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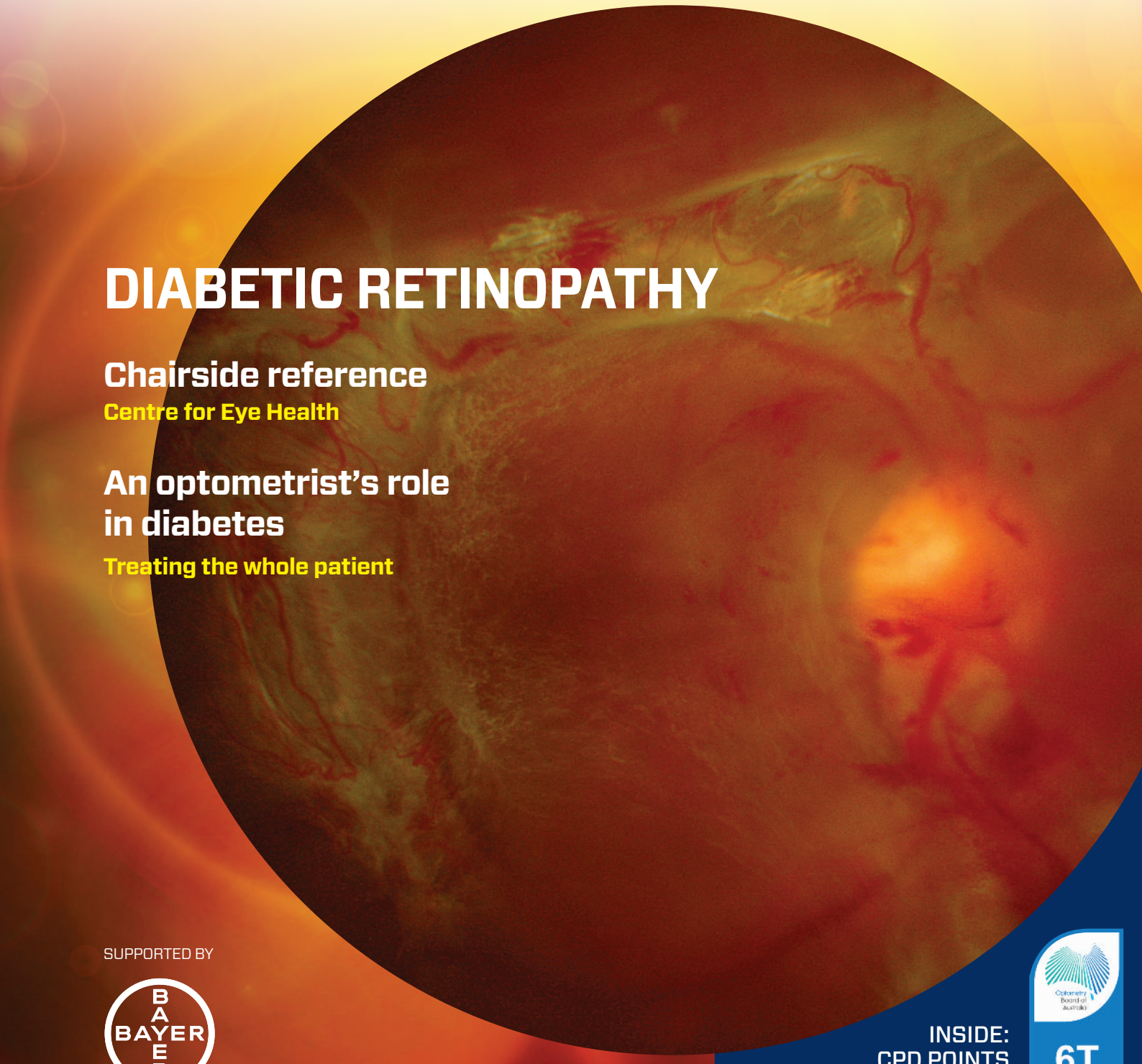

DIABETIC RETINOPATHY

Chairside reference
Centre for Eye Health

An optometrist's role in diabetes
Treating the whole patient

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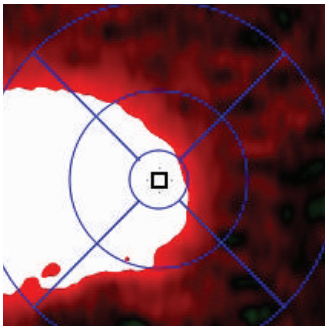

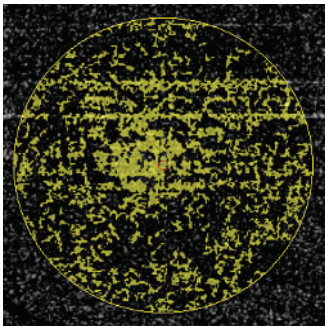

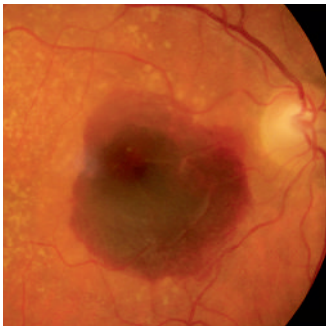

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Prolific retinopathy in a diabetic patient: fundus image showing early changes, moderate changes and severe changes
Image: MIKE JACKSON

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Editorial

If you're a kid who can use a mobile device, chances are you can take a good retinal photo. It's not that hard to push a button but it takes intense training, ophthalmic expertise and life-long learning to interpret that unique patient image.

The immediacy of the result requires quick analysis to advise and counsel the patient appropriately.

An up-to-date ophthalmic and medical history, a thorough eye examination and posterior eye imaging are the basis of the optometrist's role in diabetic retinopathy screening.

The diabetic eye is more than the retina. Only the totality of the examination, rather than just a mechanical 'retinal screening', allows a practitioner to counsel diabetic patients optimally. Reporting to all the patient's other health-care practitioners and physicians is critical in a multidisciplinary approach to diabetes.

This issue of *Pharma* focuses on diabetes. The vast body of ophthalmic literature covers this area comprehensively, so the aim of *Pharma* is to highlight key areas that are particularly clinically relevant to help practitioners keep up to date.

The authors who have contributed to this issue deserve credit for their expert contributions, with specific thanks to the team at the Centre for Eye Health for producing our centrefold chart, a great, evidence-based, in-office guide to diabetic retinopathy.

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Diabetic macular oedema and anti-VEGF therapy

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DIABETES is a growing health epidemic and the leading cause of acquired blindness in the working population in developed countries.[1] The most common cause of vision loss in these patients is diabetic macular oedema (DME).[2] Traditionally, macular focal and grid laser photocoagulation were the only treatments available for DME, with the aim of preventing further vision loss. With better understanding of the pathology and role of vascular endothelial growth factor (VEGF), intravitreal anti-VEGF injections have emerged as superior to laser and in many cases result in visual gain. In this case report our patient's management for DME echoes the developments over the past 10 years.

CASE REPORT

A 55-year-old salesman presented for diabetic review with a visual acuity (VA) of R 6/7.5 L 6/7.5 in May 2007. He had been a non-insulin dependent type 2 diabetic patient for more than 12 years with an HbA1c of eight per cent. He had a diagnosis of proliferative diabetic retinopathy (PDR) and DME in both eyes.

He initially underwent a course of macular laser for DME in both eyes, receiving three sessions on the left and two on the right over the next year. Alongside macular laser, he also underwent pan retinal photocoagulation (PRP) for PDR. The PRP was given at lower doses over an extended period to reduce the well-recognised detrimental effect of PRP on DME. Despite the macular laser treatment, after one year his vision had worsened, VA R 6/24 L 6/15, with OCT consistent with gross DME.

Over the next two years (May 2008 to April 2010) the patient received two intravitreal triamcinolone in each eye combined with two additional sessions of laser in each eye. As a result of intravitreal steroid, the patient developed elevated intraocular pressure (IOP) and posterior subcapsular white cataracts. The pressure was initially controlled with a combination of brimonidine, timolol and latanoprost. After the triamcinolone was ceased, the IOP normalised and the patient was successfully weaned off these drops.

Due to subcapsular cataracts in January 2010, the patient experienced a deterioration in vision to R 0.5/60 L 6/48. Cataract surgery was complicated by the 'Argentinian flag sign', a common complication with intumescent cataracts. It essentially describes a spontaneous tear across the equator of the capsule which is stained with trypan blue, revealing a white stripe of cataract.

Fortunately, the tear was not too extensive and we were able to insert the new lens into the capsule. At this point the patient was finding work in sales extremely difficult with binocular reading vision of N20 and was referred to the low vision clinic for assessment and assistance. Over this period of two years, he had experienced a slight deterioration in vision; R 6/30 L 6/19 and OCT still showed significant DME (Figure 1).

In April 2010 he was started on a course of intravitreal anti-VEGF, initially bevacizumab (Figure 2) then ranibizumab and finally aflibercept in August 2015. To date he has received 77 anti-VEGF injections in both eyes. Over this time, he experienced an improvement in vision and OCT revealed gradual resolution of DME (Figures 3 and 4). His vision is currently R 6/24 L 6/15.

Discussion

Since the 1980s, grid/focal macular laser has been the mainstay of treatment for DME. This was established by the Early Treatment Diabetic Retinopathy Study, which showed laser reduced the risk of

Continued page 4

Cited studies

RISE/RIDE. A study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus

RESOLVE. Safety and efficacy of ranibizumab in diabetic macular edema with center involvement

READ-2. The READ-2 Study: Ranibizumab for edema of the macula in diabetes

VISTA. Study of intravitreal aflibercept injection (IAI; EYLEA; BAY86-5321) in patients with diabetic macular edema

VIVID. Intravitreal aflibercept injection in vision impairment due to DME

BOLT. Diabetic macular oedema: a prospective randomised trial of management with intravitreal bevacizumab (Avastin) versus conventional laser therapy

RETAIN. Efficacy and safety of ranibizumab in two 'treat and extend' treatment algorithms versus ranibizumab as needed in patients with macular edema and visual impairment secondary to diabetes mellitus

DRCR.net. Diabetic Retinopathy Clinical Research Network

DME and anti-VEGF

From page 3

moderate vision loss by 50 per cent at three years.[3] The focus was on prevention of vision loss, and laser was associated with complications such as reduced colour vision and scotoma.

In the early 2000s, intravitreal triamcinolone emerged as an alternative treatment for refractory or persistent DME. In our case report, laser failed to prevent vision loss over the first year of treatment, therefore the patient was commenced on intravitreal triamcinolone. This combination of treatment also did not prevent his vision loss and he developed complications of cataract and raised IOP from the triamcinolone.

