	Authority required: bacterial keratitis	2	0

PBS list of medicines for optometrists (continued)

	Product	Restriction	Max qty	Repeats
Antibiotics (cont)				
Framycetin sulfate eye-drops 5 mg/mL (0.5%), 8 mL	Soframycin		1	2
Gentamicin sulfate eye-drops 3 mg/mL (0.3%), 5 mL	Genoptic	Restricted: Suspected pseudomonal eye infection	1	2
Ofloxacin eye-drops 3 mg per mL (0.3%), 5 mL	Ocuflox	Authority required: bacterial keratitis	2	0
Tobramycin eye-drops 3 mg per mL (0.3%), 5 mL	Tobrex	Restricted: Suspected pseudomonal eye infection	1	2
Tobramycin eye ointment 3 mg per g (0.3%), 3.5 g	Tobrex	Restricted: Suspected pseudomonal eye infection	1	0
Anti-inflammatory agents				
Dexamethasone eye-drops 1 mg / mL (0.1%), 5 mL	Maxidex	Applications for increased maximum quantities and/or repeats will not be authorised	1	0
Fluorometholone eye-drops 1mg/mL (0.1%), 5 mL	Flucon, FML Liquifilm	As above	1	0
Fluorometholone acetate eye-drops 1 mg/mL (0.1%), 5 mL	Flarex	As above	1	0
Flurbiprofen sodium eye-drops 300 µg/mL (0.03%) single dose units 0.4 mL, 5 mL	Ocufen	As above	1	0
Hydrocortisone acetate eye ointment 10 mg/g (1%), 5 g	Hycor	As above	1	0
Prednisolone acetate with phenylephrine hydrochloride eye-drops 10 mg-1.2 mg per mL (1%-0.12%), 10 mL	Prednefrin Forte	Restriction: Uveitis. Applications for increased maximum quantities and/or repeats will not be authorised.	1	0
Anti-allergy agents				
Sodium cromoglycate eye-drops 20 mg/mL (2%), 10 mL	Cromolux	Restricted: Vernal keratoconjunctivitis	1	5
	Opticrom		1	5
Tear supplements		Restricted: Severe dry eye including Sjögren's syndrome		
Carbomer eye gel 2 mg/g (0.2%), 10 g	PAA	As above	1	5
	Viscotears	As above	1	5
Carbomer + Triglyceride lipids carbomer 0.2% (2 mg/g) + triglyceride lipids 1% (10 mg/g) eye gel, 10 g	Artelac	As above	1	5
Carmellose sodium with glycerol eye-drops 5 mg-9 mg per mL (0.5%-0.9%), 15 mL	Optive	As above	1	3
Carmellose sodium eye-drops 10 mg/mL (1%), 15 mL	Refresh Liquigel	As above	1	5
Carmellose sodium eye-drops 5 mg/mL (0.5%), 15 ml	Refresh Tears plus	As above	1	5
Hypromellose eye-drops 3 mg/mL (0.3%), 15 mL (contains sodium perborate)	In a Wink Moist'ing Genteal	As above	1 1	5 5
Hypromellose eye-drops 5 mg/mL (0.5%), 15 mL	Methopt	As above	1	5
Hypromellose with carbomer 980 ocular lubricating gel 3 mg-2 mg/g (0.3-0.2%), 10 g	HPMC PAA Genteal gel	As above	1 1	5 5

PBS list of medicines for optometrists (continued)

