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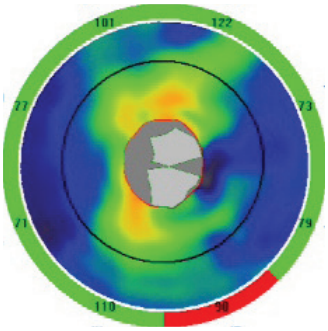

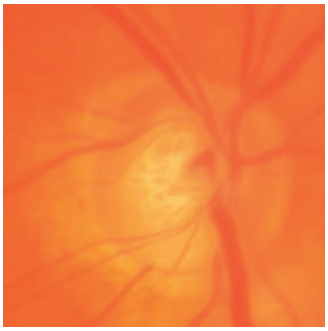

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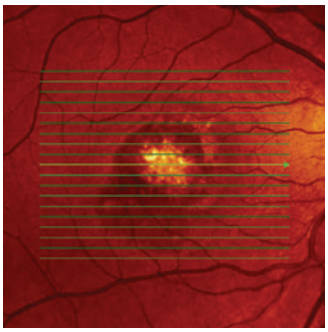

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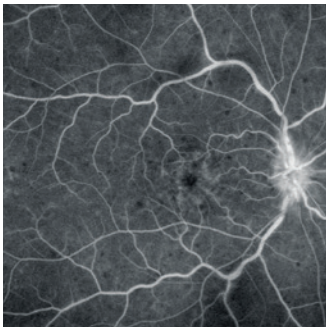

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Promising options for AMD

What's new in the management of age-related macular degeneration?

Dr Amy Cohn

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Senior Research Fellow, Centre for Eye Research Australia

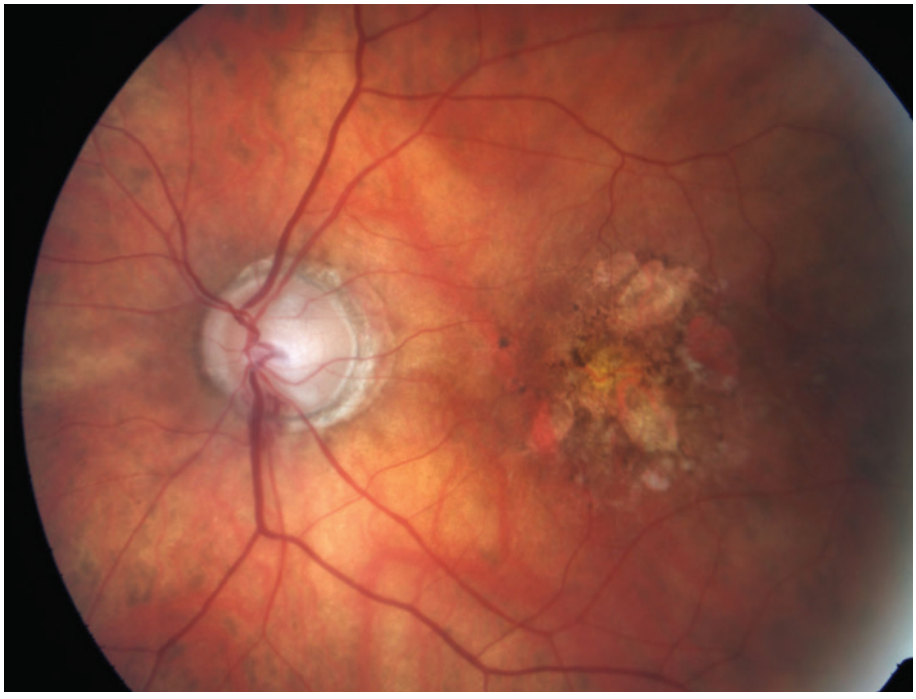
AS EYE HEALTH-CARE professionals, we are aware of the significant burden age-related macular degeneration (AMD) is on our community. It can be detected in one in seven (14 per cent) patients older than 50 years, and this increases to 25 per cent by age 90.[1,2]

AMD represents one of the major causes of vision impairment in Australia. Fortunately, in the past decade we have been able offer patients with wet (neo-vascular) AMD treatment with anti-vascular endothelial growth factor (VEGF) agents and this has completely altered the therapeutic landscape. Not only have we been able to prevent worsening of vision, in some cases we are now able to improve vision.[3-5] This has led to an increase in both doctor and patient expectations regarding what we can hope to achieve with AMD treatment.

Despite these wonderful advances, there is still very little we can offer patients who are diagnosed with early, intermediate or advanced dry AMD.

The role of vitamin and antioxidant supplementation was established in the AREDS 1 study, which suggested that for patients with intermediate drusen, one large drusen, non-central geographic atrophy, advanced AMD or loss of vision in one eye due to AMD, there could be a benefit from specific supplements.[6] In addition, secondary exploration of the AREDS 2 study showed that there may be some benefit in replacing beta-carotene with lutein/xexanthine for prevention of AMD progession.[7]

One other area that continues to be an issue is the 'plateau' effect we see after initiation of anti-VEGF for wet AMD. We are familiar with the graph of initial rapid improvement in visual acuity and macular thickness, which is then followed by a period of maintenance.[3-5] In addition, extension studies, treat and extend regimes, and PRN dosing—regardless of which agent is used—show a gradual loss of efficacy.[8,9] This has led to increasing interest in how we can better use anti-VEGFs or develop alternatives to offer sustained visual acuity gains for our patients.



▲ Figure 1. Geographic atrophy Image: Dr Stephen Cohen, RetinaGallery.com

Early dry AMD

Outside of vitamin and antioxidant supplementation, we have nothing to offer patients with dry AMD.

I am involved in a randomised controlled trial currently being conducted at the Centre for Eye Research Australia (CERA). The LEAD Study (Laser for Early Age-related Macular Degeneration) is looking at the Ellex 2RT nanosecond laser versus sham in patients with bilateral high-risk drusen and RPE change.

Our pilot study of 50 patients showed that with the nanosecond laser the drusen load decreased in the treated eye and macula function improved.[10,11] This retinal rejuvenation has led to the formal international, multicentre trial underway with preliminary results

hopefully available towards the end of the year. With the help of referring optometrists, CERA has recruited almost 300 patients for the trial.

Late dry AMD

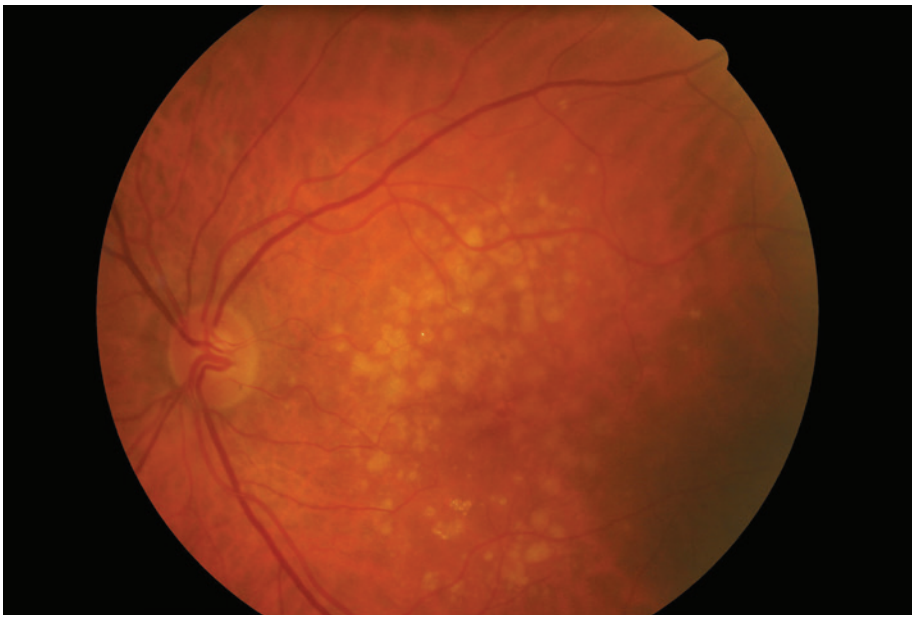
Late dry AMD affects five million people worldwide with no current treatment available. There are several studies underway both in Australia and abroad looking at treatment options. Although the underlying patho-physiological mechanisms are not completely understood, one key area of research is prevention of photoreceptor and RPE cell loss via neuro-protection, oxidative damage prevention and visual cycle modification.

One such study is a Roche-sponsored trial looking at lampalizumab versus sham in patients with bilateral geographic atrophy due to AMD. Lampalizumab is an antigen binding fragment (Fab) of a humanised monoclonal antibody directed against complement factor D. Complement factor D is an enzyme involved in activation of the alternate complement pathway. Several studies have suggested that inflammation and increased complement activation play a direct role in AMD development and progression.[12-14] In addition, certain genetic polymorphisms in complement pathway genes determine a patient's likelihood of developing AMD.[15-17]

Phase 2 study results (the MAHALO study) showed that patients treated with lampalizumab showed a reduction in progression of geographic atrophy on fundus autofluorescence and this was even more significant in patients with a certain CFI biomarker (clinicaltrials.gov identifier NCT01229215).

One of the major issues with current anti-VEGF treatment is the frequency of injections required to maintain visual acuity. New posterior segment delivery devices (PSDD) for both wet and dry AMD hope to afford patients longer drug duration and therefore reduce the number of retreatments.

Another trial for geographic atrophy due to AMD is sponsored by Allergan and is investigating a new PSDD to administer brimonidine into the vitreous cavity. Brimonidine is an α2-selective adrenergic agonist and in various studies has been shown to be neuro-protective to photo-receptor/RPE cell complexes.[18-20] The hope is that in a sustained release formula injected into the vitreous, brimonidine will slow the progression of geographic atrophy (Clinical.Trials.gov identifier NCT00658619).



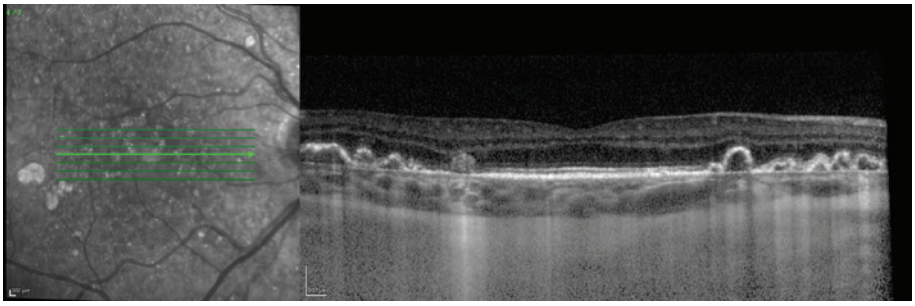
▲ Figure 2. Intermediate AMD, large drusen

Another neuro-protective agent that uses PSDD technology being studied is ciliary neuro-trophic factor (CNTF). CNTF has slowed photoreceptor cell loss in several models of retinal degeneration.[21,22] Renexus (formerly NT501) uses encapsulated cell technology with live human RPE cells that are genetically modified to secrete CNTF for up to two years. A Phase 2 trial that studied low dose CNTF versus high dose versus sham showed that at 12 months follow-up, there was a statistically significant increase in retinal thickness in the low and high dose groups compared to sham. In addition, CNTF appeared to preserve vision. There was a 0.8 letter gain in the high dose CTNF group compared with a loss of 9.7 letters in the combined low dose and sham groups. However, there was no prevention of progression of geographic atrophy on fundus autofluorescence (FAF) imaging in the treatment arms.[23] A Phase 3 study is planned.

Wet AMD

As clinicians continue to observe the significant treatment burden regular anti-VEGF treatment places on the patient and the plateau effect of therapy, research continues apace to address this. For wet AMD the current areas of research include better anti-VEGF agents, combination treatments that are additive or synergistic in their effects and longer-acting delivery systems touched on previously.

Continued page 4



▲ Figure 3. Drusen on Spectral domain OCT

Promising options for AMD

From page 3

Newer anti-VEGF

ESBA-1008 is a single chain antibody fragment that is significantly smaller than current anti-VEGF agents and will hopefully be able to be packaged into a sustained delivery device. In addition, it is a pan-VEGF inhibitor that has much greater binding capacities than current molecules.