In 2008, as part of protocol B, DRCR.net found that after two years focal/grid laser resulted in better visual acuity and fewer side-effects than intravitreal triamcinolone for DME. Since then, its popularity has diminished.[4]

At this point our understanding of the pathophysiology of DME and role of VEGF led to an explosion of research into intravitreal anti-VEGF. In diabetes, chronic hyperglycaemia results in breakdown of the retinal blood barrier leading to hypoxia, release of inflammatory mediators and expression of VEGF. VEGF leads to increased vascular permeability and neovascularisation. The level of VEGF in the vitreous has been shown to correlate directly with the severity of DME.[5]

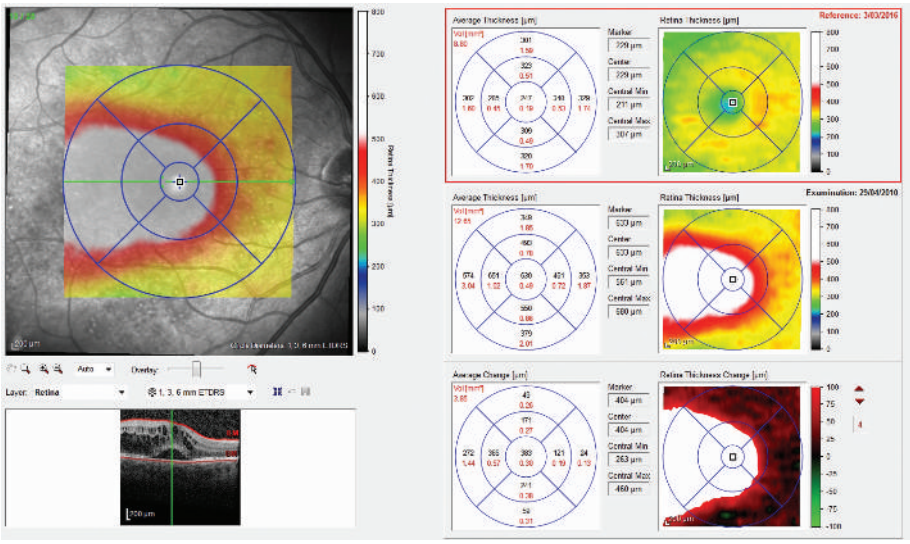
Pegatanib was the first anti-VEGF to be investigated, leading to an improvement in visual acuity compared to sham injection; however, soon more potent anti-VEGFs took over.[6]

In 2010, the READ-2 study showed that two-monthly intravitreal ranibizumab injections resulted in better visual acuity than three-monthly laser or a combination of laser and ranibizumab.[7] After three years, monthly follow-up for ranibizumab was recommended to avoid undertreatment.[8]

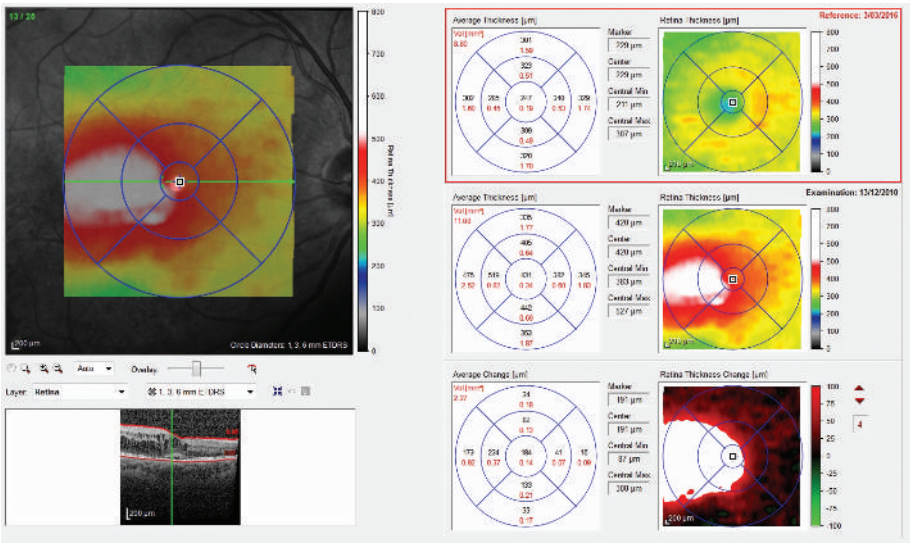
RISE and RIDE, parallel ramdomised controlled trials, found intravitreal ranibizumab resulted in better visual acuity than sham injections maintained at three years.[9,10] Interestingly, patients who subsequently crossed over from the sham injections to the treatment arm of the study achieved a limited vision gain compared to patients originally receiving ranibizumab. RESOLVE again supported the superiority of ranibizumab over sham injections.

The role for laser alongside ranibizumab has also been investigated. READ-2 initially showed that using laser to complement ranibizumab reduced the number of intravitreal injections required with similar visual outcome. However, RESTORE found ranibizumab monotherapy rather than combination with laser led to better visual acuity outcomes.[11] DRCR.net protocol-I found prompt laser treatment at the initiation of intravitreal ranibizumab no better than deferring laser treatment for more than 24 weeks. However, if laser is deferred, eyes may require more intravitreal injections to receive the same results.[12]

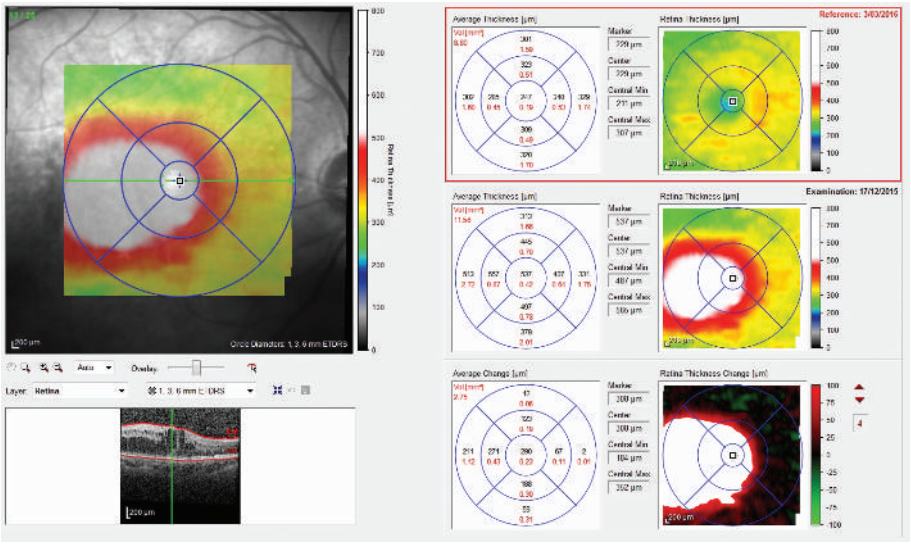
Aflibercept, another anti-VEGF, has been shown to give superior results compared to laser with sham injections in the Da Vinci study.[13]



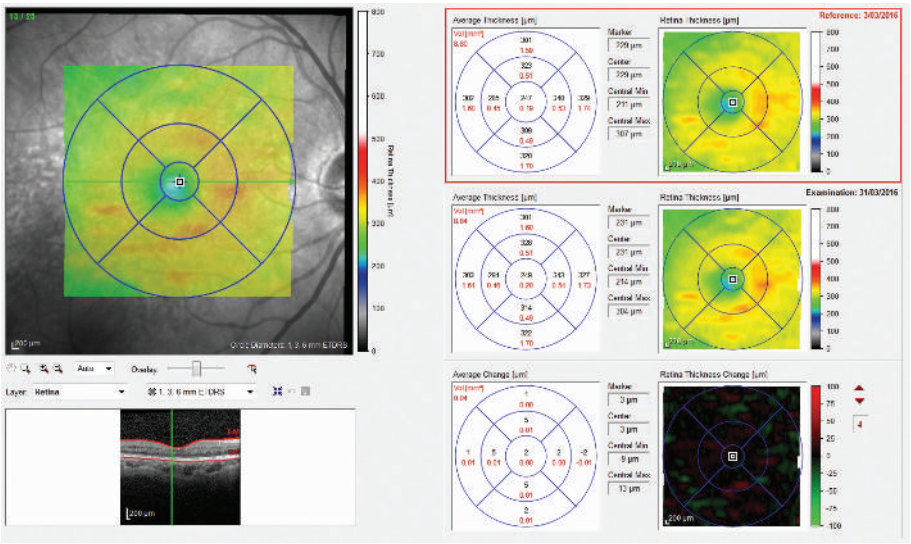
▲ Figure 1. OCT right eye April 2010 before anti-VEGF treatment



▲ Figure 2. OCT right eye December 2010 after eight months of intravitreal bevacizumab



▲ Figure 3. OCT right eye December 2015 before intravitreal aflibercept



▲ Figure 4. OCT right eye March 2016 after course of intravitreal aflibercept

VISTA/VIVID also revealed better visual gains compared to laser up to 100 weeks, with less than 10 per cent of patients receiving aflibercept alone requiring rescue laser treatment.[14] Bevacizumab has also proved itself superior to laser in the BOLT trial.[15]

DRCR.net attempted to compare the three anti-VEGF treatments currently available for DME treatment with protocol T. It found no significant difference between the agents unless visual acuity was less than 6/15, then aflibercept gave a better visual outcome.[16]

Anti-VEGF has controlled our patients previously refractory DME with great success, providing visual gain and stability over the past six years where laser and intravitreal triamcinolone had failed. However, it must be remembered that intravitreal injections involve significant risks including endophthalmitis, raised IOP and damage to surrounding structures such as retinal detachment.

Management of DME with anti-VEGF creates a significant treatment burden with patients requiring potentially lifelong monthly follow-up. Questions remain about the frequency of follow-up and injections. The RETAIN study recently showed the viability of a treat-and-extend management rather than a monthly follow-up regime.[17]

This case follows a patient through the rapid development in the management of DME over the past 10 years. For our patient anti-VEGF treatment gave him visual improvement and stability, where laser and intravitreal triamcinolone previously failed, and allowed him to continue in his employment. ▲

1. Prokofyeva E, Zrenner E. Epidemiology of major eye diseases leading to blindness in Europe: a literature review. *Ophthalmic Res* 2012; [cited 2016 Apr 24]; 47: 4: 171–188. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22123077.
2. Klein R, Klein BE, Moss SE et al. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology* 1984; [cited 2016 Apr 24]; 91: 12: 1464–1474. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6521986.
3. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* (Chicago, Ill 1960) 1985; [cited 2016 Apr 24]; 103: 12: 1796–1806. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2866759.
4. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008; [cited 2016 Apr 24]; 115: 9: 1447–1449. e1–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18662829.
5. Funatsu H, Yamashita H, Nakamura S et al. Vitreous levels of pigment epithelium-derived factor and vascular endothelial growth factor are related to diabetic macular edema. *Ophthalmology* 2006; [cited 2016 Apr 24]; 113: 2: 294–301. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16406543.
6. Sultan MB, Zhou D, Loftus J et al. A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. *Ophthalmology* 2011; [cited 2016 Apr 24]; 118: 6: 1107–1118. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21529957.
7. Nguyen QD, Shah SM, Khwaja AA et al. Two-year outcomes of the ranibizumab for edema of the macula in diabetes (READ-2) study. *Ophthalmology* 2010; [cited 2016 Apr 24]; 117: 11: 2146–2151. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20855114.
8. Do DV, Nguyen QD, Khwaja AA et al. Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. *JAMA Ophthalmol* 2013; [cited 2016 Apr 24]; 131: 2: 139–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23544200.
9. Nguyen QD, Brown DM, Marcus DM et al. Ranibizumab for diabetic macular

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edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012; [cited 2016 Apr 24]; 119: 4: 789–801. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22330964.
10. Brown DM, Nguyen QD, Marcus DM et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 2013; [cited 2016 Apr 24]; 120: 10: 2013–2022. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23706949.
11. Schmidt-Erfurth U, Lang GE, Holz FG et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology* 2014; [cited 2016 Apr 24]; 121: 5: 1045–1053. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24491642.
12. Diabetic Retinopathy Clinical Research Network, Elman MJ, Qin H et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology* 2012; [cited 2016 Apr 24]; 119: 11: 2312–2318. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22999634.
13. Do DV, Nguyen QD, Boyer D et al. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology* 2012; [cited 2016 Apr 24]; 119: 8: 1658–1665. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22537617.
14. Brown DM, Schmidt-Erfurth U, Do DV et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology* 2015; [cited 2016 Apr 24]; 122: 10: 2044–2052. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26198808
15. Michaelides M, Kaines A, Hamilton RD et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology* 2010; [cited 2016 Apr 24]; 117: 6: 1078–1086.e2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20416952.
16. Diabetic Retinopathy Clinical Research Network TDRCR, Wells JA, Glassman AR et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015; [cited 2016 Apr 24]; 372: 13: 1193–1203. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25692915.
17. Prünte C, Fajnkuchen F, Mahmood S et al. Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema: the RETAIN study. *Br J Ophthalmol* 2015; [cited 2016 Apr 24]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/26453639.