	Product	Restriction	Max qty	Repeats
Tear supplements		Restricted: Severe dry eye including Sjögren's syndrome		
Hypromellose with dextran eye-drops 3 mg-1 mg/mL (0.3%-0.1%), 15 mL	Poly-Tears Tears Naturale	As above	1 1	5 5
Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); 15 mL	Systane	As above	1	5
Polyethylene glycol 400 eye drops 2.5 mg per mL (0.25%), 15 mL	Blink Intensive Tears	As above	1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL	PVA Tears, Liquifilm Tears	As above	1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL	PVA Forte, Liquifilm Forte	As above	1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative)	Vistil	As above	1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative)	Vistil Forte	As above	1	5
Unpreserved tear supplements		Authority required:		
Carbomer 974 ocular lubricating gel 3 mg/g (0.3%), single dose units 0.5 g, 30	Poly Gel	Severe dry eye syndrome in patients sensitive to preservatives in multi-dose eye-drops	3	5
Carbomer 980 eye-gel 2 mg per (0.2%) , single dose units 0.6 mL, 30	Viscotears Gel PF	As above	3	5
Carbomer + Triglyceride lipids carbomer 0.2% (1.2 mg/600 mg) + triglyceride lipids 1% (6 mg/600 mg) eye gel, 30 x 600 mg unit doses	Artelac	As above	3	5
Carmellose sodium eye-drops 5 mg/mL (0.5%), single dose units 0.4 mL, 30	Cellufresh	As above	3	5
Carmellose sodium eye-drops 10 mg/mL (1%) , single dose unit 0.4 mL, 30	Celluvisc	As above	3	5
Carmellose sodium eye-drops 2.5 mg/mL (0.25%), single dose units, 0.6 mL, 24	TheraTears	As above	4	5
Carmellose sodium ocular lubricating gel 10 mg/mL (1%), single dose 0.6 mL, 28	TheraTears	As above	3	5
Carmellose Sodium with Glycerol eye drops 5 mg-9 mg per mL (0.5%-0.9%), single dose units 0.4 mL, 30	Optive	As above	3	5
Hypromellose with dextran eye-drops 3-1 mg/mL (0.3-0.1%), single 0.4 mL, 28	Bion Tears	As above	3	5
Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); single dose units 0.8 mL, 28	Systane	As above	2	5
Polyethylene glycol 400 eye-drops 2.5 mg per mL (0.25%), single dose units 0.4 mL, 20	Blink Intensive Tears	As above	5	5
Sodium Hyaluronate sodium hyaluronate 0.1% (1 mg/mL) eye-drops, 10 mL	Hylo-Fresh	As above	1	5
Sodium Hyaluronate sodium hyaluronate 0.2% (2 mg/mL) eye-drops, 10 mL	Hylo-Forte	As above	1	5
Soy lecithin eye spray 10 mg/mL (1%), 10 mL	Tears again	As above	2	5
Topical ocular lubricant ointments				
Paraffin compound eye ointment 3.5 g	Polyvisc, Duratears		2	5
Paraffin pack containing 2 tubes compound eye ointment 3.5 g	Polyvisc, Ircal, Refresh Night Time		1	5
Pariffin paraffin + retinyl palmitate 138 microgram/g (equivalent to 250 units/g vitamin A) eye ointment, 5 g	VitA-POS		2	5

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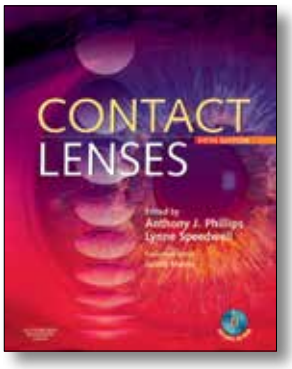

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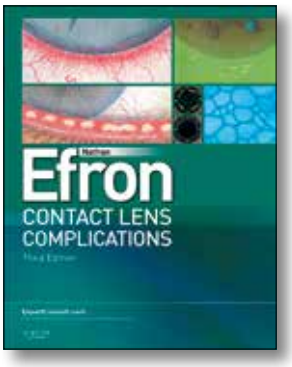

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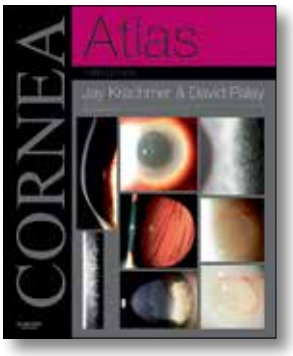

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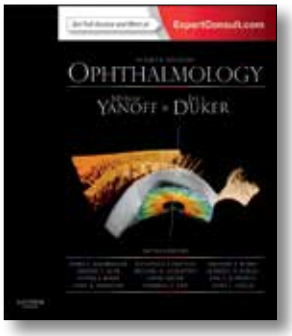

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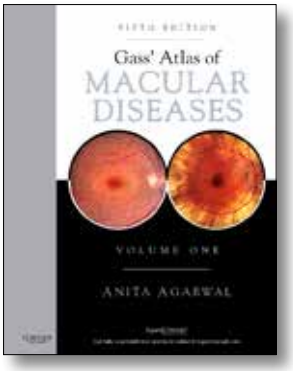

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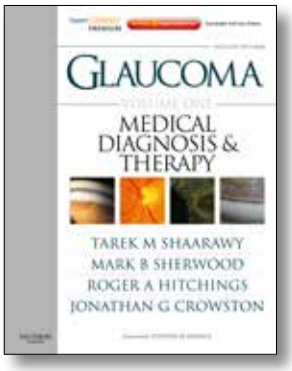

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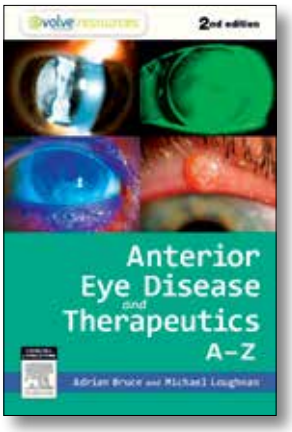

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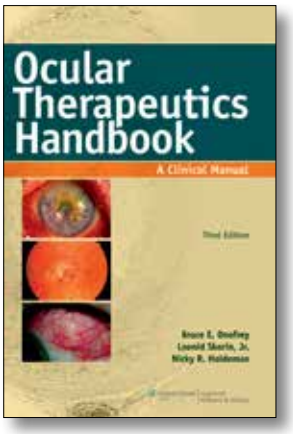

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