A Phase 2 study comparing ESBA-1008 to Lucentis shows that it was non-inferior at the two higher doses and there was a trend to increased efficacy at the highest dose. In addition, there was a 30-day difference in the time needed to re-treat, which is of obvious benefit to patients on monthly injection regimes.[24]

Designed ankyrin repeat proteins (DARP-ins) are genetically engineered small molecular weight proteins that have a higher affinity for VEGF-A binding sites than antibodies or antibody fragments. A current Phase 2 study is underway comparing them to Lucentis.

Conbercept is a recombinant fusion protein that combines extra-cellular domains of VEGFR1 and 2 with the Fc region of human immunoglobulin. It is able to target multiple isoforms of VEGF and is already approved in China for treatment of wet AMD.[25]

Combination treatments

Much of the early work in this area was done by our oncology colleagues who identified the way in which neo-vascular complexes develop in tumours. Sprout or tip cells lead the growth of tumour vasculature. The tip cells secrete platelet derived growth factor (PDGF) and VEGF which recruits pericytes to cover and protect the neo-vascular complex. The tips themselves are not protected by pericytes and therefore are the only part vulnerable to anti-VEGF agents.[26]

When anti-VEGF treatment is initiated, it is presumed the tip cells die but the underlying neo-vascular membrane remains. One new agent, Fovista, is a pegylated aptamer against PDGF and prevents PDGF binding to pericyte receptors. This renders the new vessels more susceptible to effects of anti-VEGF agents. Phase 2 studies showed that combination Lucentis/Fovista was superior to Lucentis monotherapy (ClinicalTrials.gov identifier NCT01089517) and Phase 3 studies are underway.

Squalamine (OHR-102) binds to calmodulin to inhibit downstream activation of VEGF, PDGF and basic fibroblast growth factor. Is has been developed as an emollient eye-drop. Current Phase 2 studies are comparing baseline Lucentis plus PRN Lucentis with Lucentis and BD Squalamine plus PRN Lucentis.

A Phase 3 study has also been approved. Interim analysis from the Phase 2 IMPACT study showed there was an improvement in visual acuity in the combination group compared with Lucentis monotherapy.[27]

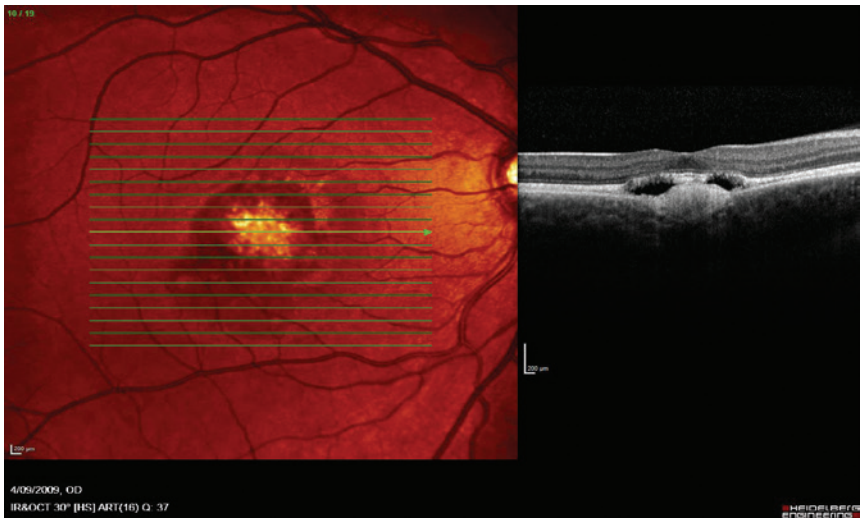
Other options

The INTREPID study is a randomised controlled trial to assess safety and efficacy of low voltage, external beam stereo-tactic radiotherapy (STR) in patients with neovascular AMD. Patients enrolled were not treatment-naïve and had to have had three or more anti-VEGF injections in the preceding 12 months.

The primary outcome was to track the number of PRN Lucentis injections over 52 weeks. All patients had baseline Lucentis and then PRN Lucentis defined by set criteria. SRT was associated with 26 per cent reduction in the number of anti-VEGF treatments over the two-year follow-up.[28]

Conclusion

Research into all forms of AMD continues rapidly. While this is not an exhaustive review of all agents currently being investigated, it does provide a snapshot of the exciting times ahead. One hopes that we will soon have options to treat our patients at all stages of AMD successfully and safely. ▲



▲ Figure 4. Neovascular AMD

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TGA authorises substitutes for Zovirax ophthalmic ointment following recall

TWO PRODUCTS are now commercially available in lieu of Zovirax ophthalmic ointment (3% aciclovir) for the treatment of keratitis of the eye caused by herpes simplex virus.

The Therapeutic Goods Administration (TGA) granted a section 19A exemption so that these products do not have to be supplied through the Special Access Scheme; they are available from pharmacies with an optometry prescription. The TGA granted an exemption for AciVision 30mg/g Aciclovir in February 2015 and a second product, Virgan 0.15% w/w Ganciclovir eye gel in April.

There are supply issues across Australia and these substitutes may not be kept in stock at your local pharmacy. They are available for pharmacists to order and supply but they may take one to three days to arrive. Some members of Optometry Australia have reported success liaising with their local pharmacies to keep one of the substitutes in stock.

These substitute products are currently not available with the PBS subsidy and cost between $50 and $90, depending on urgent freight costs. Optometry Australia has been in contact with the Pharmaceutical Evaluation Branch of the Department of Health to secure temporarily listing of these substitute products.

Zovirax Ophthalmic ointment was recalled in October 2014, after metal particles were found in three different lots of the active pharmaceutical ingredient aciclovir, which was used in 11 batches of Zovirax ophthalmic ointment. Two of these batches were supplied in Australia.

The affected batch numbers are 3L942 (expiring October 2015) and 4B909 (expiring February 2016). The size of the metal particles in the raw materials used to manufacture the Zovirax ophthalmic ointment range in size from 0.15 to 0.875 mm.

Zovirax is scheduled to return on 31 March 2016.

Integrated approach closes gap between evidence and eye care

Dr Laura Downie

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AGE-RELATED macular degeneration (AMD) is a leading cause of blindness in developed countries, accounting for more than 50 percent of blindness in Australia.[1] With an ageing population, the number of Australians with AMD is predicted to almost double over the next 20 years.[1]

While treatments for late-stage neovascular AMD exist, in the form of intravitreal vascular endothelial growth factor inhibitors, there is currently no approved treatment for earlier stages of AMD or one of the two late stages of AMD, geographic atrophy.

At present, attenuating the progression to late-stage disease is the most valuable approach to reducing vision loss and the associated individual and community burden of AMD.

Smoking

High quality evidence exists relating to the natural history of AMD[2] and in particular, the benefit of lifestyle modifications relating to smoking cessation and nutrition, for reducing the risk of progression to late-stage AMD. Cigarette smoking, which almost doubles the risk of developing AMD,[3] is the most important modifiable risk factor.[4] A direct association also exists between the number of cigarettes smoked over time and the risk of late-stage AMD.[5]

While there is relatively strong public awareness about the systemic disease associations with smoking, including cancer, heart disease and stroke, knowledge of the link between smoking and blindness is less well recognised.[6]

To address a need for enhanced community awareness of this potential side-effect, for the past eight years the Australian Government has strongly supported advertising campaigns aimed at educating people of the ocular risks of smoking. These forms of public awareness programs have been shown to be of value for changing smoking behaviours.[7,8]

Nutrition

Nutrition is another important area for AMD risk modification in primary eye care. As recently reviewed,[9] there is a wealth of epidemiological data that confirm the potential benefit of a healthy diet, rich in the macular carotenoids (zeaxanthin and lutein) and omega-3 long-chain essential fatty acids (EFAs), for lowering the risk of developing late-stage AMD.

Two large, National Eye Institute-sponsored, multi-centre, randomised, controlled clinical trials, namely the Age-Related Eye Disease Study (AREDS)[2] and AREDS2,[10] have evaluated the safety and efficacy of high dose antioxidant dietary supplements for AMD. AREDS [2] showed that daily consumption of a specific combination of antioxidant vitamins and nutrients could reduce the risk of progression from intermediate-stage to late-stage AMD from 28 per cent to 20 per cent over five years.

Clearly the decision to recommend such formulations to patients requires consideration of the patient's systemic health status, as well as the relative benefits versus risks of the intervention.

> 'Overall, there is scope for optometrists to undertake improved questioning and counselling to patients about smoking status and nutrition, which are the key modifiable risks factors for AMD.'

As key providers of primary eye care in the community, optometrists play an important public health role in providing advice to patients about the major modifiable risk factors for ocular disease.

In recent years, studies have been undertaken to gain insight into self-reported optometric practice behaviours in these areas. Overall, findings from these studies, which have surveyed clinicians in a range of developed countries[11-14] including Australia,[15] suggest that there is scope for advice about smoking cessation to be more proactively provided by optometrists to their patients. A study conducted in the United Kingdom also reported a need to improve awareness among optometrists about the research evidence underlying the use of

Clinical teaching centre established to address modifiable risks for AMD

nutritional supplements for AMD.[11]

Clinical behaviours

In 2013, Associate Professor Peter Keller and I undertook a study to examine self-reported optometric clinical behaviours in the areas of smoking and nutrition, in order to gain further understanding of the clinical practices of Australian optometrists. The paper from this study has been accepted for publication in the open-access refereed journal *PLoS One*.

The results of the study indicated that fewer than 50 per cent of respondents would routinely question their patients whether they smoked. Many respondents indicated that they considered smoking counselling to be a medical issue that was the responsibility of the patient's general medical practitioner. Other common reasons that were cited by practitioners for not routinely providing advice about smoking cessation were a lack of time, a perception that there was sufficient advertising about the health risks associated with smoking and that this type of questioning was too personal or intrusive.

Almost two-thirds of respondents indicated that they would routinely counsel patients about their diet and about half specified routinely asking their patients if they were taking nutritional supplements. Optometrists who recommended nutritional supplementation to their patients most commonly did so for AMD (91.2 per cent) and dry eye disease (63.9 per cent). Of the supplements recommended for AMD, the most common were various forms of high-dose antioxidants (89.8 per cent) and omega-3 EFAs (8.5 per cent).

Our findings are similar to those reported in other parts of the world and suggest that overall, there is scope for optometrists to undertake improved questioning and counselling to patients about smoking status and nutrition, which are the key modifiable risks factors for AMD.

Through the award of a 2015 NHMRC Translating Research Into Practice (TRIP) Fellowship, I am undertaking a two-year project, with Associate Professor Keller as my TRIP mentor, which aims to improve the translation of research evidence into clinical practice by optometrists, in relation to modifiable risk factors for AMD. This is the first TRIP Fellowship to have been awarded to an optometrist.

A major component of the project is the creation of a new AMD optometric clinical teaching centre at the University of Melbourne Eyecare clinic.

This AMD Clinical Teaching and Demonstration Service (CTDS) will be made available for Victorian optometrists to attend, at no cost, towards the end of 2015. Optometrists who participate in the program are expected to receive accredited continuing professional development points. The key outcome of the project is predicted to be enhanced primary eye care delivery to patients with early stages of AMD. ▲

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Management of giant cell arteritis

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GIANT CELL ARTERITIS (GCA) affects one in 150,000 patients over the age of 60 years.[1] By the ninth decade of life, the incidence of GCA rises to 44/100,000.[1] The condition occurs twice as often in women and is most commonly seen in Caucasians of Northern European decent.[2]

GCA, also known as temporal arteritis or cranial arteritis, results in chronic inflammation of medium-sized and large arteries, particularly the branches of the carotid arteries. The pathology behind this inflammation appears to be multinucleated giant cells (MGCs). MGCs promote degradation of the vessel's elastic fibres of the internal elastic lamina by the release of proteinase and peroxisome enzymes[3] (Figure 1). These cells also release the angiogenic factors, vascular endothelial growth factor and platelet derived growth factor, which result in the formation of a vascular bed. This bed provides nourishment for myofibroblast proliferation from the vessel tunica media.[3] The combination of events ultimately results in vessel obstruction and ischaemia to downstream tissues. The most common cranial arteries involved are the temporal, ophthalmic and short posterior ciliary arteries.[4]

Polymyalgia rheumatica (PMR) is often found concurrently with GCA. It presents with symmetrical aching, tenderness, and stiffness of the proximal muscles of the neck, shoulders and pelvic girdle, most notably in the morning. PMR is an inflammatory disease thought to represent a different end of the GCA spectrum.[5]

Symptomatology

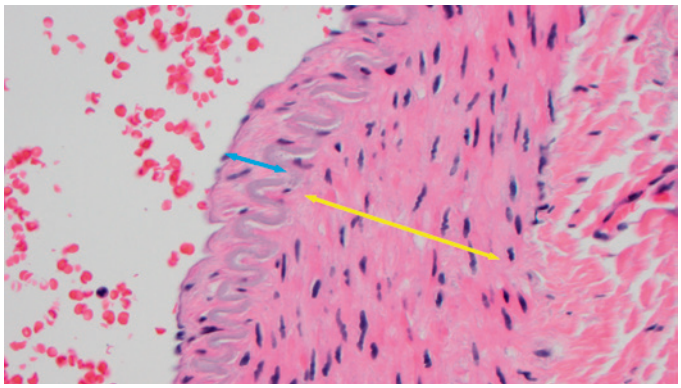
Sudden painless vision loss (often preceded by amaurosis fugax), temporal headache, jaw claudication, scalp tenderness, fever, occipital tenderness, dental abscess, vertigo and unexplained weight loss are all common GCA signs and symptoms. Jaw claudication and temporal headache are highly correlated with GCA diagnosis, as 30-80 per cent of diagnosed patients present with these symptoms.[5] Visual related findings may also include diplopia and visual hallucinations. Vision loss is most commonly the result of anterior arteritic ischemic optic neuropathy.