An optometrist's role in

Look beyond

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DIABETIC retinopathy is a leading cause of vision loss in working-age adults in the developed world. According to the Melbourne Vision Project, approximately 29 per cent of Australians with diabetes have some degree of diabetic retinopathy and 4.2 per cent have proliferative diabetic retinopathy.

Another important fact is the sheer magnitude of the number of people with diabetes in Australia and the world. Put these two things together and we have a disease that is becoming more relevant. Optometrists are often on the front line of diagnosing both diabetes and its ocular complications. We need to be looking for not just clinically-significant macular oedema (CSME) but also other signs of diabetic eye diseases that are a window or predictor to ocular and systemic health.

Treatments for diabetic macular oedema, the most common cause of vision loss in diabetes,[1] have advanced dramatically in the past decade. Even with studies showing us which anti-VEGF injection is best, if there really is one that is best,[1] early identification and referral for treatment remain the most important factors in ultimate success and visual outcome.

Early diagnosis is not confined to early signs of CSME. Detection of early peripheral lesions, which are often the first sign, is significant in determining overall risk of retinopathy progression or progression to proliferative diabetic retinopathy (PDR), even if the peripheral lesions are the primary pathology seen before macular changes.[2] These are often seen with a thorough dilated posterior eye examination or with wide-field imaging as a screening procedure.

Although intravitreal injections are the standard of care for CSME, there are treatments for diabetic retinopathy that need to be considered by optometrists and which may prevent progression or retinopathy and less need for rescue laser. For instance, treatment with fenofibrate has been shown to be beneficial in two separate studies, and commonly prescribed in Australia.[3,4]

It is also imperative to consider the patient beyond their eyes. An important question to ask patients about is their haemoglobin A1c. It is well documented that better control as measured by A1c is more likely to protect against unwanted ocular and systemic side-effects of diabetes.[5] Making sure that patients understand this correlation can help prevent poor outcomes.

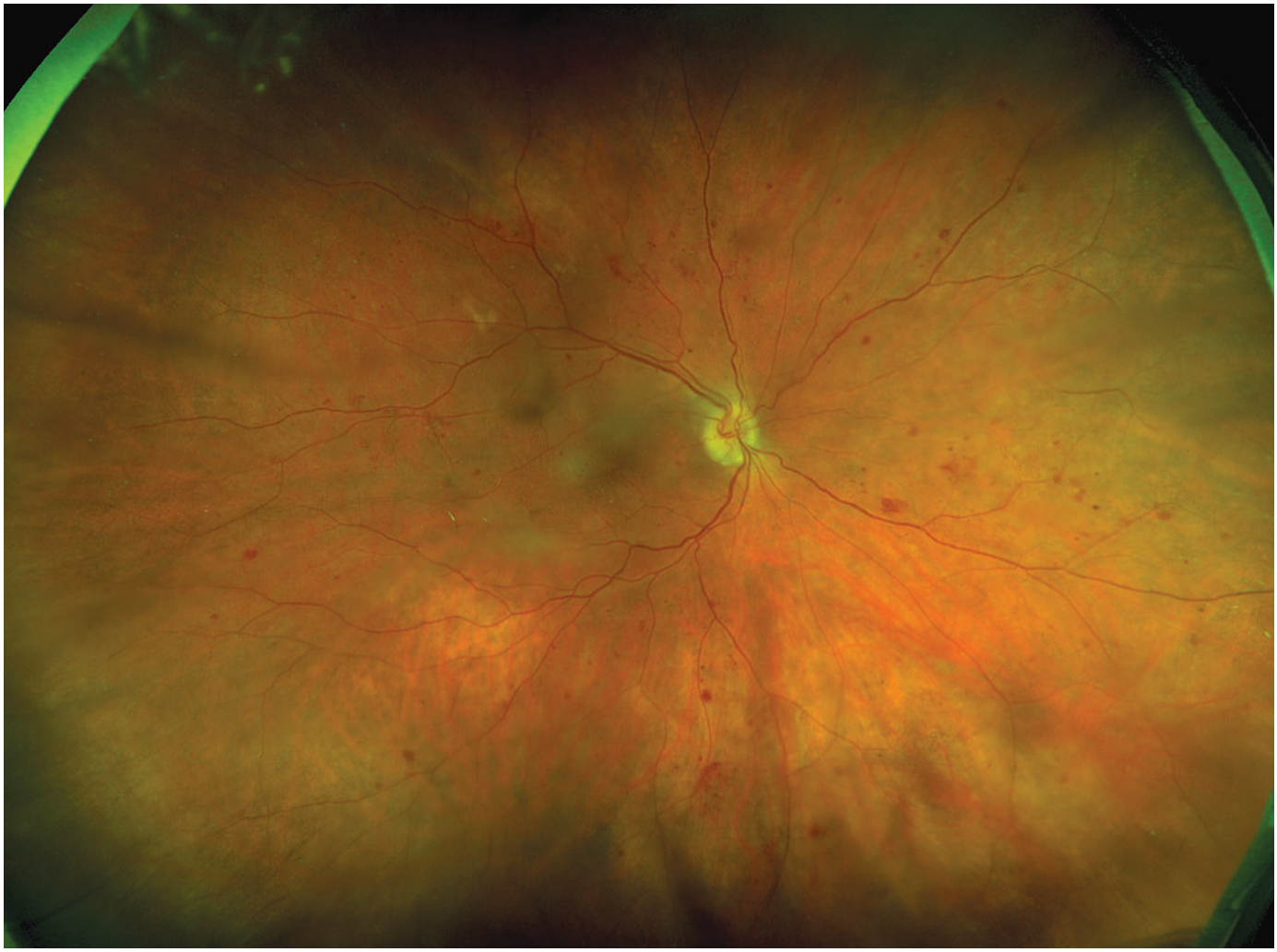
Besides just asking patients about their blood sugar and medications, lifestyle changes that can be made to improve glycaemic control can also be discussed. Factors such as diet, exercise, smoking status and overall general health have a big impact on our patients. We can take just a few minutes to help educate our patients and help secure our place in their health-care team.

People with diabetes need not only their general practitioner or endocrinologist, but also a dietitian and an eye-care professional, which is where we fit in.

We may be the person that takes care of their eyes and eye health but we should address systemic concerns as well. For people with diabetes, like patients with AMD, loss of vision is of paramount concern. The first step in preventing vision loss is simply to spend time. That time could be in the form of education or just a careful refraction. This gives us an opportunity to use the

diabetes

detection and refraction to treat the whole patient



▲ Figure 1. Optos optomap ultra-widefield image showing proliferative diabetic retinopathy (PDR)

time we have with each person to make a positive impact.

Our positive impact comes through both better eye care that we provide and better overall health care, which we may be able to help our patients to seek. This integrated approach benefits everyone involved. ▲

1. Wells JA, Glassman AR, Ayala AR et al. Aflibercept, bevacizumab or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology* in press. Published online February 27, 2016.
2. Silva PS, Cavallerano JD, Haddad NM et al. Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 years. *Ophthalmology* 2015; 122: 5: 949-956.
3. Keech AC, P Mitchell P, Summanen PA et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. 2007; 370: 9600: 1687–1697.
4. Chew EY, Davis MD, Danis RP et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the action to control cardiovascular risk in diabetes (ACCORD) eye study. *Ophthalmology* 2014; 121: 12: 2443-2451.
5. White NH, Sun W, Cleary PA et al. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. *Arch Ophthalmol* 2008; 126: 12: 1707-1715.

Exudative macular degeneration and OCT angiography

Dr Alan Burrow

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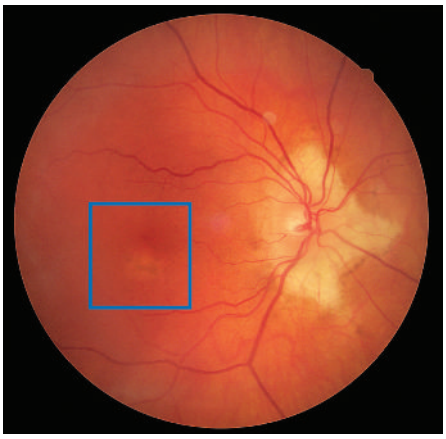
AGE-RELATED macular degeneration is the major cause of severe visual loss in older adults[1] with approximately 10 to 15 per cent associated with a neo-vascular form of the disease resulting in severe visual loss.[2] Traditionally, this condition has been further classified according to histopathology with type 1 presenting with a choroidal neovascular membrane (CNV) between Bruch's membrane and the retinal pigment epithelium (RPE) and type 2 with the CNV in the retina above the RPE.[3]

This classification has been largely dependent on angiographic patterns of fluorescence using the invasive techniques of systemic injection of either fluorescein or less frequently, indocyanine green and tracking the flow photographically through the retinal vasculature.[3]

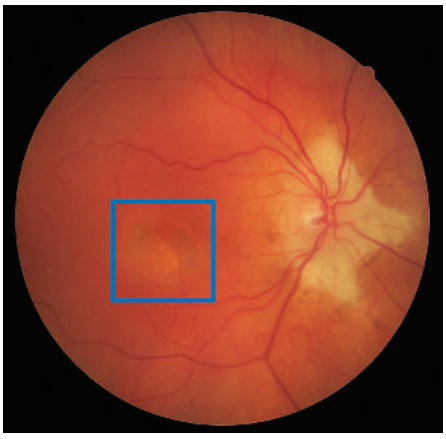
The advent of ocular coherence tomography (OCT) provides a valuable, non-invasive method of detecting structural changes commonly associated with CNV but without the ability to observe the vascular changes.[3]

The recent release of commercial OCT angiography enables observation of vascular changes non-invasively *in vivo* at different levels within the retina without the limitations associated with the dynamics of the dye.[4,5]

The Optovue XR-Avanti OCT Angiovue software utilises a high-speed (70,000 axial scans per second) spectral domain (SD) OCT platform with amplitude decorrelation to assess blood flow through the superficial and deep capillary retinal plexuses, outer retina and choroid capillary layer.[4,6]

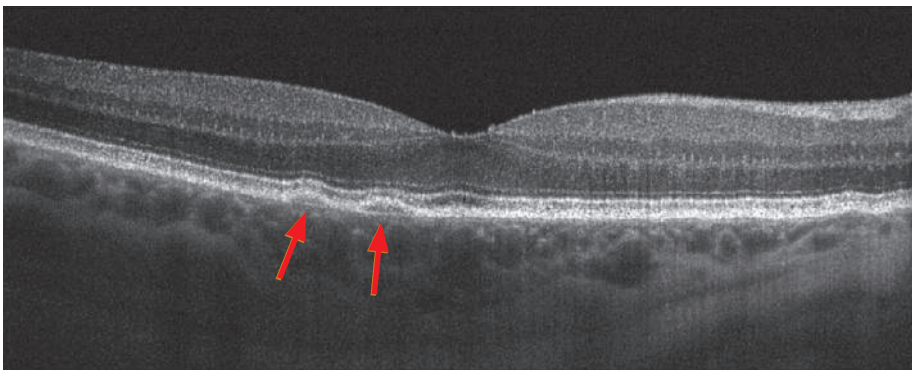


▲ **Figure 1**. Long-standing pigmentary change in the para foveal area (Dec 2015)

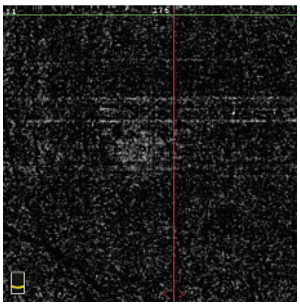


▲ **Figure 2**. Increased area of depigmentation and macular oedema (March 2016)

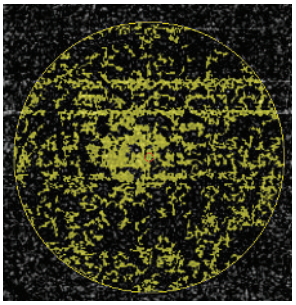
Numerous authors have highlighted the benefits of OCT angiography when compared with fluorescein and indocyanine green techniques.[6,7,8,9,10,11] In exudative macular degeneration, changes in the normally avascular outer retina and vascular choroid capillary layer are of primary interest.



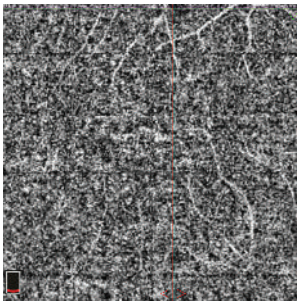
▲ **Figure 3**. 2015: line scan shows hyper reflective drusen (Dec 2015)



▲ **Figure 4A**. Normal avascular of the outer retinal layer



▲ **Figure 4B**. Normal outer retinal layer highlighting the angio flow

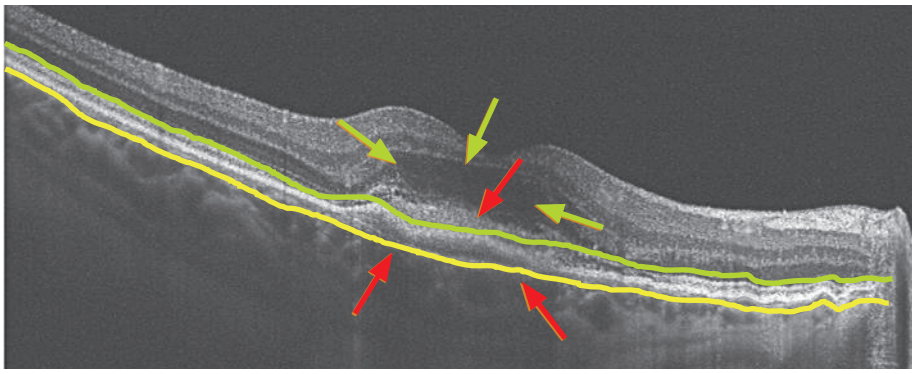


▲ **Figure 4C**. Normal choriocapillaris.

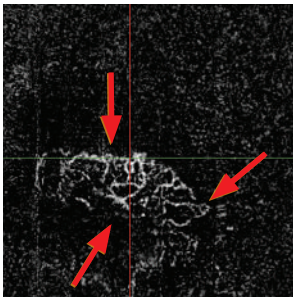
CASE REPORT

A 75-year-old symptom-free Caucasian male presented in December 2015 for a routine optometric examination. Corrected acuities were right and left 6/5 with normal intraocular pressures of right and left 15 mmHg. There was a small area of depigmentation infero-temporally to the fovea as well as a large peripapillary scar, both of which had been present since at least 2008 (Figure 1). The left fundus was unremarkable. As the area of depigmentation had undergone a minor change, a structural OCT scan was performed which demonstrated drusenoid changes but no cystic formation (Figure 3).

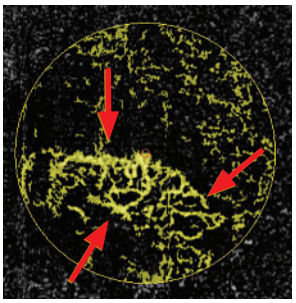
Three months later, the patient presented with symptoms of a central scotoma associated with deterioration in vision over a four-day period which then appeared to stabilise. The right acuity had dropped to <6/90 while the left eye was unchanged in acuity and appearance.



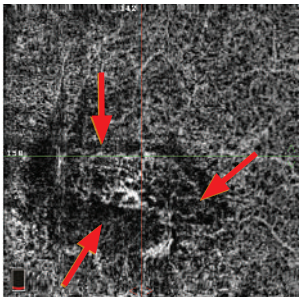
▲ **Figure 5**. Structural OCT of the macular area with a fibrovascular membrane (red arrows) and subretinal fluid (green arrows) with the approximate position of the outer retina between the green and yellow lines. The choriocapillaris is below the yellow line.



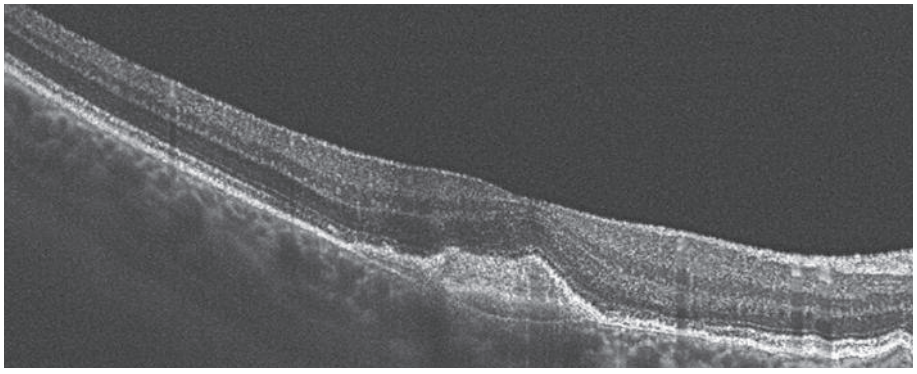
▲ **Figure 5A**. The neovascular membrane (red arrows) in the outer retinal layer



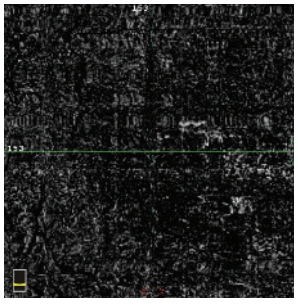
▲ **Figure 5B**. The neovascular membrane in the outer retina highlighted with the Angioflow



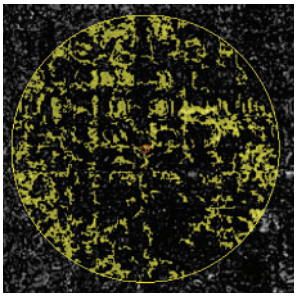
▲ **Figure 5C**. The neovascular membrane in the choriocapillaris (red arrows)



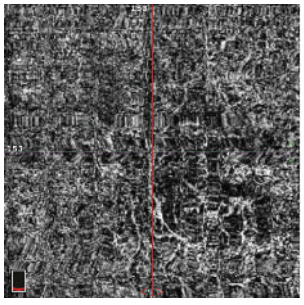
▲ **Figure 6**. Structural OCT illustrating the fibrovascular scar with a significant decrease in subretinal fluid following anti-VEGF injection



▲ **Figures 6A**. Significant decrease in the neovascular membrane in the outer retina after anti-VEGF



▲ **Figure 6B**. Some normalisation of the outer retinal angio flow



▲ **Figure 6C**. Partial normalisation of the vasculature of the choriocapillaris after anti-VEGF, some disorganisation still evident

The change in the macular area is evident in Figure 2. The structural OCT of the right macula demonstrates a thick opaque lesion with marked disruption of the outer retinal layers including the photoreceptors and associated sub-retinal fluid (Figure 5).

OCT angiography was performed with the newly-acquired, upgraded equipment. The appearance of the avascular outer retinal area choriocapillaris and angioflow of a normal subject is shown in Figures 4A, 4B and 4C for comparison. The neovascular formation of this patient is clearly visible in Figures 5A, 5B and 5C.

The patient was referred to an ophthalmologist who performed a fluorescein angiogram but commented that the results were less revealing than that of the Angio OCT. The right eye was treated with an anti-VEGF injection. The OCT findings one month after injection are illustrated in Figures 6A, 6B and 6C, which show a significant decrease in sub-retinal fluid as well as the neovascular membrane in the outer retina and choriocapillaris.

Continued page 10

OCT angiography

From page 9

Discussion

These results clearly demonstrate the potential benefit of OCT angiography in optometric and ophthalmological practice. If OCT angiography had been available at the previous examination, it may have been possible to detect the early stages of neovascularisation.

The impact of anti-VEGF treatment is also clearly demonstrated, which has been reported previously.[4,9] However, as with any new modality which reveals previously unseen changes, it is important to establish relevance to prevent inaccurate diagnosis and unnecessary treatment. This emphasises the need for continuing education of clinicians in a time of unprecedented technological advancement if these benefits are to be delivered in practice.

1. Friedman DS, O'Colmain BJ, Munoz B etal. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol* 2004, 122: 4: 564-572.
2. Ferris FL 3rd, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984; 102: 11: 1640-1642.
3. Huang D et al. Imaging the eye from front to back with RTVue Fourier-domain optical coherence tomography. Thorofare, NJ: Slack, ©2010; 2010.
4. Lumbroso Bruno, Huang David, Jia Yali et al. Clinical guide to angio-OCT: non invasive, dyeless OCT angiography, 2015 ed. New Delhi: Jaypee, the Health Science Publishers; 2015.
5. Coscas Gadriel LM, Coscas Florence. Atlas OCT: Angiography in AMD: Comparison with Multimodal Imaging. In: Societe Francaise De Retine; 2015.
6. Lumbroso B, Huang D, Jia Y et al. Clinical OCT angiography atlas: New Delhi: Jaypee, the Health Science Publishers; 2015.
7. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). *Int J Retina Vitreous* 2015; 1: 5.
8. Marduel R. Angio OCT, dye less angiography, a new approach of age related macular degeneration (ARMD). *Adv Ophthalmol Vis System* 2015; 2: 2: 1-4.
9. Kuehlewein L, Sadda SR, Sarraf D. OCT angiography and sequential quantitative analysis of type 2 neovascularization after ranibizumab therapy. *Eye* (Lond) 2015; 29: 7: 932-935.
10. Lommatzsch A, Farecki ML, Book B et al. [OCT angiography for exudative age-related macular degeneration : Initial experiences]. *Der Ophthalmologe: Zeitschrift der Deutschen Ophthalmologischen Gesellschaft* 2016; 113: 1: 23-29.
11. Jia Y, Bailey ST, Wilson DJ et al. Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. *Ophthalmology* 2014; 121: 7: 1435-1444.

Diabetic eye examination is more than a retinal photo

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BScOptom GradCertOcTher

THE MAINSTAY of the ophthalmic assessment of patients with type 1 or type 2 diabetes is a comprehensive eye examination. Routine diabetic eye reviews are suggested every 12 months or more frequently if there is any evidence of diabetic retinopathy, macular oedema or high risk of diabetic changes.