While PMR causes pain in proximal joints, distal joints can also be affected in GCA patients. Peripheral arthritis with swelling and pitting oedema in the hands and feet may occur in 25 per cent of patients.[6] Likewise, the carotid branches are not the only arteries involved. Some cases manifest occlusion of the subclavian and axillary arteries. This results in claudication of the arms, and weak pulses in these distributions.[6]

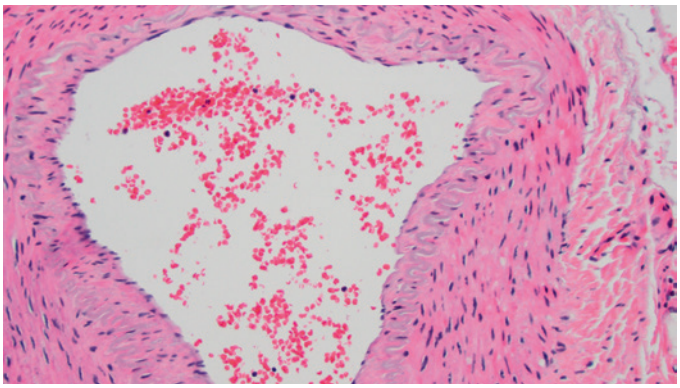
Detection and diagnosis

The American College of Rheumatology (ACR) released diagnostic criteria for GCA in 1990.[5] It requires patients to meet three or more of the following criteria: age over 50 years, new onset localised temporal headache, temporal artery tenderness or decreased pulse, erythrocyte sedimentation rate (ESR) of at least 50 mm/hour and abnormal temporal artery that shows characteristic histopathologic changes of mononuclear or granulomatous inflammation.[5] However, the weight that a clinician should place on these criteria is questioned.[7]

Muchison and colleagues performed a retrospective review of all patients who underwent a temporal artery biopsy at Wills Eye Institute in Philadelphia, Pennsylvania.[7] The authors found several patients with positive temporal artery biopsies whom the criteria failed to diagnose.[7] The ACR criteria should be used as a guide and clinical judgment is still vital.



▲ Figure 1A. Magnified view of normal arterial wall. Blue arrow demarcates internal elastic lamina (note its uniform organisation), yellow arrow demarcates tunica media.



▲ Figure 1B. Cross section of normal temporal artery vessel wall

Temporal artery biopsy

As shown in Figure 2, temporal artery biopsy has long been considered the gold standard for the diagnosis of GCA. How good is it? Niederkohr and Levin set out to answer this question.[8] The authors performed a Bayesian analysis on patients who underwent bilateral biopsies to determine the sensitivity of a unilateral temporal artery biopsy. The reported sensitivity of unilateral temporal artery biopsy was 87.1 per cent.[8] With this high degree of sensitivity, the clinician must now determine when a biopsy should be undertaken.

Hassan and colleagues have reported on symptoms that are most correlated with a positive temporal artery biopsy.[9] This was performed through a meta-analysis. The authors report that jaw claudication, diplopia and abnormality of palpation of the temporal artery had the highest predictive value of a positive temporal artery biopsy. Of slightly less predictive value were temporal headache, scalp tenderness, ESR over 100 mm/hour and anaemia.[9] Suelves and colleagues found high association between a positive biopsy and elevated C-reactive protein (CRP).[10] We recommend that a temporal artery biopsy be performed on all patients who present with any combination of these signs and symptoms.

Shortcomings

Temporal artery biopsy is the best diagnostic test we have but it does have its faults. The most problematic is the occurrence of skip lesions. A skip lesion refers to a location along the arterial wall not affected by inflammation. Skip lesions cause false negative results if they occur within the segment of the artery that was excised. Long specimen size—between 10 and 30 millimetres—decreases the risk of a skip lesion obscuring the diagnosis. If the initial biopsy is negative in patients with highly suspected GCA, the doctor must use their clinical judgment to decide the correct diagnosis. Biopsy of the other side's temporal artery may help increase a positive yield.

Recently, Doppler ultrasound has been used to help with the diagnosis of GCA. Nesher and colleagues found that a negative halo sign on colour Doppler ultrasound has a negative predictive value of 88 per cent.[11] In other words, ultrasound without a positive Doppler sign corresponded correctly with negative temporal artery biopsy in 88 per cent of cases. This ultrasound procedure is very technician-dependent but when done properly, it can be of great assistance; however, a positive halo sign did not correlate highly with a positive biopsy.

While ESR was originally deemed most valuable for diagnosis, it remains normal in two per cent to 30 per cent of confirmed GCA cases.[12] It has since been discovered that elevated CRP is of higher sensitivity (97.5 per cent), than ESR (76 per cent to 86 per cent). The best way to use these tests is to run them simultaneously, resulting in 97 per cent specificity and 99 per cent sensitivity rates.[12]

Treatment

Corticosteroids have long been the drug of choice for treating GCA. Adding 100 mg/day of aspirin to the steroid regimen has been shown to lower the risk of loss of vision and strokes from GCA.[13]

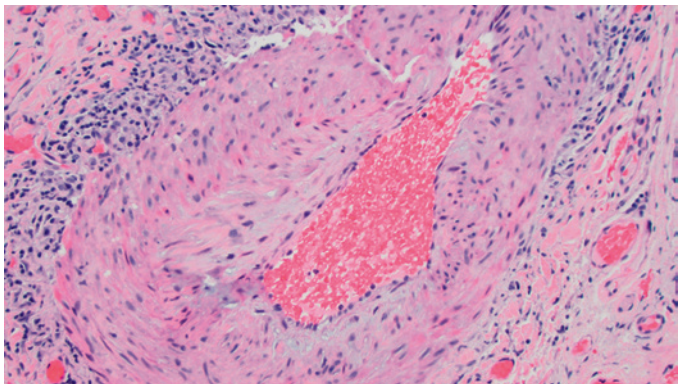
The steroid regimen used depends on the initial presentation. Unwin and colleagues report that a prednisone dose between 40 and 60 mg per day is required to suppress GCA.[2] When patients present with ischaemic symptoms such as jaw claudication, a dose of 60 mg/day should be initiated.[5] Initiation of treatment should be prompt, as it does not alter biopsy results for the first four weeks. When patients present with visual symptoms, intravenous methylprednisolone may be a better approach. In these cases, the steroid should be given in pulsed doses of 1,000 mg per day for three days.[6] A rapid response to treatment is expected. If this does not occur, the diagnosis should be reassessed.

Relapses in GCA are common and up to one third occur in the first 18 months of treatment.[12] A relapse is treated with administration of the last effective steroid dose. Patients should be monitored for relapse with both ESR and CRP monthly, for up to one year after treatment has ended. An abnormal result alone does not necessitate an increase in treatment but it does call for closer clinical scrutiny.

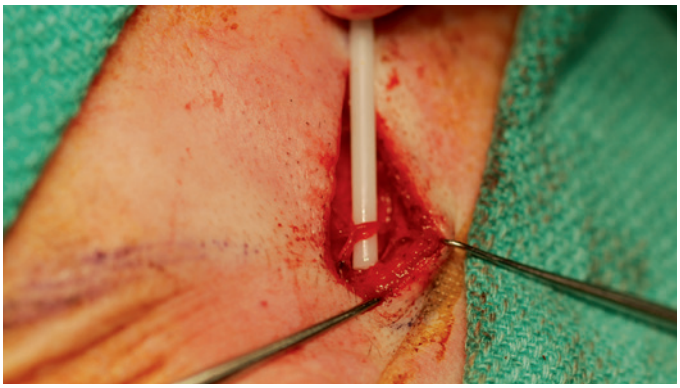
Thoracic artery aneurysm is another risk in GCA patients. Salivarani and colleagues report these aneurysms are 17 times more likely in patients with GCA and may occur several years after the classical symptoms of GCA subside.[6] As a result, they recommend a yearly chest radiograph for GCA patients.[6]

Once treatment is started, the next decision is when to begin reducing the dose. Treatment may be long-term and

Continued page 10



▲ Figure1C. Positive temporal artery biopsy. Note the proliferation of the tunica media and destruction of internal elastic lamina.



▲ Figure 2. Bifurcation of frontal branch of left temporal artery to be excised and undergo histopathologic analysis

Giant cell arteritis

From page 9

requires a slow taper. Salivarani and colleagues recommend tapering in 10 per cent deduction every four weeks.[3]

The chronic use of steroids can cause many side-effects. Fifty-eight percent of patients being treated with systemic steroids suffer serious complications.[6] As a result, patients need to be monitored for conditions such as diabetes, osteoporosis, cataracts, ocular hypertension, Cushing's syndrome and gastrointestinal ulcers. Practitioners need to be vigilant of these complications and proactive in preventing them. Supplementation with calcium, vitamin D and bisphosphonates can help safeguard against osteoporosis. Likewise, proton pump inhibitors such as omeprazole and esomeprazole can prevent gastrointestinal problems.

The prevalence and seriousness of steroid-induced side-effects have prompted research into alternative or adjunct means of treatment. Immunosuppressants such as methotrexate and cyclophosphamide have been investigated; however, multiple sources reject their effectiveness.[2,15,16] For now, steroid with the adjunct application of low dose aspirin remains the only proven means of treatment.

With its grave consequences and rapid progression, both detection and initiation of treatment in GCA must be timely. Though temporal artery biopsy is the only means to obtain a definite diagnosis, there are ways to help confirm or reject the diagnosis. Once treatment has begun, its course may be lengthy. Corticosteroids, despite their many side-effects, continue to be the mainstay of GCA treatment. ▲

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Study suggests most GCA cases contain varicella-zoster virus

THE AETIOLOGY of giant cell arteritis (GCA) remains unknown. To examine a possible association of GCA with varicella-zoster virus (VZV), investigators collected 82 GCA-positive temporal artery biopsies (TAs).

The authors found VZV antigen in 61 (74 per cent) of the pathologically-confirmed TAs, compared with one of 13 healthy-control TAs—a significant difference. VZV antigen was most frequently located within 'skip areas,' and giant cell vasculitis was adjacent to such areas.

Writing for the *NEJM Journal Watch*, Robert T Naismith suggested the discovery that at least some cases of giant cell arteritis may be due to VZV could have substantial clinical implications.

One of the concerns in diagnosing GCA is obtaining a negative temporal artery biopsy of a skip area. If VZV testing is confirmed to have high sensitivity and specificity in the setting of high clinical suspicion, a negative biopsy that is VZV-antigen-positive may provide the needed evidence for long-term treatment of GCA.

However, Naismith points out that although the authors make a strong case that the virus should be considered as the aetiology of the vasculopathy instead of an aberrant reactivation of latent virus due to inflammation, a definitive cause/effect relationship cannot be discerned from cross-sectional biopsies.

Gilden D et al. Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis *Neurology* 2015 Feb 18 [e-pub ahead of print].

Disc haemorrhage offers strong diagnostic clue

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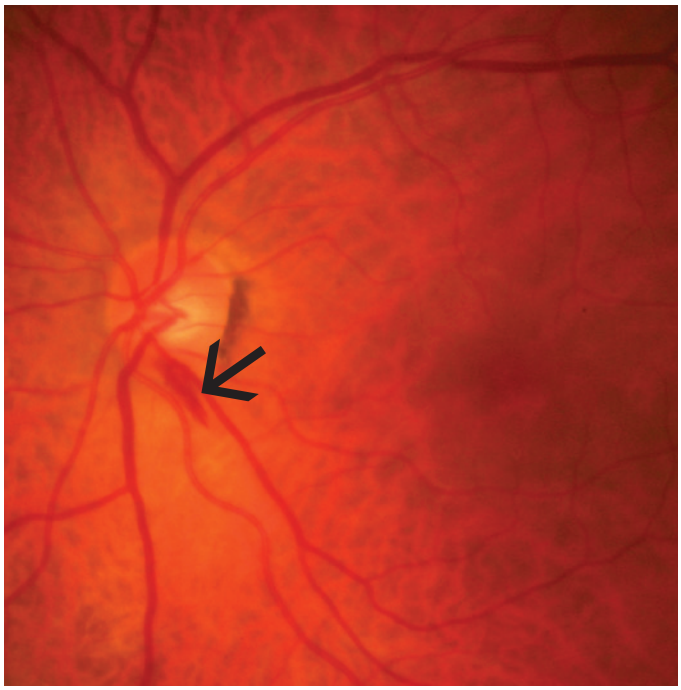
PHOTO CLINIC

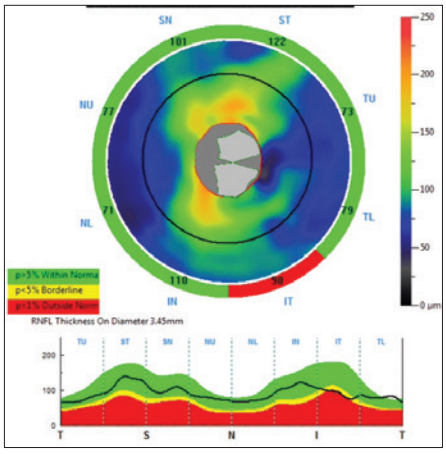
A 78-YEAR-OLD female patient reported for a routine eye examination. The intraocular pressures were right 18 mmHg and left 19 mmHg. Both anterior chamber angles were open. There was a left drance haemorrhage, as illustrated by the arrow in Figure 1.

The visual field analysis demonstrated an arcuate field defect. The OCT scan displayed thinning of the retinal nerve fibre layer. Both defects were consistent with the location of the haemorrhage.

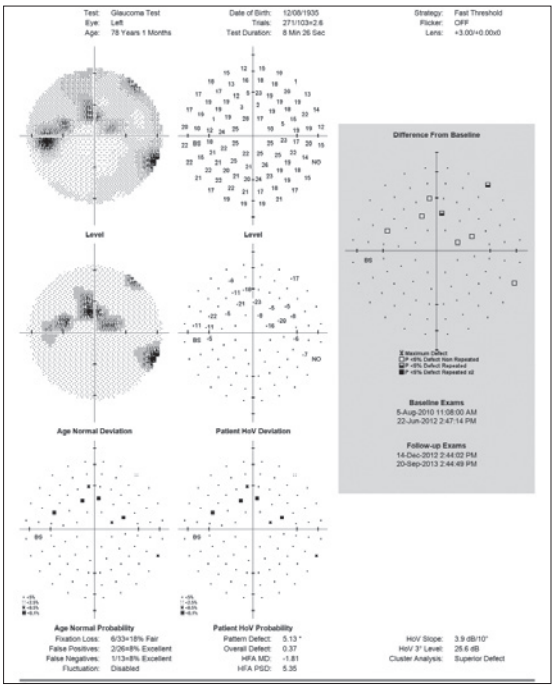
The diagnosis was normal tension glaucoma. Treatment was commenced with Xalatan but subsequently modified to Xalacom, which reduced the IOP to right 13 mmHg and left 15 mmHg. ▲



▲ Figure 1. Left drance haemorrhage (arrow)



▲ Figure 2. RNFL thinning



▲ Figure 3. Arcuate field defect

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ABSTRACTS

Association between self-reported calcium supplement consumption and AMD

Self-reported calcium supplement consumption has been shown to be associated with an increased prevalence of AMD. A cross-sectional study involved 3,191 participants, aged at least 40 years, in the 2007-2008 National Health and Nutrition Examination Survey. Participants were interviewed regarding dietary supplement and antacid use during the 30-day period preceding enrolment.

The presence or absence of AMD was determined by retinal fundus photography. Multivariable logistic regression models were used to determine the odds of an AMD diagnosis among participants who self-reported calcium consumption versus those not self-reporting supplementary calcium consumption, after adjusting for confounders.

A total of 248 participants (7.8 per cent) were diagnosed with AMD. After adjusting for potential confounders, participants who self-reported consuming more than 800 mg/day of supplementary calcium were found to have relatively higher odds of an AMD diagnosis (OR 1.85; 95% CI 1.25 to 2.75).

The association between self-reported supplementary calcium intake and AMD was stronger in older than younger participants (OR 2.63; 95% CI 1.52 to 4.54). A clear dose-response association between the quintiles of self-reported supplementary calcium intake and AMD was not established.

JAMA Ophthalmol; ePub 9 April 2015.

Misidentification of objects in people with AMD

Patients with AMD show impaired performance with identifying objects and scenes. This contrasts with previous studies that have shown that people with AMD can detect a predefined target object or scene with high accuracy.

In this study, photographs of isolated objects, natural scenes and objects in scenes were centrally displayed for two seconds each. Participants (n = 20 with AMD, n =15 age-matched controls and n = 12 younger controls) were asked to name the stimuli.

Naming accuracy and the speed of naming were impaired in people with AMD, compared with age-matched controls, in the three categories of images. More than 20 per cent of the misidentifications resulted from a structural and/or semantic similarity between the object and the name (for example, spectacles for dog plates or dolphin for shark).

The authors reported that accuracy and naming times did not differ significantly between young and older normally-sighted participants, suggesting that the deficits in AMD patients were related to pathological changes rather than normal ageing.

It was concluded that these findings indicate that in AMD patients, peripheral vision may be adequate for object and scene detection, but not for precise scene or object identification.

Ophthalmic Physiol Opt; ePub 6 April 2015.

Smoking, antioxidant supplementation and diet in Australians with AMD

Adherence to smoking and dietary recommendations have been found to be relatively poor among older Australians with AMD, and the uptake of antioxidant supplements increases significantly among those with late-stage AMD.

A study undertaken in Sydney compared the micronutrient usage and other lifestyle behaviours of people with and without AMD, over a 10-year period. Participants (n = 1612) were aged at least 49 years at baseline. AMD status was assessed using retinal fundus photographs. Dietary data were collected using a semi-quantitative food frequency questionnaire. Smoking status was self-reported.

At baseline, 56 people had AMD; of these, 25 per cent ceased smoking at five years and were still not smoking at the 10-year follow-up. Among participants who had below the recommended intake of vitamins A, C or E supplements at baseline, those who did compared to those who did not develop late AMD over 10 years were more likely to report vitamins A (total), C or E supplement intake above the recommended intake at the 10-year follow-up: multivariable-adjusted OR 4.21 (95% CI 1.65 to 10.73); OR 6.52 (95% CI 2.76 to 15.41); and OR 5.71 (95% CI 2.42 to 13.51), respectively.

Compared to those participants without AMD at baseline, those with AMD did not significantly increase their intake of fish, fruit or vegetables or change their overall diet quality over the 10-year follow-up period.

PLoS One 2015; 10: 3: e0122548.

Visual function losses in early AMD

Eyes in the earliest stages of AMD, where visual acuity and contrast sensitivity are not yet impaired, show significantly delayed rod-mediated dark adaptation compared with age-matched eyes with normal macular health.

Adults (n = 640) aged 60 years or older had their macular health assessed using colour stereographic retinal fundus photographs by an experienced grader. Each eye was classified as having either normal macular health or early stages of AMD (grades 2 to 4 using the nine-step AREDS classification system for AMD severity). Visual function was assessed using best-corrected visual acuity (VA), low luminance VA, contrast sensitivity, macular cone-mediated light sensitivity and rod-mediated dark adaptation.

A total of 1,260 eyes were tested (n = 1,007 with normal macular health, n = 253 with early AMD). Following

adjustment for age and gender, early AMD eyes had twice the odds of having delayed rod-mediated dark adaptation than eyes with normal macular health. Visual acuity, low luminance visual acuity, contrast sensitivity and macular light sensitivity did not differ between early AMD eyes and those with normal macular health.

Curr Eye Res 2015; 24: 1-7.

AMD in patients with AIDS

Patients with acquired immuno-deficiency syndrome (AIDS) have an increased, age-adjusted prevalence of intermediate-stage AMD compared with non-HIV-infected individuals. This finding is consistent with a higher prevalence of other age-related diseases in antiretroviral-treated, immune-restored, HIV-infected persons compared with non-HIV-infected persons.

The findings were from a cross-sectional study of AIDS patients (n = 1825) who were enrolled in the Longitudinal Study of the Ocular Complications of AIDS in the United States. Retinal photographs were taken of each participant at enrolment; masked graders identified participants with intermediate-stage AMD.

Almost 10 per cent of participants had intermediate-stage AMD. The prevalence of AMD ranged from four per cent of participants 30-39 years old to 24.3 per cent of participants aged at least 60 years. Other risk factors for AMD included the HIV risk groups of injection drug use (OR 2.4, 95% CI 1.5 to 3.9) or heterosexual contact (OR 1.9, 95% CI 1.3 to 2.8).

Compared with an HIV-uninfected population in the Beaver Dam Offspring Study, there was an approximate four-fold increase in age-adjusted prevalence of intermediate-stage AMD in this population of AIDS patients.

Am J Ophthalmol; Epub 11 March 2015.

Reticular pseudodrusen associated with a diseased Bruch's membrane in pseudoxanthoma elasticum

Reticular pseudodrusen (RPD) are most commonly associated with AMD and are recognised as an independent risk factor for disease progression. This study reports a high prevalence of RPD in eyes of younger patients with pseudoxanthoma elasticum (PXE).

The single-centre, prospective, cross-sectional case series sought to describe the prevalence, phenotype and topographic distribution of RPD, as well as the association of RPD with diseased Bruch's membrane, in patients with PXE.

Patients with PXE (n = 57) were evaluated with multiple retinal imaging modalities. A sub-group (n = 15) was excluded due to the presence of large central fibrosis or atrophy. RPD were detected in 22 of the remaining 42 patients with PXE (52%; 95% CI, 38 to 67%). The prevalence of RPD was highest in the fifth decade.

The authors concluded that the association of RPD with a diseased Bruch's membrane in PXE suggests a pathogenic role for changes in this anatomical structure in the development of RPD.

JAMA Ophthalmol; Epub 12 March 2015.

Association between neovascular AMD and dementia

A population-based, case-control study in Taiwan has reported an association between neovascular AMD and dementia.

Data for the study were retrospectively collected from the Taiwan National Health Insurance Research Database. Two populations were analysed: people with a diagnosis of dementia (n = 13,402) and those without dementia (controls, n = 40,206). A conditional logistic regression was used to examine the association of dementia with previously diagnosed neovascular AMD.

In the patient groups with dementia and the controls, 1.35 per cent and 0.90 per cent had been previously diagnosed with neovascular AMD, respectively ($p < 0.001$). Conditional logistic regression analysis suggested that the odds ratio for prior neovascular AMD for people with dementia was 1.37 (95% CI 1.14 to 1.65) compared with controls, after adjusting for potential confounding factors.

PLoS One 2015; 6: 10: 3: e0120003.

Serum leptin and AMD

Leptin is an amino acid protein that is secreted by adipocytes. It has been shown in a study to reduce beta-amyloid deposition and intracellular lipid concentration in animal models, which are two key pathogenic mechanisms that occur with ageing.

The aim of the study was to examine the association between serum leptin levels and AMD. The population-based, case-control study included Chinese and Indian adults aged 40 to 80 years, who participated in the Singapore Epidemiology of Eye Diseases Study (2007–2011). AMD was assessed using graded retinal photographs, performed using a modified Wisconsin Age-Related Maculopathy Grading System (n = 426; early AMD, n = 389, late AMD, n = 37). Controls (n = 927) showed no signs of AMD and were matched for age, sex and ethnicity. Serum leptin levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit.