A thorough diabetic eye examination involves the following

- Comprehensive history including diabetic medication, RBG levels and HbA1c, if known.
- Visual acuity and refraction if change in the acuity or if new spectacles are required.
- Assessment of the anterior eye including anterior chamber angles to determine suitability for pupil dilation.
- Measurement of intraocular pressure.
- Dilation with 0.5% tropicamide and 2.5% phenylephrine if the dilation is poor or has been poor in the past.
- Evaluation of posterior pole using non-contact fundus lens (90 D, superfield, 78 D or similar) with particular emphasis on macular and disc with regard to macular oedema and new vessels on the disc.
- Assessment of peripheral retina with BIO (20 D or 2.2 or similar) to monitor any diabetic retinal changes in the entire ocular fundus.
- Macular OCT to help detect macular oedema and photo of retinal posterior pole.
- Appropriate review based on findings and the current NHMRC guidelines for diabetic retinopathy which can be viewed at: www.nhmrc.gov.au > Guidelines and Publications > Search. The grading system for diabetic retinopathy is listed in Table 1 with the review recommendations in Table 2.
- Advice to the patient about blood glucose control and the importance with regard to long-term diabetic changes.
- Schedule recall to be sent to patient at the appropriate interval.
- Written report to GP and endocrinologist.

Retinopathy stage	Definition	Rate of progression (%)			
		to PDR		to high-risk stage	
		1 yr	3 yrs	1 yr	5 yrs
Minimal NPDR (level 20)	Ma only	not documented			
Mild NPDR (level 35)	Ma and one or more of: retinal haem, HEx, CWS, but not meeting Moderate NPDR definition	5	14	1	15
Moderate NPDR (levels 43, 47)	H/Ma ≥ std photo 2A in at least one quadrant and one or more of: CWS, VB, IRMA, but not meeting Severe NPDR definition	12-26	30-48	8-18	25-39
Severe NPDR preproliferative (level 50+)	Any of : H/Ma > std photo 2A in all four quadrants, IRMA > std photo 8A in one or more quadrants, VB in two or more quadrants	52	71	15	56
PDR (level 60+)	Any of: NVE or NVD < std photo 10A, vitreous/preretinal haem and NVE < ½ disc area (DA) without NVD			46	75
High-risk PDR (level 70+)	Any of: NVD > ¼ to ⅓ disc area, or with vitreous/ preretinal haem, or NVE > ½ DA with vitreous/preretinal haem	Severe visual loss (VA ≤ 5/200) develops in 25-40% within 2 years			
Advanced PDR	High-risk PDR with tractional detachment involving macula or vitreous haem obscuring ability to grade NVD and NVE				
Macular oedema	Retinal thickening within 2 disc diameters of macular centre	Can occur at any stage of DR			
Clinically significant macular oedema (CSME)	Retinal thickening within 500 µm of macular centre or hard exudates within 500 µm of macular centre with adjacent thickening	Can occur at any stage of DR			

▲ Table 1. Classification of diabetic retinopathy into retinopathy stages (Wisconsin level) and predictive value of retinal lesions (adapted from Focal Points)

Retinopathy stage	CSME¶	Focal/Grid laser	Panretinal laser	Follow-up (months)
Normal	No	No	No	24
Minimal NPDR	No	No	No	12
Mild NPDR	No	No	No	12
	Yes	Yes *†	No	2-4
Moderate NPDR	No	No	No	6-12
	Yes	Yes *†	No	2-4
Severe NPDR	No	No	Sometimes§	2-4
	Yes	Yesϕ	Sometimes§	2-4
Proliferative DR	No	No	Usually§	2-4
	Yes	Yesϕ	Usually§	2-4
High risk proliferative DR‡	No	No	Yes	2-4
	Yes	Yesϕ	Yes	2-4

* Deferral of photocoagulation for a brief period of medical treatment may be considered in cases of hypertension or fluid retention associated with heart failure, renal failure, pregnancy or other causes that may aggravate DME.

† Deferral of CSME treatment is an option when the centre of the macula is not involved, visual acuity is excellent, close follow-up is possible, and the patient understands the risks.

§ Treatment should be considered especially in patients with T2DM, poor follow-up compliance, impending cataract extraction, renal disease, pregnancy, and severe disease in the fellow eye.

ϕ To minimise PRP-induced exacerbation of macular oedema, focal photocoagulation is suggested prior to PRP.

¶ CSME (clinically significant macular oedema) is defined by the ETDRS as variously:
- Thickening of the retina at or within 500 µm of the centre of the macula, or
- Hard exudates at or within 500 µm of the centre of the macula associated with adjacent retinal thickening, or
- A zone or zones of retinal thickening one disc area or larger, any part of which is within one disc diameter of the centre of the macula.

‡ High-risk features of PDR include variously:
- New vessels within one disc diameter of the optic nerve head that are larger than one-third disc area, or
- Vitreous or preretinal haemorrhage associated with less extensive neovascularisation on or within one disc diameter of the optic disc, or
- Neovascularisation elsewhere in the retina greater than one disc diameter from the optic disc margin at least one-half disc area in size.

▲ Table 2. Summary of diabetic retinopathy management recommendations (adapted from the AAO, ICO, ETDRS and NHMRC guidelines)

An endocrinologist's perspective

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DIABETES is a complex and chronic condition, contributing to significant physical and psychological morbidity. The most recent estimates of the burden of diabetes in Australia are from the Australian Health Survey, which was undertaken by the Australian Bureau of Statistics from 2011 to 2012, and the prevalence of diabetes was estimated to be approximately one million people.

It has been predicted that if the prevalence continues to rise at the current rates, by 2025 up to three million Australians will have diabetes. The majority of this increase in prevalence of diabetes is due to type 2 diabetes in adults, driven predominantly by the increasing problem of obesity and the ageing population. However, an increasing incidence of type 2 diabetes in children and teenagers, and increasing incidence of type 1 diabetes in children have also been noted.

There is also an increasing recognition that the spectrum of diabetes-related complications extends beyond the classic acute metabolic and chronic vascular and neuropathic complications. In people with type 2 diabetes this includes various cancers, dementia, fractures, liver disease, heart failure, hearing loss, periodontal disease and depression. For those with type 1 diabetes there are increased rates of autoimmune endocrinopathy, in particular thyroid disease and coeliac disease, as well as other autoimmune conditions.

Multidisciplinary

This all contributes significantly to the physical, emotional and financial burden of diabetes, and notably increases the complexity of care and need for multidisciplinary health-care involvement. The current paradigm of diabetes care is centred on the prevention, detection and treatment of complications associated with diabetes. This ideally requires intensive involvement of patients themselves, as well as a wide variety of health-care professionals, and therefore is associated with high direct and indirect health-care costs.

With the predicted increase in diabetes prevalence and therefore burden of diabetes complications, there is an urgent imperative to shift the focus of attention and efforts to the prevention of type 2 diabetes, as well as more aggressive management strategies earlier in the natural history of type 2 diabetes. Both strategies are supported by evidence from clinical trials.

There are immediate opportunities for a significant impact in the prevention of type 2 diabetes by targeting the major risk factors of obesity and prediabetes. The benefit of lifestyle intervention with associated weight loss has been shown in a number of studies, of which the two largest were the United States Diabetes Prevention Program and the Finnish Diabetes Prevention Study. Intervention has the potential to more than halve the incidence of type 2 diabetes. Studies in Asian populations have shown similar benefits.

Several drugs that are used in the treatment of type 2 diabetes have also been shown to prevent progression of prediabetes to type 2 diabetes. These include liraglutide, pioglitazone, acarbose and in particular, metformin, which has been shown to be effective in reducing the risk of type 2 diabetes in a number of clinical trials, particularly in those at highest risk of progression.

Observational studies have also shown bariatric surgery to be effective in the prevention of type 2 diabetes in obese persons. Findings from many of the clinical trials of pharmacotherapy and lifestyle intervention in type 2 diabetes seeking to reduce cardiovascular morbidity and mortality consistently indicate that the most convincing benefit is in the early phase of the natural history of type 2 diabetes.

Efficient, cost-effective, acceptable

In terms of diabetes complications, more innovative models of care are needed to deliver the wide scope of proven effective therapies in ways that are efficient and cost-effective, and acceptable to people with diabetes to ensure adherence. This is particularly pertinent in light of the expanding spectrum of recognised diabetes related complications, and the already wide treatment gap that continues to be shown to exist when the quality of current diabetes care is measured against recommended treatment guidelines.

Further challenges lie in reducing the inequities in diabetes service provision, in particular for Indigenous Australians and other disadvantaged groups. The evidence base for structured self-management education interventions is encouraging, with the application of self-management strategies having been shown to be associated with improvements in health outcomes in diabetes.

Innovative technological advances ranging from developments in drugs, drug delivery devises, monitoring systems and systems of health-care delivery, including the greater use of telemedicine, also offer hope of improved health outcomes and quality of life. However, the effective translation of these advances into clinical practice can be costly and require substantial time for appropriate engagement, education and interaction of patients, families and health-care professionals to ensure the optimum use of these technological advances.

There are many challenges in refocusing clinical attention on the prevention of type 2 diabetes, as well as the development and implementation of innovative effective models of care in relation to diabetes related complications. The imperative for this is fast becoming more important than ever. ▲

Identify patients at risk

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Prompt diagnosis can mean the difference between beneficial treatment and vision loss

AGE-RELATED macular degeneration (AMD) is the most common cause of legal blindness in Australia and is divided into dry and neovascular forms.[1] Up to 90 per cent of AMD-related blindness is caused by neovascular AMD (nvAMD).

Without treatment, over 50 per cent of patients with nvAMD lose three or more lines of Snellen visual acuity within one year of diagnosis.[2] Although vision loss due to nvAMD tends to be rapid, vision may be preserved by timely treatment with intravitreal antivascular endothelial growth factor (anti-VEGF) injections.

Optometrists are well positioned by virtue of their training, equipment and accessibility in the community to identify, educate and monitor patients at risk of nvAMD. They have a critical role in detecting and referring patients suspected of having nvAMD to an ophthalmologist for specialist assessment and treatment.

The majority of patients with the dry form of early AMD can be managed by optometrists. The decision regarding whether to refer a patient with dry AMD to an ophthalmologist will depend on the individual optometrist's personal experience and confidence in managing dry AMD, as well as their access to imaging technology such as retinal photography, fundus autofluorescence and optical coherence tomography (OCT).

Important clinical features of nvAMD that warrant urgent referral to an ophthalmologist include:

- Rapid deterioration of visual acuity
- Recent onset of visual distortion or increased visual distortion
- Retinal haemorrhage, retinal thickening or exudates in the macula
- Suspicious OCT imaging findings: intraretinal fluid, subretinal fluid or pigment epithelial detachment.

Determining the risk of nvAMD

The simplified severity scale for AMD is an evidence-based scale developed using data from the landmark Age Related Eye Disease Study (AREDS). It provides busy optometrists with a quick and easy way to clinically grade patients with AMD, providing a useful prognosis regarding their risk of progression to the potentially blinding advanced forms of AMD. The scale is based on clinical examination and does not require the use of a retinal camera or OCT.[3]

For each eye, one point is assigned for the presence of one or more large drusen (>/= 125 µm or the width of a large vein at disc margin) and one point for the presence of any pigment abnormality (hyperpigmentation, hypopigmentation, or non-central geographic atrophy) (Figure 1). If no large drusen are present in either eye, the presence of intermediate drusen in both eyes is counted as one point. The points from both eyes are added together to give a total score from 0 to four. The approximate five-year risk of developing advanced AMD (nvAMD or geographic atrophy involving the foveal centre) is based on the total score.