Compared with controls, participants with AMD had lower levels of serum leptin (mean [sd]: 10.0 [11.5] ng/mL versus 12.9 [16.4] ng/mL; $p = 0.001$). The mean levels of serum leptin among those with late, early and without AMD were 8.8, 10.1, and 12.9 ng/mL, respectively (p trend = 0.005). In multivariable models adjusting for potential confounders, increasing quartiles of leptin were associated with lower odds of AMD (OR 0.56, 95% CI 0.35 to 0.92) comparing highest to lowest quartile of serum leptin.

Higher serum leptin levels were inversely associated with AMD. These findings, if confirmed in prospective studies, may provide insights into new pathogenic pathways and possibly therapeutic targets in AMD.

Invest Ophthalmol Vis Sci 2014; 56: 3: 1880-1886. ▲

Tear neuropeptides for dry eye

Topical application to the ocular surface may be a promising treatment

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NERVE GROWTH factor (NGF), substance P (SP) and calcitonin gene-related peptide (CGRP) are the key neuropeptides on the ocular surface and may be a remedy for dry eye in the near future. NGF at the ocular surface promotes nerve growth,[1,2] and reinnervation after injury[3] by preventing the death of neurons. NGF also regulates the level of neuropeptides, including SP and CGRP,[1,4,5] on the ocular surface. The role of the neuropeptide SP and CGRP is not only limited to pain sensation at both cornea and conjunctiva, but also involved in epithelial wound healing, local inflammation, corneal reinnervation and maintaining ocular surface integrity.[1,3,4,6-9]

In general, neuropeptides are associated with cell and nerve function and subsequently maintain homeostasis in peripheral tissues, including the ocular surface.

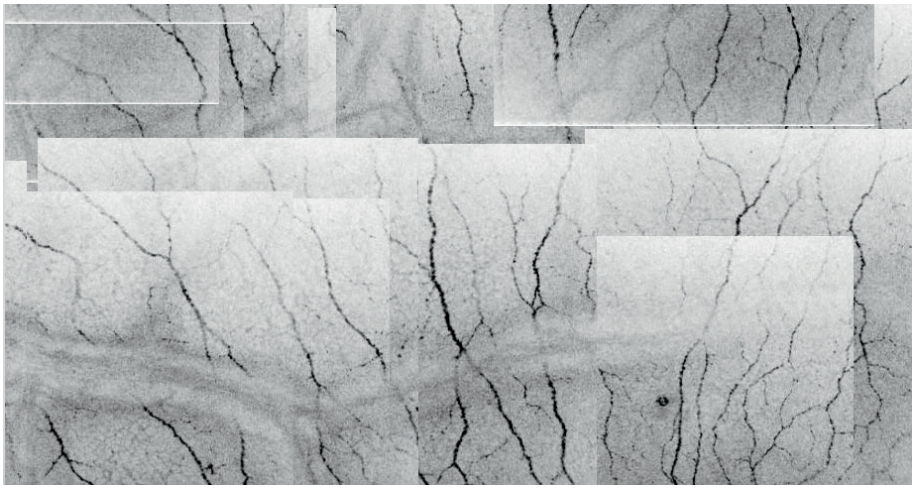
NGF concentration in tissues rises when tissues or nerves are injured and returns to normal levels once the wound or nerves are healed.[1,10-14] This explains the elevated NGF levels found in tears after LASIK refractive surgery.[15]

Administration of SP *in vitro* results in increased corneal epithelial cell numbers, and it is speculated that SP acts to enhance cell proliferation.[16] Conversely, a reduction in corneal epithelial cell density (cells detached from the culture plate) was observed when CGRP was administered *in vitro*.[16] It is likely that CGRP induces cell differentiation, which causes cells to detach and migrate, thus enabling wound healing.[16]

Our recent work has confirmed the importance of these neuropeptides in corneal nerve regeneration and maintenance of ocular surface integrity after LASIK refractive surgery (Chao et al 2014, under review). We found that tear SP concentration increases immediately after LASIK alongside the marked reduction of corneal nerve density, further supporting that SP has an important role in cell and nerve proliferation after injury.

In contrast, tear CGRP was positively associated with reinnervation (higher nerve fibre density and tortuosity) post-LASIK. This is consistent with the role of CGRP in reinnervation by cell differentiation after injury. Also, tear CGRP concentration was associated with better tear function (lower tear osmolarity and longer non-invasive tear break-up time) after LASIK. It is likely to be due to the restoration of nerve function.

Altered neuropeptide concentrations in tears commonly occur with dry eye and compromised ocular surface integrity. Higher tear NGF levels have been found in dry eye patients and in contact lens wearers with dry eye.[14] Higher NGF levels in these patients are associated with greater dry eye severity,[14,17] especially the degree of



▲ Pre-LASIK

corneal staining and conjunctival hyperaemia.[17] A reduction of tear CGRP concentration occurs in chronic dry eye and is associated with greater corneal staining and lower tear volume.[17] Changes in SP levels were not significantly different in the same study.[17]

Other studies have also shown altered SP and CGRP levels in tears of contact lens wearers, dry eye patients with diabetes and post-refractive surgery patients,[5,15,17-19] and have found altered levels of both neuropeptides to be associated with changes in corneal staining, corneal sensitivity and corneal sub-basal nerve density. Such findings suggest that administration of neuropeptides to the ocular surface could improve signs of dry eye, including neuropathic dry eye which results from diabetes or from corneal nerve damage due to mechanical/chemical injury such as that induced by refractive surgery.

The topical administration of neuropeptides to the ocular surface may ameliorate dry eye, including neuropathic dry eye, by facilitating corneal wound healing and reinnervation. NGF has previously been used in the management of peripheral (legs) diabetic neuropathy. Although this approach caused hyperalgesia at the injection site in the legs,[20-23] this is less likely to be an issue for topical application (but not injection) at the ocular surface.

Topical NGF, SP (combined with insulin-like growth factor-1) and CGRP administration improves reinnervation and nerve function (restoration of sensory impairment), and promotes epithelial healing on damaged or injured ocular surface in both animals and humans.[8,9,13,24-30] These neuropeptides may likewise be a promising treatment for dry eye, particularly ocular surface staining and dry eye symptoms resulting from nerve damage.

Tear neuropeptides are important in wound healing and integrity of the ocular surface, including maintenance of corneal nerves. They show promise as a future treatment of dry eye but clinical trials are required to confirm their merits.

Acknowledgement

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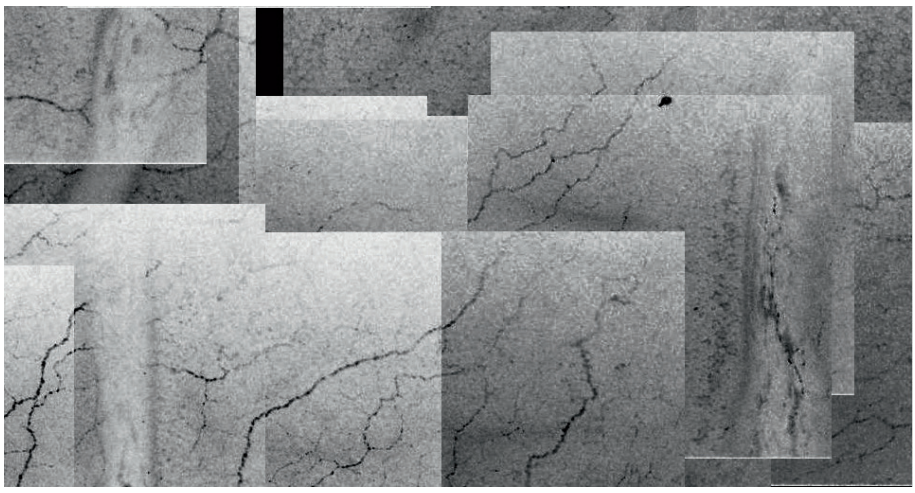
Conflict of interest disclosure

All authors have no proprietary or commercial interests in any concept or product discussed in this article. ▲



▲ Post-LASIK

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Tear neuropeptides

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Diabetes and the ocular

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BOptom(Hons)

DIABETES MELLITUS (DM) is a metabolic disorder characterised by hyperglycaemia and is one of the most common systemic diseases in the world. It is projected that the prevalence of the disease in people aged 25 years or older in Australia will reach 2.9 million by 2025, increasing the financial strain on the health system.[1] Diabetes is associated with premature mortality, macrovascular complications such as cardiovascular disease, and microvascular complications including nephropathy leading to kidney failure, potentially blinding diabetic retinopathy, and diabetic neuropathy.[2,3]

While the retinal complications of diabetes are well recognised by eye-care professionals, the effects on the ocular surface are poorly understood.

Diabetic keratopathy, for example, is estimated to affect between 47 and 64 per cent[4] of people with diabetes during the course of their disease and can ultimately lead to neurotrophic ulcers and significant visual morbidity.[5]

Corneal denervation from chronic hyperglycaemia[6-8] can lead to loss of corneal sensitivity.[9,10] Epithelial fragility as a result of reduced epithelial adhesion to the underlying basement membrane,[11,12] together with poor wound healing,[13,14] increase the susceptibility to persistent epithelial erosions[15] and corneal infection.[11,16]

▲ Figure 1. *In vivo* confocal microscopy using the HRT II Corneal Rostock Module (Heidelberg Engineering, Dossenheim, Germany). Image: Vinod Maseedupally

surface

The role of *in vivo* confocal microscopy in the monitoring of diabetic neuropathy

Quality of life in people with diabetes can also be compromised with corneal neuropathy, which may lead to dry eye discomfort and significant visual impairment from loss of ocular surface integrity.[11]

It is not well understood how these ocular surface conditions relate to the duration of diabetes, the severity of the systemic disease such as peripheral neuropathy, or the timeline in which they occur.

Diabetic peripheral neuropathy, defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes,[17,18] can have a devastating effect on a patient's quality of life. Painful neuropathy affects 30 per cent of people with diabetes, foot ulceration in seven per cent of patients with neuropathy, and lower limb amputation in advanced cases.[11,19,20,21]

Examination of nerve morphology in skin is via skin punch biopsy,[22] which allows for objective and sensitive assessment of small nerve fibre damage but is invasive and non-repeatable.[23] Nerve conduction,[24] using biothesiometry which measures large nerve fibre function, is a sensitive, objective technique and is currently the 'gold standard' for diagnosis.

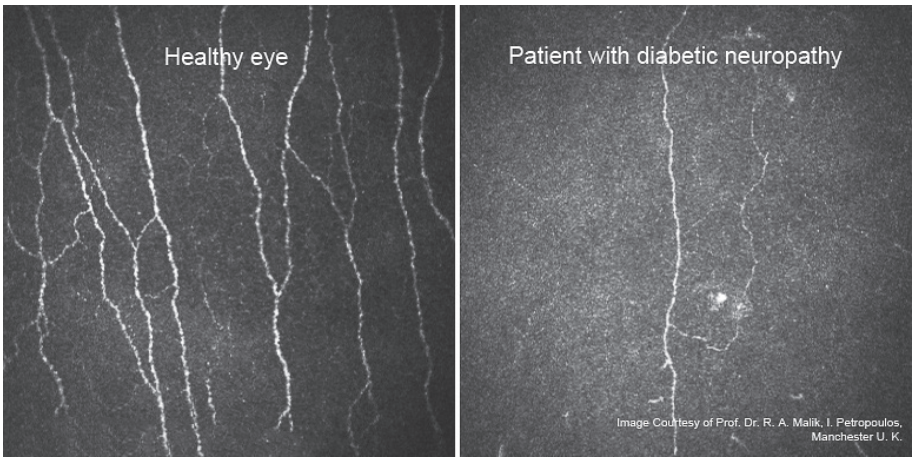
Non-invasive measurement

Unlike nerves elsewhere in the body, corneal nerves can be imaged *in vivo* and non-invasively with *in vivo* confocal microscopy (Figure 1).