- 0 points = 0.5 per cent
- 1 points = 3 per cent
- 2 points = 12 per cent
- 3 points = 25 per cent
- 4 points = 50 per cent

It should be remembered that the simplified severity scale provides only an approximate guide to prognosis and is not accurate in every patient. In many patients, as AMD progresses, drusen may spontaneously regress, giving the cursory impression that the condition is improving while the risk of losing vision is actually increasing.[4,5] Therefore, it is important to assess the changes on retinal photography over time whenever possible.

The increasing availability of fundus autofluorescence (FAF) imaging in optometric practice may lead to better recognition of areas of retinal pigment epithelial pathology and risk of AMD progression. FAF is an indirect measure of the metabolic function of the RPE, with areas of hyperautofluorescence and hypoautofluorescence representing areas of sick or atrophic RPE. For example, in a case where drusen have regressed, FAF may demonstrate AMD related changes to the RPE that are not obvious on fundus examination.[5]

OCT imaging enables additional risk factors for AMD to be identified. Reticular pseudodrusen (RPD) are yellowish subretinal lesions arranged in a reticular pattern most commonly seen in the superotemporal

Continued page 14

Patients at risk

From page 13

quadrant of the macula. They are an increasingly recognised risk factor for progression to advanced AMD and often missed on slitlamp examination but visible on OCT as multiple tiny subretinal deposits. RPD may also be often be visualised on FAF or near infra-red photography. In eyes with AMD-related geographic atrophy, up to 62 per cent of eyes show RPD.[6]

Pigment epithelial detachments (PEDs) are easily seen with OCT imaging and assessing them can present a challenge to the optometrist. PEDs vary in appearance and may be optically clear or hyperreflective.[7]

The presence of a PED is a risk factor for vision loss with reports that over a 10-year period, up to 25 per cent will develop nvAMD and up to 75 per cent will develop geographic atrophy.[8] PEDs may be due to drusen or choroidal neovascular membranes (CNV) and are also a common feature of central serous chorioretinopathy (CSCR). Optometrists should have a low threshold for referring patients with PEDs to an ophthalmologist because fluorescein angiography may be indicated to exclude the presence of CNV and early treatable nvAMD.[9]

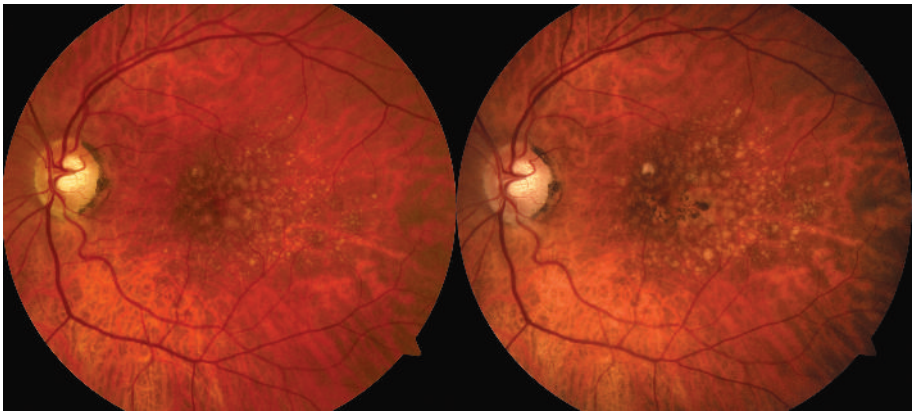
Differential diagnoses

Optometrists should be keenly aware that several retinal conditions can mimic AMD and that misdiagnosis is frequent. The prognosis, management and implications for systemic health associated with each condition can differ significantly from those associated with AMD and therefore, accurate diagnosis is important. Some of these conditions include macular dystrophies (for example, Stargardt's disease), polypoidal choroidal vasculopathy, central serous chorioretinopathy, acquired vitelliform lesions, retinal vascular occlusions, diabetic retinopathy as well as many others. If in any doubt about the diagnosis, referral to an ophthalmologist is appropriate.

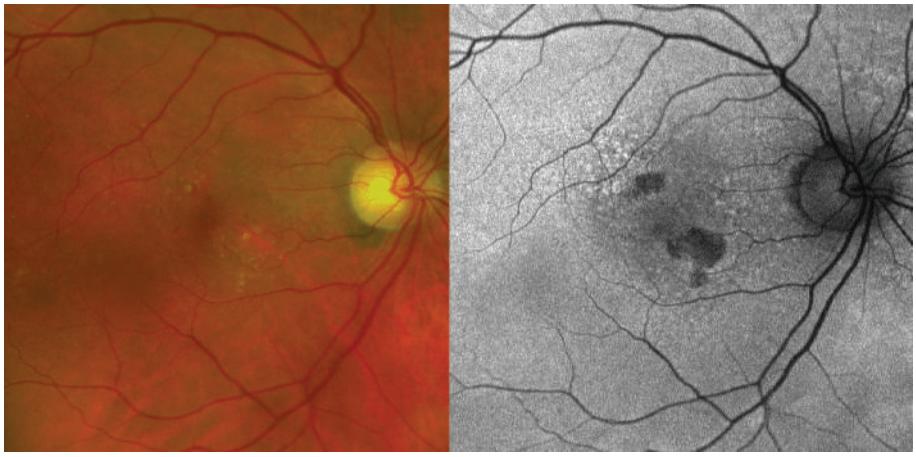
Management of nvAMD

When a diagnosis of nvAMD is suspected, urgent referral to an ophthalmologist is indicated for assessment and possible intravitreal anti-VEGF therapy. Fluorescein angiography can be considered the gold standard for identifying CNV and must be used to diagnose nvAMD to access Pharmaceutical Benefits Scheme subsidised anti-VEGF therapy.[10]

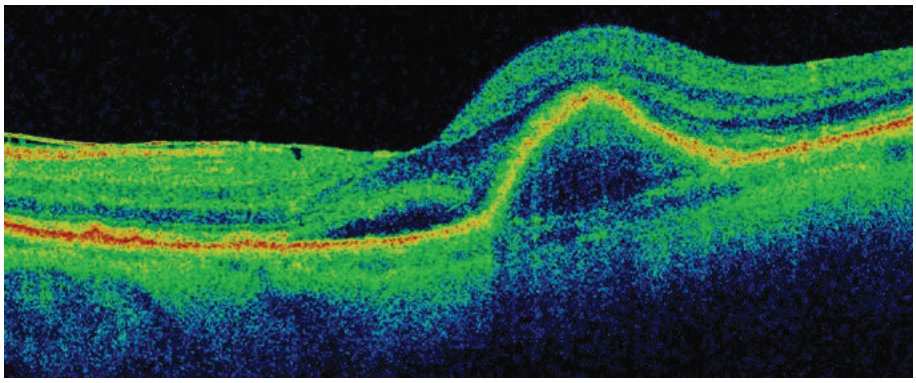
A recent major advance in OCT imaging is the ability to perform OCT angiography (OCT-A) without the need for intravenous dye injection.[11] In the future, OCT-A may obviate the need to perform fluorescein angiography in some patients with nvAMD, potentially leading to cheaper, safer



▶ Figure 1. Progression of dry AMD. (L) Large drusen without pigment changes. (R) Same eye five years later with development of pigment spots indicating increased risk of progression to advanced AMD.



◀ Figure 2. Fundus autofluorescence (FAF) imaging. (L) Dry AMD with drusen and subtle signs of geographic atrophy. (R) FAF image clearly showing areas of geographic atrophy.



◀ Figure 3. OCT in a patient with nvAMD showing a pigment epithelial detachment and adjacent area of subretinal fluid

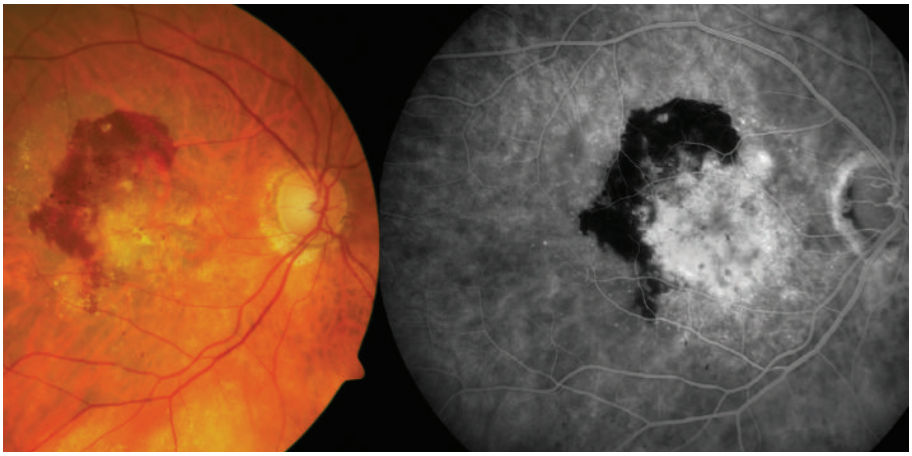
and more accessible angiography.

The current standard of care for the treatment of nvAMD is intravitreal anti-VEGF therapy with bevacizumab (Avastin), ranibizumab (Lucentis) or aflibercept (Eylea). These agents have been shown to reduce the risk of severe visual loss by over 90 per cent and are associated with a three-line improvement in visual acuity in more than 30 per cent of patients.[12,13]

Conclusion

Neovascular AMD is a common, blinding disease. Identification, education and monitoring by optometrists of patients at risk of developing nvAMD are essential to ensure that those patients do not develop nvAMD. Prompt diagnosis and referral for anti-VEGF treatment of nvAMD can often save sight. ▲

▶ Figure 4. (L) Retinal photo of a patient with nvAMD showing drusen, retinal haemorrhage and exudates. (R) Fluorescein angiogram showing a subfoveal choroidal neovascular membrane.



1. Deloitte Access Economics and Professor Paul Mitchell. Eyes on the future. A clear outlook on Age-related Macular Degeneration. [Internet]. [cited 2016 Apr 16]. Available from: http://www.mdfoundation.com.au/LatestNews/Deloitte_Eyes_on_the_Future_Report_web.pdf.
2. Wong TY, Wong T, Chakravarthy U et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. *Ophthalmology* 2008; 115: 1: 116–126.
3. Ferris FL, Davis MD, Clemons TE et al. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. *Arch Ophthalmol* 2005;123: 11: 1570–1574.
4. Bressler NM, Munoz B, Maguire MG et al. Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities. Waterman study. *Arch Ophthalmol* 1995; 113: 3: 301–308.
5. Toy BC, Krishnadev N, Indaram M et al. Drusen regression is associated with local changes in fundus autofluorescence in intermediate age-related macular degeneration. *Am J Ophthalmol* 2013; 156: 3: 532–42.e1.
6. Schmitz-Valckenberg S, Alten F, Steinberg JS et al. Reticular drusen associated with geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2011; 52: 9: 5009–5015.
7. Casswell AG, Kohen D, Bird AC. Retinal pigment epithelial detachments in the elderly: classification and outcome. *Br J Ophthalmol* 1985; 69: 6: 397–403.
8. Roquet W, Roudot-Thoraval F, Coscas G. Clinical features of drusenoid pigment epithelial detachment in age related macular degeneration. *Br J Ophthalmol* 2004; 88: 5: 638–642.
9. Sandhu SS, Talks SJ. Correlation of optical coherence tomography, with or without additional colour fundus photography, with stereo fundus fluorescein angiography in diagnosing choroidal neovascular membranes. *Br J Ophthalmol* 2005; 89: 8: 967–970.
10. Australian Government Department of Health. Aflibercept, solution for intravitreal injection, 40 mg per mL, Eylea - March 2012 [Internet]. Australian Government Department of Health; [cited 2016 Apr 17]. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-03/aflibercept.
11. Spaide RF, Klancnik JM, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol* 2015; 133: 1: 45–50.
12. Heier JS, Brown DM, Chong V et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology* 2012; 119: 12: 2537–2548.
13. Spitzer MS, Ziemssen F, Bartz-Schmidt KU et al. Treatment of age-related macular degeneration: focus on ranibizumab. *Clin Ophthalmol* 2008; 2: 1: 1–14.

Centre for Eye Health

Chair-side Reference:

Diabetic retinopathy is a retinal microvascular disease. Typical lesions display a characteristic evolution and progression from non-proliferative to proliferative; however, macular oedema can occur at any level of retinopathy.

Diabetic retinopathy grading scales are critical to the appropriate management of the disease and are currently based on the appearance of retinal lesions using dilated fundus examination and/or retinal photography. OCT imaging is now used frequently in clinical practice and can assist practitioners to determine the nature and extent of diabetic retinopathy and other ocular pathology.

To assist in grading and interpreting diabetic retinopathy in clinical practice, Centre for Eye Health has developed a Diabetic Retinopathy Chair-side Reference which aims to provide optometrists with an overview of the appearance of diabetic retinopathy lesions using colour, red-free and OCT images. The reference also contains succinct information on pathophysiology and differential diagnoses associated with each of the lesions. Finally, it outlines the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales.

This reference was developed by Paula Katalinic and Michael Yapp with input from the CFEH clinical team. During 2016, through the Centre's continuing education program *Learning for Vision* and in conjunction with Optometry NSW/ACT, a series of chair-side references will be released to provide optometrists with a succinct reference summary of common ocular conditions.

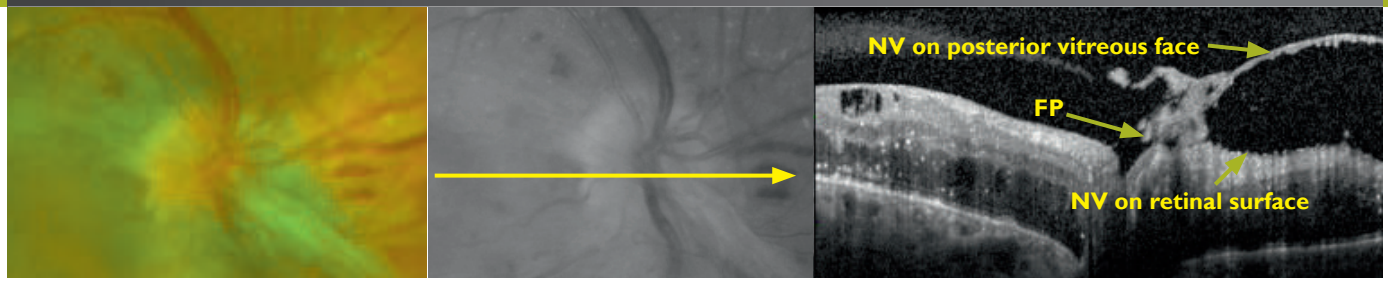
For more details, visit the Centre www.centreforeyehealth.com.au > For Referrers > Chairside References.

Michael Yapp
BOptom(Hons) MOptom GradCertOcTher FAAO

PROLIFERATIVE DIABETIC RETINOPATHY

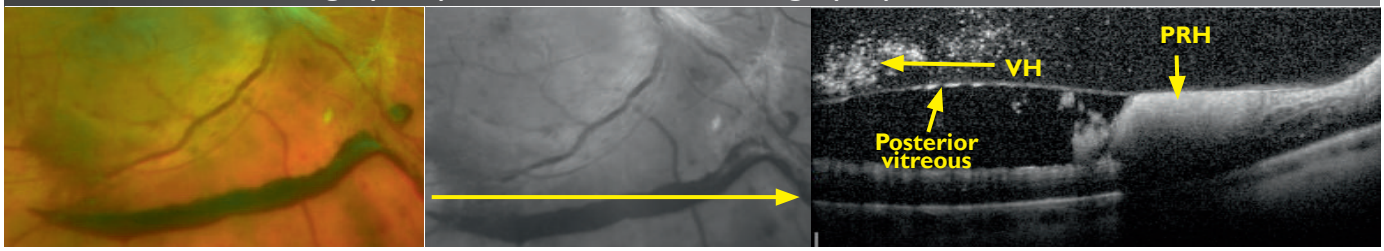
Colour photo | Red-free photo | Optical coherence tomography (OCT)

Neovascularisation (NV) and fibrous proliferation (FP)



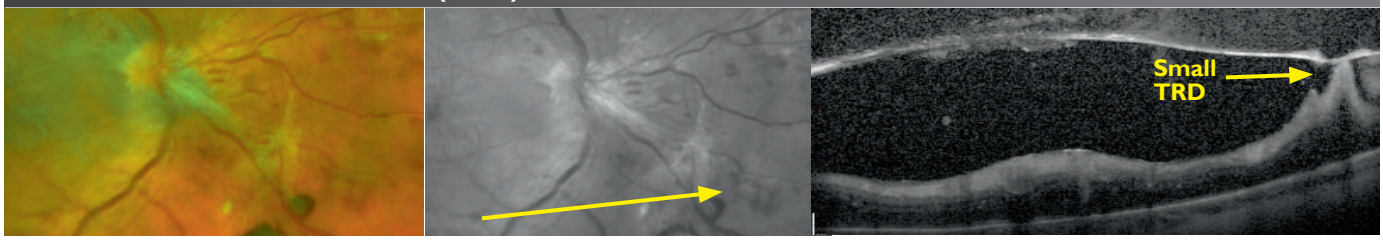
Neovascularisation (NV) appears as new vessels which loop back around or form a disorganised net, distinguishing them from normal capillaries. They are on the surface of the RNFL, internal limiting membrane (ILM) or posterior hyaloid face of the vitreous and occur at the border between healthy retina and areas of capillary occlusion (retinal ischaemia). They are prone to bleeding, resulting in pre-retinal (PRH) or vitreous haemorrhage (VH). Dynamic interaction between NV and the vitreous can lead to an inflammatory response and subsequent fibrous proliferation (FP). Any bleeding from IRMA or loop formation should be considered as NV until proven otherwise. NV of the disc (NVD) describes new vessels on or within 1 disc diameter of the disc as opposed to NV elsewhere (NVE).

Pre-retinal haemorrhage (PRH) and vitreous haemorrhage (VH)



PRH or VH can occur when fibrous scars contract and new vessels become elevated off the surface of the retina. This is especially true if there is strong adherence between the vitreous and the retina at the area of NV or FP. PRH may present as a D-shaped or boat-shaped haemorrhage trapped between the ILM and the posterior hyaloid face of the vitreous, although they can appear almost blot-like, linear or arcuate. VH will appear as a reddish or greyish area of haze obscuring the underlying retinal detail. OCT assists in identifying the location of the haemorrhage (which appears hyper-reflective).

Tractional retinal detachment (TRD)



Retinal folds or tractional retinal detachment (TRD) can occur if the vitreous is adherent to the retina in an area of fibrovascular scar formation. These changes are more likely to occur along the major vascular arcades. TRDs are concave and usually progress slowly, however a hole can form in the detached retina leading to a combined TRD and rhegmatogenous retinal detachment. Clinically, TRD will be associated with NV and FP and appear elevated.

International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales

RETINOPATHY STAGE	OPHTHALMOSCOPY FINDINGS
No apparent retinopathy	No abnormalities
Minimal NPDR	Microaneurysms only
Mild-Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any one of the following (and NO signs of PDR): • More than 20 intraretinal haemorrhages in each of 4 quadrants • Definite VB in 2+ quadrants • Prominent IRMA in 1+ quadrant
Proliferative DR	One of the following: Neovascularisation, vitreous/pre-retinal haemorrhage

MACULAR OEDEMA	OPHTHALMOSCOPY FINDINGS
Absent	No retinal thickening or hard exudates in the posterior pole
Present Can occur at any level of DR	• **Mild** – some retinal thickening or hard exudates in posterior pole but distant from the macula • **Moderate** – retinal thickening or hard exudates approaching the centre of the macula but not involving the centre • **Severe** – retinal thickening or hard exudates involving centre of the macula

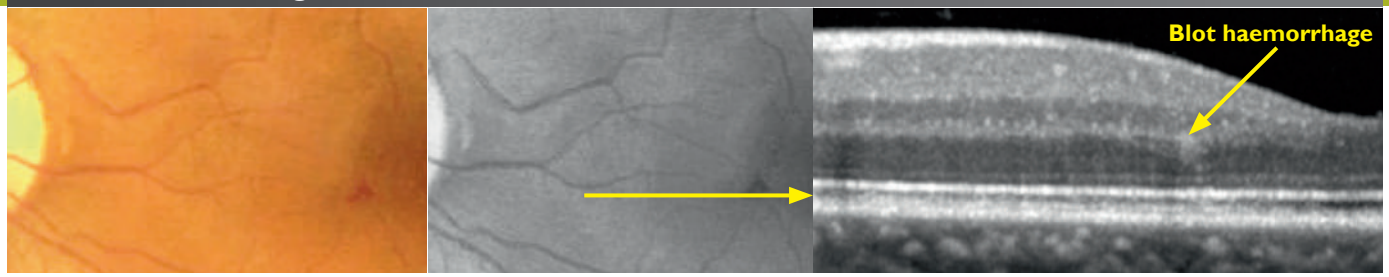
Diabetic Retinopathy

Optometry
NEW SOUTH WALES
AUSTRALIAN CAPITAL TERRITORY

NON-PROLIFERATIVE DIABETIC RETINOPATHY AND MACULAR OEDEMA

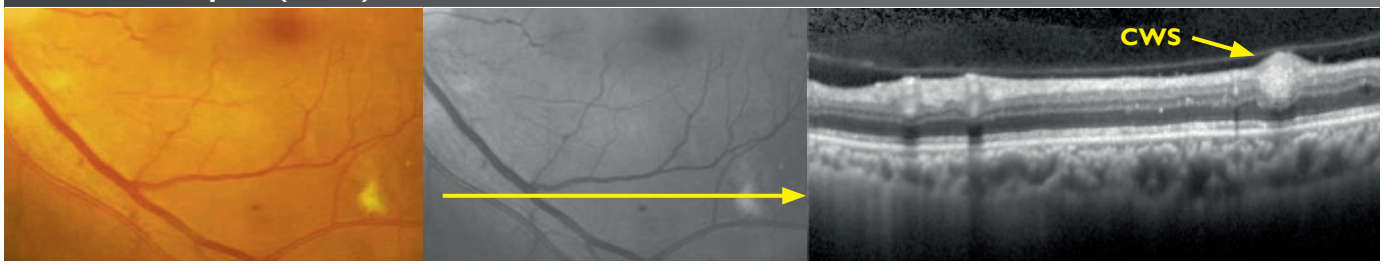
Dot/blot haemorrhages

Colour photo | Red-free photo | Optical coherence tomography (OCT)