There is an emerging body of evidence showing that morphological changes in the corneal subbasal nerve plexus correlates with changes in the peripheral nerves, and may be a good surrogate measure for diabetic peripheral neuropathy (Figure 2).[11,25,26]

Edwards and colleagues[27] conducted a five-year observational study measuring the change in corneal nerve morphology in people with diabetes using *in vivo* confocal microscopy. Participants with diabetic peripheral neuropathy were found to have significantly reduced corneal nerve fibre length and branch density compared to controls and participants with diabetes but without peripheral neuropathy.[27]

Significantly, a 2015 study reports that *in vivo* confocal microscopy can predict the onset of peripheral neuropathy in individuals with type 1 diabetes.[28]



▲ Figure 2. Central corneal nerve images acquired with *in vivo* confocal microscopy

Detection of those at risk

Optometrists and other eye-care practitioners routinely monitor corneal health and regularly screen people with diabetes for retinopathy. With the development of rapid automated analysis of corneal nerves in *in vivo* confocal microscopy,[29] this technique may become more commonly available in clinical practice, with eye-care professionals playing an important role in the management of peripheral diabetic neuropathy through the detection of those at risk through the surrogate measure of corneal nerve density changes.

The underlying mechanisms relating to corneal neuropathy are multifactorial and not completely understood. Corneal nerves provide trophic support to the epithelial cells by releasing soluble mediators that stimulate epithelial cell growth, mitosis, differentiation and migration.[6] These mediators include Substance P, Insulin-like Growth Factor-1 (IGF-1), calcitonin gene-related peptide, neuropeptide Y, and vasoactive-intestinal peptide.[30]

Epithelial cells, in turn, provide trophic support to corneal neurons by secreting growth factors (such as NGF) that promote neurite extension.[6] In diabetes, there is thought to be a reduction in the concentration of these mediators, leading to a disruption in epithelial integrity, and a flow-on effect

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Diabetes and the ocular surface

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that causes further neuron loss and ultimately neurotrophic ulcers.[10,31]

An understanding of these underlying mechanisms may contribute to the development of treatments and preventative measures. For example, Substance P is a sensory neurotransmitter secreted by the trigeminal nerve. Substance P alone has no effect on epithelial migration; however, in conjunction with IGF-1 it has been shown to promote epithelial migration in a synergistic manner.[32,33]

Topical treatment with Substance P derivatives and IGF-1 have been shown to have good efficacy in healing epithelial defects and restoring ocular surface integrity in neurotrophic keratopathy, including diabetic keratopathy.[5,34] Various studies have similarly demonstrated the ability of topical NGF to restore corneal sensitivity and ocular surface integrity after corneal neurotrophic keratitis.[35,36]

Early detection and treatment

Being able to elucidate the pathophysiology of diabetic corneal neuropathy through monitoring the subbasal nerve plexus *in vivo* and understanding the underlying mechanisms may lead to a better understanding of the processes that occur in peripheral neuropathy, and lead to earlier detection and treatment.

Optometrists and other eye-care practitioners play an important role in the management of diabetes through the early detection and management of microvascular complications including both retinopathy and corneal neuropathy. ▲

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Reading difficulty and glaucoma

Perceptual processes can be affected by paracentral scotoma

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WHEN PEOPLE HAVE difficulty reading, it is common for them to attend their primary care optometrist for assistance. DC, an 85-year-old woman who describes herself as an avid reader, had noticed that she was not reading as easily as in the past and requested a review of her vision.

Clinical findings

Her BCVA was 6/9 R and 6/9- L with her current bifocal spectacles, which she preferred to use for reading rather than her single vision near spectacles of the same prescription.

CASE REPORT

She had a mild cataract in the RE and the LE was seeing better following a successful cataract operation and intraocular lens insertion three years previously. Despite this her RE was dominant and her LE had mild exotropic amblyopia and ptosis, which reduced her BCVA slightly in that eye, with no diplopia reported for distance or near fixation.

She had known glaucoma in both eyes with marked glaucomatous notching inferiorly RE > LE (Figures 1A and 1B).

Her macular area was relatively stable (Figures 2A and 2B) but there was an Amsler grid defect reported in the RE, to the upper right of fixation.

Intraocular pressures were 16 mmHg RE and 12 mmHg LE, which was controlled by timolol 0.5% BID OU.

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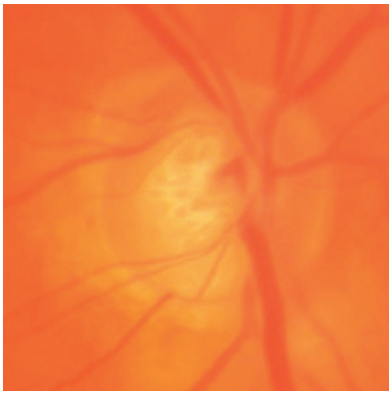
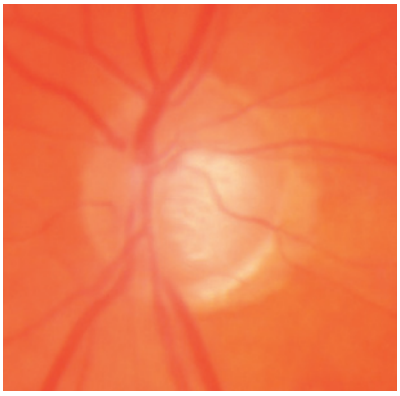
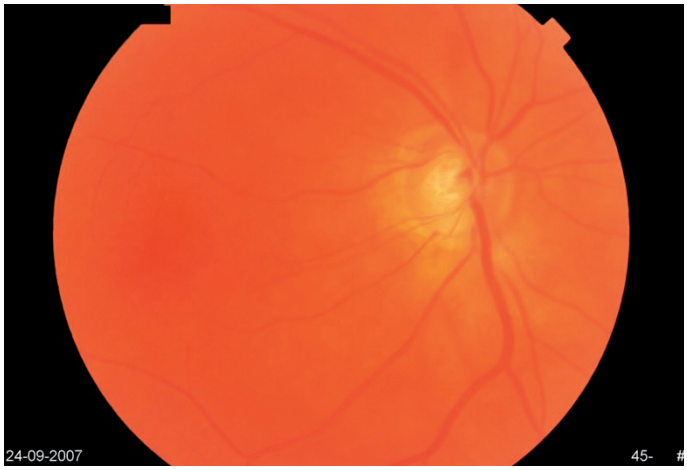


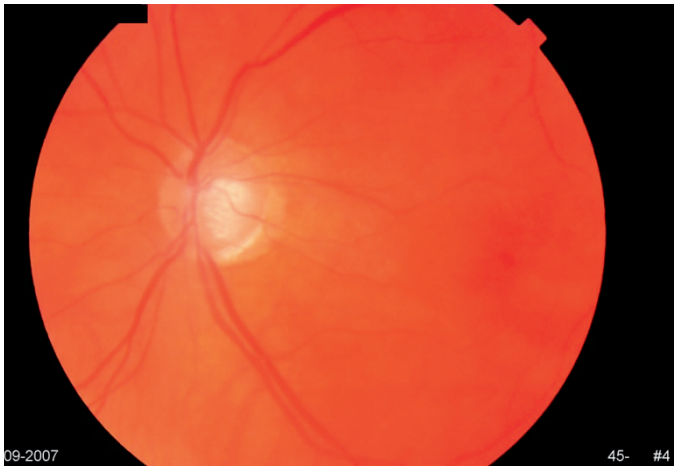
▲ Figure 1A. Right optic disc with marked glaucomatous damage



▲ Figure 1B. Left optic disc, also with significant glaucoma



▲ Figure 2A . Right eye was her preferred eye despite vision reduction from cataract and glaucomatous damage



▲ Figure 2B. Left eye was weaker due to longstanding binocular vision issues

Reading and glaucoma

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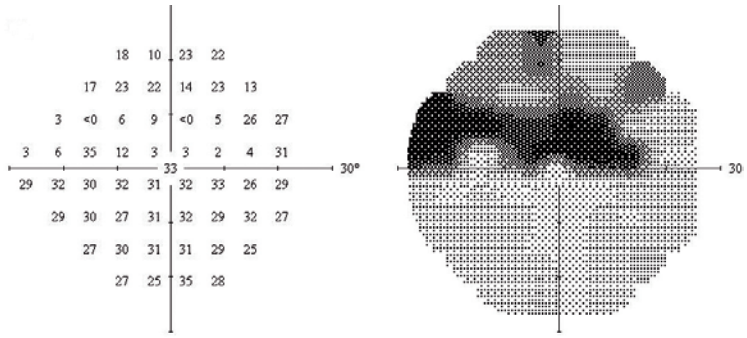
Visual field showed relatively central glaucomatous defect of the RE and some glaucomatous nasal step defect in the LE (Figures 3A and 3B).

Conclusions

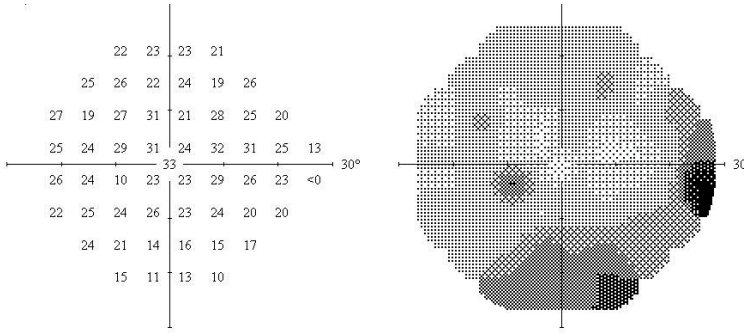
Although DC was relieved that she did not have signs of macular degeneration and that to a certain extent, her glaucoma management could be improved, without a significant reduction in visual acuity her reading difficulties were difficult to explain. DC found benefit in reading large print in good light and was happy to follow up with her regular ophthalmologist for further surgical and pharmaceutical options for glaucoma control.

Reading is a complicated but rewarding task and recently-identified aspects of vision can help explain some of DC's difficulties. Glaucoma has been associated with 'slower reading and increased reading impairment with advanced bilateral field loss'.[1]

There is experimental evidence of an age-related decline in extra foveal letter perception with age.[2] With DC, both the effects of age and glaucoma are important to consider as skilled reading in particular is understood to involve the processing of upcoming words in the parafovea.[3]



▲ Figure 3A. Right eye visual field with fixation intact but with marked altitudinal parafoveal impairment particularly to the right of fixation.



▲ Figure 3B. Left eye visual field with some glaucomatous change and an overall reduction in threshold sensitivity.

DC's paracentral glaucomatous scotoma may explain some of her reading difficulties because even though vision at fixation is relatively intact, her scotoma masks surrounding words and thus interferes with the oculomotor and perceptual processes[4] that are active before a word is fixated.

Further research in this field will help people with both foveal and parafoveal impairment understand the reduction in their reading ability and regain their reading fluency. ▲

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Central retinal vein occlusion and anti-VEGF treatment

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CASE REPORT

CC, A 59-YEAR-OLD Caucasian male, presented with a five-day history of right visual symptoms. He complained of 'patchy and sort of splotchy vision' with 'some scattered areas of vision loss'. He was not concerned as his 'central vision seemed fine'. His general health was good with no history of trauma or past ophthalmic issues. He had no family history of any ocular or cardiovascular health problems and was not on medications. His blood pressure was 126/78.

His uncorrected acuity was R 6/12 L 6/12. He was astigmatic and presbyopic. His spectacle prescription was:

R plano/-1.50 x 155 6/7.5
L plano/-1.75 x 45 6/6 Add +1.75 N5.

His pupil reactions were normal with no relative afferent pupil defect. IOP was R 11 mmHg L 11 mmHg at 10:00 am

His fundus examination showed features consistent with a right central retinal vein occlusion (CRVO). The left fundus was unremarkable. His right fundus (Figure 1) shows extensive haemorrhages, slight swelling of his optic nerve head and an area of central macular oedema. It is important to note that his acuity was still good at this stage (6/7.5) with very little ischaemic damage since the occlusion occurred five days earlier.

The patient was referred to a retinal specialist ophthalmologist and was seen 48 hours later. At this stage, his right acuity had decreased to 6/12 and he was now very aware of the decrease in his vision levels.

His Spectralis OCT scan (Figure 2) showed marked central macular oedema. The wide-field fluorescein angiogram (Figures 3-5) showed some leakage at the optic nerve, leakage of vessels at the macula and extensive peripheral retinocapillary drop-out.

The decision was made to treat CC with anti-VEGF therapy. At this stage he was injected with 0.05 mL (1.25 mg) of Avastin (bevacizumab) in his right eye and booked for review in one month. He was referred for a full blood examination, which showed his HDL and LDL cholesterol levels to be within normal limits. There were no abnormalities of his clotting factors and his ESR, serum homocysteine and blood glucose levels were normal.

At one month post-treatment, his right acuity had returned to 6/6 and he had no visual problems. His IOP was R 12 mmHg L 13 mmHg. His Spectralis OCT scan (Figure 6) showed that his macular oedema had completely resolved and his fundus photo (Figure 7) showed that his retinal haemorrhages were starting to resolve. He will be reviewed again in another month to check for further macular oedema and may need further anti-VEGF treatment.

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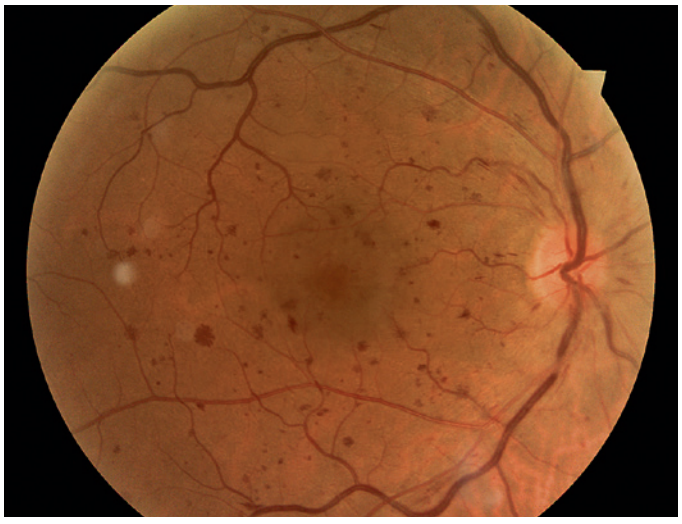
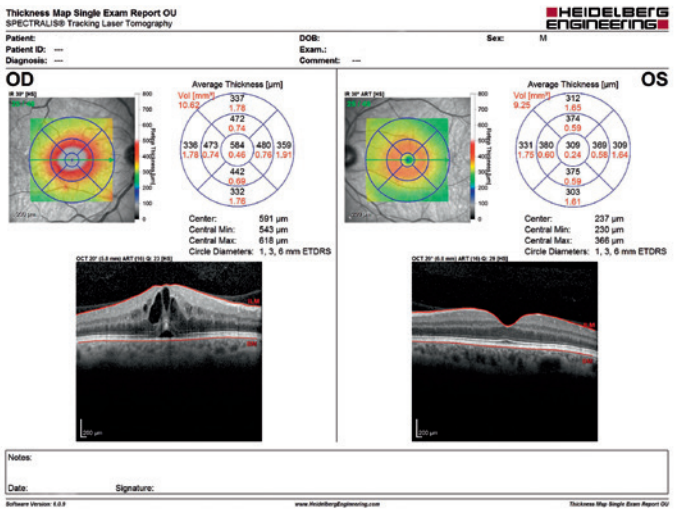
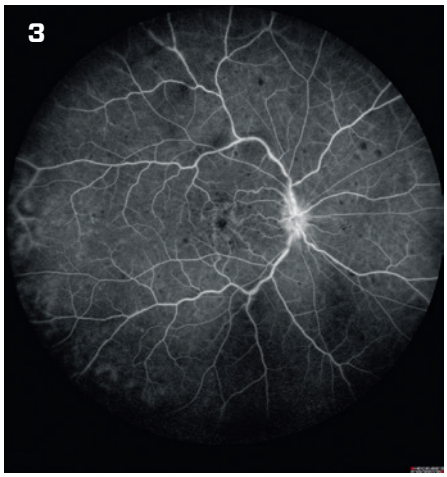
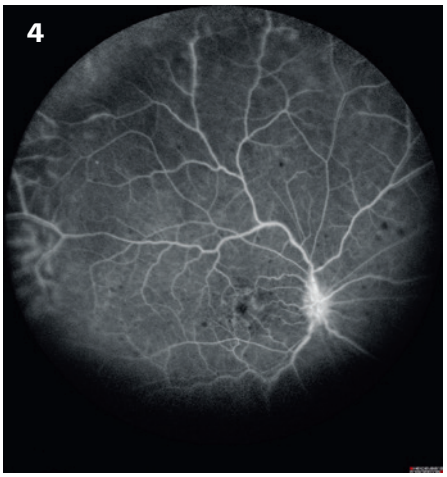


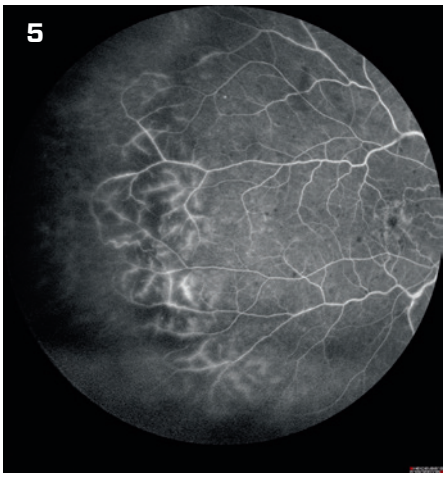
▲ Figure 1. Fundus photo five days post CRVO showing extensive retinal haemorrhages



▲ Figure 2. Spectralis macular OCT scan showing marked macular oedema and thickening







▲ Figures 3-5. Wide-field fluorescein angiography showing macular and optic disc leakage and leakage of the peripheral retinal capillaries

CRVO

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Discussion

This case illustrates the importance of prompt, timely treatment of CRVO with anti-VEGF therapy. If treatment is initiated prior to ischaemic changes developing, then the prognosis for visual recovery is very good. Initial presentation acuity can be a good indicator for the likelihood of ischaemia and hence visual prognosis.[1,2]

Non-ischaemic CRVO cases can still deteriorate and become ischaemic so they need to be closely monitored after treatment. CRVO has a higher association with glaucoma and post-treatment patients need to have monitoring of their IOP and optic discs. Risk factors for CRVO include age, hypertension, hyperlipidaemia, diabetes, oral contraception,[3] elevated serum homocysteine,[4] low vitamin B12 levels,[4] raised IOP and smoking. In this case the only risk factor was age. ▲

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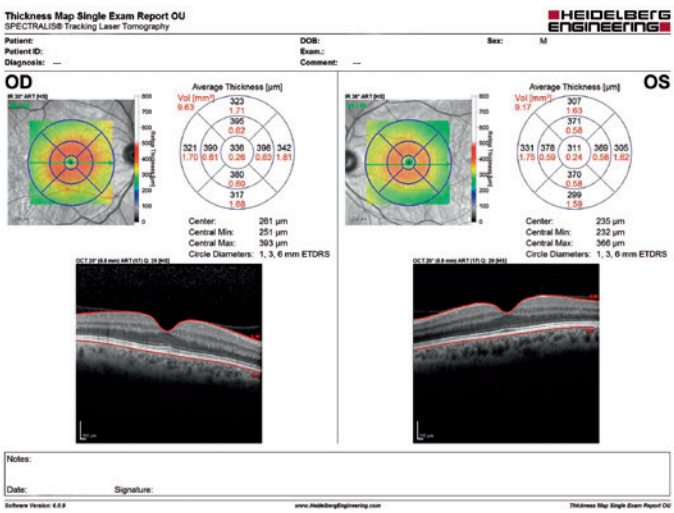
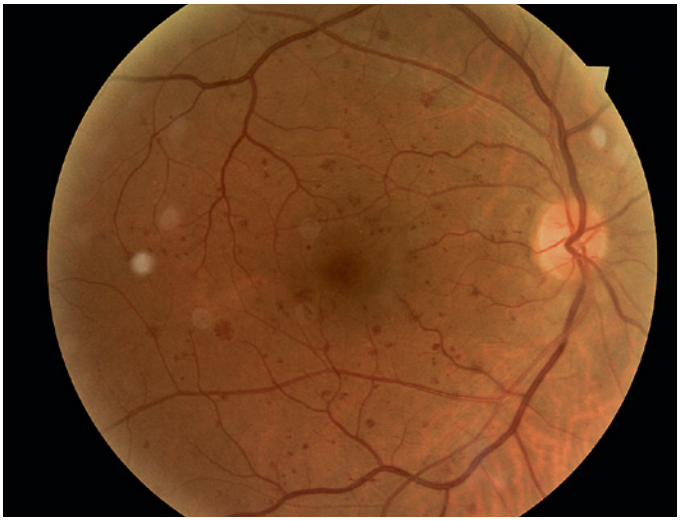


▲ Figure 6. Spectralis macular OCT scan showing normal macular thickness one month post-treatment with complete resolution of the macular oedema



▲ Figure 7. Fundus photo one month post-treatment showing resolution of the macular oedema and haemorrhages

Differentiate choroidal naevii from melanoma

Channel separation confirms location of malignant lesions

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CASE REPORT

OPTOMETRISTS frequently encounter patients with choroidal naevii and are called on to distinguish them from the much more sinister choroidal melanoma. Estimates of the prevalence of choroidal naevii vary between 4.6 per cent and 7.9 per cent in a white US population.[1] The Blue Mountains Eye Study gave an incidence of 6.5 per cent in a white Australian population.[2]

There is a large overlap in the size of naevii and melanoma at initial presentation, both in terms of the largest linear basal diameter and the thickness of the lesion.[3] For smaller lesions without other distinguishing features, it is reasonable to monitor them. With easier access to imaging devices, it is possible for optometrists to undertake this monitoring process with greater confidence.

The annual rate of malignant transformation of choroidal naevii has been estimated to be one in 8,845.[1] Distinguishing features often associated with malignant transformation include the shape, colour, size and thickness of the tumour.

The presence of symptoms, surface clumps of orange pigment (lipofuscin), surface drusen, associated serous sub-retinal fluid and invasive clinical features—such as focal eruption through Bruch's membrane, retinal invasion and optic disc invasion—can all be indicators of transformation to melanoma. Another important indicator is a documented increase in size, which imparts an almost

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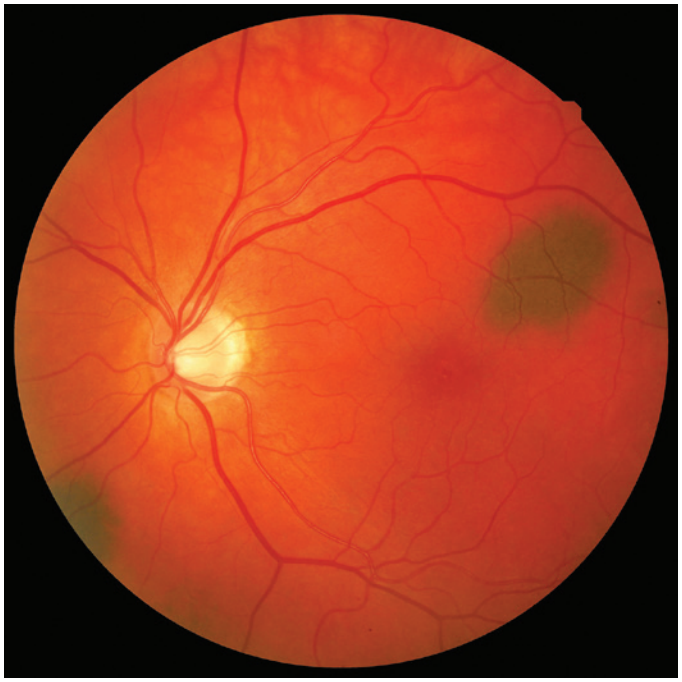
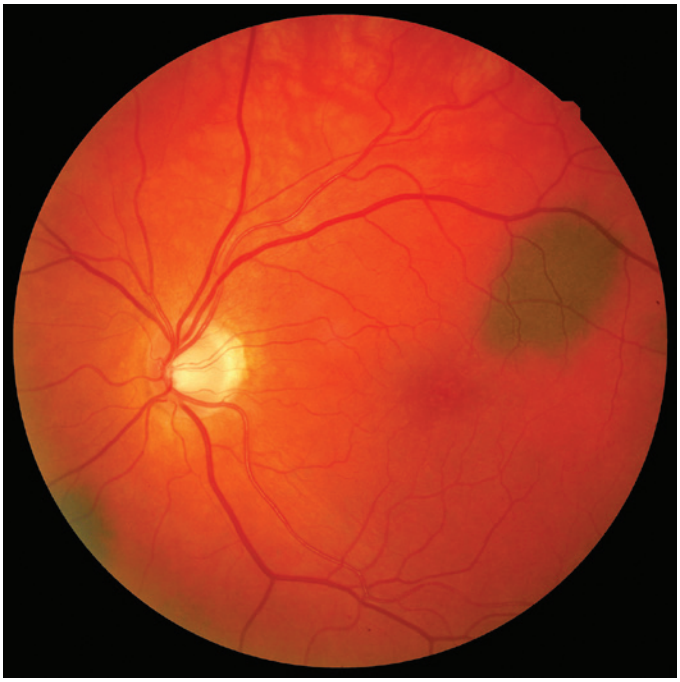
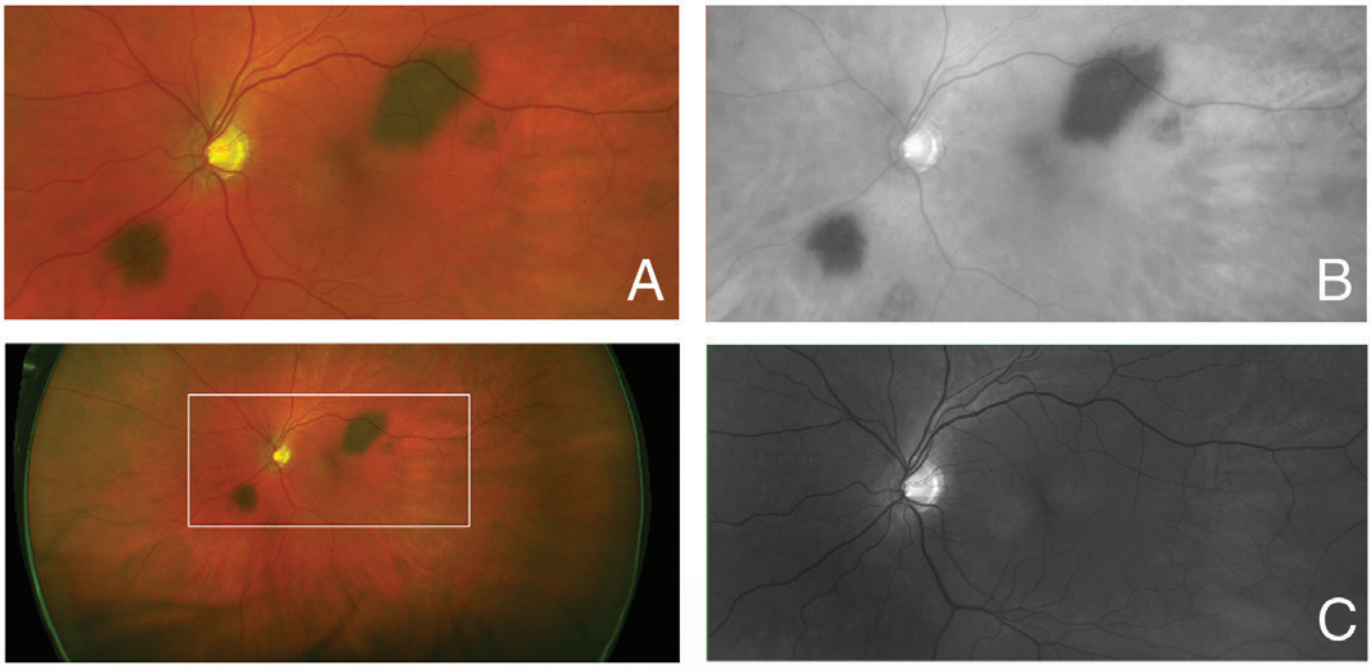


▲ Figure 1. Retinal photograph, 2011



▲ Figure 2. Retinal photograph, 2014



▲ Figure 3. Optomap ultra-wide field retinal image, 2015: (A) composite view (B) red channel view (C) green channel view

Choroidal naevii

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eight-fold greater risk for metastasis.[4] However, slow growth of 0.5 mm over many years or decades may simply reflect the natural progression of a benign choroidal naevus.[5]

Initial presentation

In March 2011, a 63-year-old male presented for a routine eye examination. Fundus photographs revealed the presence of two presumed choroidal naevii in his left eye (Figure 1). These were small with no distinguishing features and were monitored every six months. By January 2014, enlargement of the superotemporal lesion was evident (Figure 2).

The patient was referred for an ophthalmological opinion. Both lesions were flat on B-scan ultrasound. At this stage, it was considered that the risks for transformation were low and further monitoring was suggested.

The patient next presented in February 2015. On this occasion images were obtained with the Optomap wide-field imaging device (Figure 3A). This showed that the superotemporal lesion had further increased in size, now extending beyond the superior arcade vessel.

Separate channels

One feature of the Optomap is that it is possible to split the composite image into separate red and green laser channels. The red channel images the choroidal layer, which is where the lesions are seen (Figure 3B). The green channel images the retinal layer. Typically, in malignant lesions there is a 'bright' appearance in the retinal layer[6] but fortunately for this patient there is no extension of either lesion into the retinal layer (Figure 3C).

The patient has been referred back for further investigation and may require transpupillary thermotherapy treatment as a precaution. This uses infrared light to heat and eliminate the tumour. It is most effective for small tumours as it may not fully penetrate the deeper parts of thicker melanomas, where plaque radiotherapy or even enucleation are indicated because of the risk of metastasis. ▲

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4. Shields CL, Shields JA, Kiratli H, De Potter P, Cater JR. Risk factors for growth and metastasis of small choroidal melanocytic lesions. *Ophthalmology* 1995; 102: 9: 1351-1361.
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T2D GUIDELINES

role of fenofibrate:[1]

2014/15 RACGP/Diabetes Australia 'General practice management of type 2 diabetes'

Patients with Dyslipidaemia

It is reasonable to consider the introduction of fenofibrate in high-risk patients on statin therapy who have raised triglycerides (>2.3 mmol/L) and low HDL-c (<0.9mmol/L).[1]

Patients with Diabetic Retinopathy

The TGA has now approved the use of fenofibrate for the treatment of diabetic retinopathy. Its use in patients with T2D with evidence of retinopathy should now be considered.[1]

LIPIDIL does not replace appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy.[2]

LIPIDIL® 145mg
fenofibrate

Precaution[2]

There have been reports of severe myositis and myoglobinuria (rhabdomyolysis) when fenofibrate and HMG-CoA reductase inhibitors are used concurrently. Please review the full Product Information before prescribing LIPIDIL.

PBS Information: Restricted Benefit. For use in patients that meet the criteria set out in the General Statement for Lipid-Lowering Drugs. Not listed for the treatment of diabetic retinopathy.

Please review the full Product Information (PI) before prescribing.
Full PI available on request by calling 1800 225 311 or at: www.medicines.org.au

LIPIDIL® (fenofibrate): 145 mg tablets, 30's; 48 mg tablets, 60's. Indications: Adjunct to diet in the treatment of hypercholesterolaemia, types II, III, IV and V dyslipidaemia, dyslipidaemia associated with type 2 diabetes. Reduction in the progression of diabetic retinopathy in patients with type 2 diabetes. Does not replace appropriate control of blood pressure, blood glucose and blood lipids. **Dosage: Dyslipidaemia and Diabetic Retinopathy:** 145 mg tablet to be taken with or without food. Consider dose of 48 mg in patients with renal impairment (CrCl<60ml/min). **Contraindications:** Children; liver dysfunction; severe renal dysfunction; existing gallbladder disease; co-administration with another fibrate; hypersensitivity to fibrates or ketoprofen; chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia. **Precautions:** Attempt diet and lifestyle modifications before initiating therapy for dyslipidaemia; effect on CHD mortality/morbidity not established; renal impairment; may increase LFT; hepatic impairment, cholelithiasis; haematologic changes; paradoxical decreases in HDL-C; pregnancy and lactation; drugs exacerbating hypertriglyceridaemia (oestrogen, β-blocker, thiazides); fructose and/or galactose intolerance; lecithin or related product allergy. **Interactions:** Oral anti-coagulants; HMG-CoA reductase inhibitors (risk of muscle toxicity is increased if used concurrently); other fibrates; cyclosporin (monitor renal function); phenylbutazone; drugs metabolised by cytochrome P450 isoenzymes CYP2C19, CYP2A6, and CYP2C9. **Adverse Effects:** GI disorders; skin reactions (including rash, photosensitivity, severe cutaneous reactions); raised LFT; increase in serum creatinine; pancreatitis; gallstones; thromboembolism; muscle toxicity and rarely rhabdomyolysis. Updated 4th July 2014. **References:** 1. The Royal Australian College of General Practitioners and Diabetes Australia. General practice management of type 2 diabetes. 2014-15 ed. 2. Lipidil Approved Product Information. Lipidil® is a registered trademark of BGP Products Pty Ltd (trading as Mylan EPD), 299 Lane Cove Road, Macquarie Park NSW 2113. Free call: 1800 225 311. Date prepared: May 2015. AU-LIP-2014-14(1).

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20/200

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20/70

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20/30

20/25

20/20

ONE INJECTION EVERY TWO MONTHS*

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

PBS Information: Authority Required. Refer to PBS Schedule for full Authority Required information for wet AMD. EYLEA is not PBS listed for CRVO and DME.

Before prescribing please review full Product Information.

MINIMUM PRODUCT INFORMATION EYLEA® [aflibercept (rch)] INDICATIONS: EYLEA (aflibercept) is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (wet AMD); visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO); diabetic macular oedema (DME)*. **CONTRAINDICATIONS:** Known hypersensitivity to aflibercept or excipients; ocular or periocular infection; active severe intraocular inflammation. **PRECAUTIONS:** Endophthalmitis, increase in intraocular pressure; immunogenicity*; arterial thromboembolic events; bilateral treatment*; risk factors for retinal pigment epithelial tears*; treatment should be withheld in case of rhegmatogenous retinal detachment, stage 3 or 4 macular holes, retinal break, decrease in best-corrected visual acuity of ≥ 30 letters, subretinal haemorrhage or intraocular surgery*; treatment not recommended in patients with irreversible ischemic visual function loss*; population with limited data (diabetic macular oedema due to type 1 diabetes, diabetic patients with HbA1c > 12 %, proliferative diabetic retinopathy, active systemic infections, concurrent eye conditions, uncontrolled hypertension)*; see full PI for effects on fertility, pregnancy, lactation, effects on ability to drive or use machines. **ADVERSE EFFECTS:** Very common: conjunctival haemorrhage, visual acuity reduced*, eye pain. Common: retinal pigment epithelial tear, detachment of retinal pigment epithelium, retinal degeneration*, vitreous haemorrhage*, cataract, cataract nuclear, cataract subcapsular, cataract cortical*, corneal erosion, corneal abrasion, 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, punctate keratitis*, conjunctival hyperaemia, ocular hyperaemia. Others: see full PI. **DOSAGE AND ADMINISTRATION*:** Injection volume of 50 µL EYLEA (equivalent to 2 mg aflibercept). The interval between doses injected into the same eye should not be shorter than one month. Once optimal visual acuity is achieved and/or there are no signs of disease activity, treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes. If disease activity persists or recurs, the treatment interval may be shortened accordingly. Monitoring should be done at injection visits. There is limited information on the optimal dosing interval and monitoring interval especially for long-term (e.g. > 12 months) treatment. The monitoring and treatment schedule should be determined by the treating ophthalmologist based on the individual patient's response. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, EYLEA should be discontinued. *For wet AMD:* Treatment is initiated with one injection per month for three consecutive months, followed by one injection every two months. Long term, it is recommended to continue EYLEA every 2 months. Generally, once optimal visual acuity is achieved and/or there are no signs of disease activity, the treatment interval may be adjusted based on visual and/or anatomic outcomes. The dosing interval can be extended up to every 3 months. *For CRVO:* Treatment is initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes. *For DME:* Treatment is initiated with one injection per month for five consecutive months followed by one injection every two months. After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes. **DATE OF PREPARATION:** April 2015. Please review the full Product Information before prescribing. Approved PI available at www.ebs.tga.gov.au or upon request from Bayer Australia Ltd, ABN 22 000 138 714, 875 Pacific Highway, Pymble NSW 2073.

*Please note changes in Product Information.

Reference: 1. EYLEA Product Information. †wAMD = Wet age-related macular degeneration

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