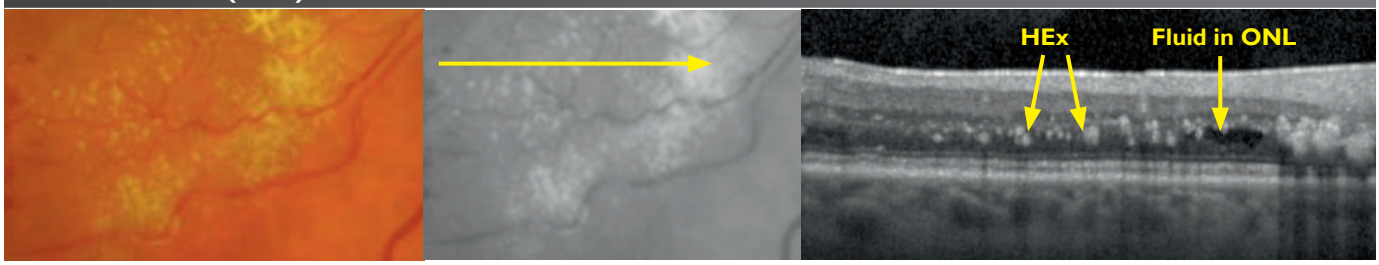
Dot and blot haemorrhages are usually caused by a ruptured or leaking microaneurysm or retinal capillary, typically within the inner nuclear layer (INL) or outer plexiform layer (OPL). Dot haemorrhages lie deeper in the retina than blot haemorrhages and can be difficult to distinguish from microaneurysms. Dot/blot haemorrhages take longer to resolve than more superficial flame-shaped haemorrhages. They may be undetectable on OCT or present as an area of hyper-reflectivity. Dot/blot haemorrhages can also occur in other conditions frequently associated with diabetes, such as hypertensive retinopathy, retinal vein occlusion and ocular ischaemic syndrome.

Cotton wool spots (CWS)



CWS appear as slightly elevated, yellow-white or grey-white, cloud-like lesions. They are typically found in the posterior pole and are less than 1/3 disc diameter in size. OCT imaging shows an elevated, hyper-reflective lesion in the retinal nerve fibre layer (RNFL) which may distort the underlying retinal layers. In DR, CWS result from ischaemia in the retinal nerve fibre layer (RNFL) however other factors responsible for focal disruption of axoplasmic flow in the RNFL may result in a similar presentation. Differential diagnoses include ischaemic, immune, infectious or inflammatory conditions as well as embolic, neoplastic, medication, traumatic, idiopathic and other miscellaneous causes. They may resolve in 6-12 weeks but can persist longer in DR.

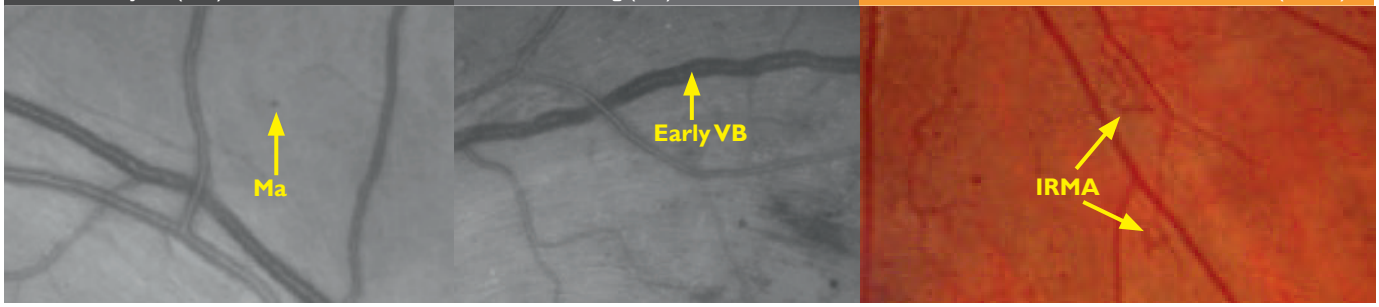
Hard exudates (HEx) and intraretinal oedema



Hard exudates present clinically as discrete, yellow-white lipid deposits in the OPL (Henle's layer in the macula) and may be isolated, diffuse, circinate (circular), or star-shaped. With OCT, they appear as hyper-reflective deposits in the outer retina. Intraretinal oedema can present, both clinically and with OCT, as retinal thickening or as cystic spaces in the outer retinal layers. In DR, both result from increased vascular permeability/ breakdown of blood retinal barrier causing leakage of lipids, proteins and serous fluid into the retina. Differential diagnoses include conditions such as hypertensive retinopathy, retinal arterial macroaneuysm, Coats disease and choroidal neovascularisation.

Changes not typically visible on OCT

Microaneurysm (Ma) | Venous beading (VB) | Intraretinal microvascular abnormalities (IRMA)



Microaneurysms are the earliest clinical sign of DR. They appear as isolated, round red dots of varying size which can resolve spontaneously. They are outpouchings of the capillary wall, due to ischaemia and subsequent pericyte loss, which can rupture and leak leading to intraretinal haemorrhage, hard exudate or oedema. They may be undetectable on OCT or present as a small area of hyper-reflectivity in the inner retinal layers.

Venous Beading is a venous calibre irregularity which occurs in areas of severe retinal hypoxia. A sausage-link appearance occurs in severe cases. Other calibre changes include dilation, reduplication and loops.

IRMA: Abnormal, intraretinal branching or dilation of capillaries within the retina in areas of ischaemia/ non-perfusion. Similar appearance to NV but with slightly larger vessel calibre. NV may form in close proximity.

Therapeutic news of note

Rob Cummins

Research and Policy Manager
Macular Disease Foundation
Australia

Anti-VEGF treatment regimens: which is best?

Debate continues globally regarding the optimal treatment regimen for people with wet AMD receiving anti-VEGF injections to reduce the significant treatment burden while maintaining optimal visual outcomes. In Australia, the majority of ophthalmologists use a treat-and-extend regimen, which typically involves three initial doses given one month apart, with subsequent visits and injection intervals being extended by two weeks at a time, if the leakage has stabilised, up to a maximum interval of 12 weeks. If reactivation occurs, the interval is reduced to the last interval with no leakage.

In some countries, there has been a preference for a 'PRN' regimen where people are seen monthly and injections given only when there is evidence of leakage.

Two papers by Hatz and Prünte in Switzerland have provided additional evidence that Australia's preference for the treat-and-extend approach may be preferable. In the first study,[1] a retrospective analysis of 140 eyes from 140 patients, half the patients received ranibizumab via a treat-and-extend regimen and the other half a PRN regimen.

At baseline, both groups had similar mean best corrected visual acuity (20/51). The treat-and-extend approach resulted in fewer visits (8.6 vs 11.9) but more injections (8.6 vs 6) over a 12-month period. Most significantly, the visual outcomes for people receiving the treat-and-extend regimen were superior (mean BCVA of 20/35 vs 20/43, p = 0.015) at 12 months, with reduced central retinal thickness. Both groups experienced an initial average improvement in vision but this improvement fell away after the initial three doses in the PRN group, with significant fluctuations in vision suggesting undertreatment. BCVA remained much more stable in the treat-and-extend group and the improvements were maintained until the end of the study at 12 months.

In a second study,[2] the same clinicians measured responses in 146 eyes from 134 patients who were initiated on a PRN regimen (mean BCVA after an average 17 months treatment = 20/41), but were then switched to treat-and-extend. Following the switch, BCVA improved slightly to a mean 20/36 at six and 12 months, with reduced fluctuations in BCVA and decreased central retinal thickness.

Compared to a PRN approach, treat-and-extend can improve and stabilise visual outcomes, with fewer patient visits. Although treat-and-extend patients received more injections, compliance may potentially be improved as patients considered clinic visits more worthwhile as they knew they would be receiving an injection.

1. Hatz K, Prünte C. *Acta Ophthalmologica* 2016; online 24 March.
2. Hatz K, Prünte C. *BJO* 2016; online 11 January.

Do computers screens pose a blue light hazard?

Many media reports suggest that the blue light emitted by computer monitors, smartphones, tablets and LED lights poses a significant risk to the health of the retina and may increase the risk of diseases such as macular degeneration. Much of the evidence for these claims is based on rodent models receiving a brief exposure to very high intensity blue light. How significant is this hazard?

Researchers at the Centre for Radiation, Chemical and Environmental Hazards in the UK measured the blue light exposure to a range of compact fluorescent and LED lights, computer monitors, laptops, smartphones and tablets, and compared this to the safe level of exposure to blue light proposed by the International Commission on Non-Ionizing Radiation Protection.

Even allowing for the possible long, extended viewing time of computers, smartphones and other devices, and using the most extreme viewing conditions such as close viewing with full intensity, none of the assessed sources suggested any cause for concern for public health.

The authors mentioned that the percentage transmission of blue light to the retina is age-related, with higher transmission for children. This study also did not assess the impact of blue light on circadian rhythm. Some other research has indicated that extensive use of blue-light emitting screens and lights in the evening may impact sleep patterns.

O'Hagan J et al. *Eye* 2016; online 15 January.

Novel eye chart may detect early MD

A major challenge with the management of macular degeneration is to be able to obtain an earlier diagnosis of those who are more likely to progress. A team of scientists at Moorfields Eye Hospital and the University of Ulster has designed a modification of the conventional logMAR eye chart, which may be able to detect earlier changes in vision loss in age-related macular degeneration.

Regular eye charts also do not have the sensitivity or specificity to diagnose early changes or to monitor the progression of disease. Visual acuity often remains 'normal' in even later stage disease with the use of conventional eye charts.

The new Moorfields Acuity Chart is essentially a logMAR chart that uses high-pass filtered letters that are made from fine black and white stripes. The chart uses a grey background with the same mean luminance as the letters. Previous work by this group indicated that the high-pass letters are more equally readable than standard letters and that they seem to disappear when they are too small to be recognised.

Two versions of the Moorfields Acuity Chart were tested with 38 normal subjects and 80 people with a range of VA from AMD. Results were compared to two versions of the normal logMAR chart.

The difference between the Moorfields Acuity Chart and the regular logMAR chart was approximately 4.5 lines in people with AMD and better visual acuity (around 0.0 logMAR). In people without AMD but similar visual acuity, the difference between the two charts was only 1.5 lines.

Regular logMAR charts exhibit significantly greater test-retest variability in people with AMD compared to normal subjects, whereas the variability with the Moorfields Acuity Chart appeared to be unaffected by the presence of disease. A larger clinical trial is now being planned to confirm the initial study.

Shah N et al. *BJO* 2016; online 4 February.

Visual hallucinations in people with low vision

Charles Bonnet syndrome (CBS), the rather strange phenomenon of complex visual hallucinations in people with vision loss but no neurological or psychiatric problem, continues to be an under-recognised and poorly understood issue.

The prevalence of CBS from a study of 2,565 new low vision clients aged 40 years and older at a national low vision service in Canada, was published in the *Canadian Journal of Ophthalmology*.

Following carefully-worded questioning, 18.8 per cent of people attending the low vision clinic reported that they experienced hallucinations, forming visual images that they knew were not there. Perhaps surprisingly, about 15 per cent of people with only mild vision loss (BCVA between 6/6 and 6/17 in the better eye) experienced hallucinations. People with BCVA between 6/18 and 6/59 experienced a rate of hallucinations similar to those with worse vision (approximately 20-21 per cent).

Similar rates of CBS were reported by people with AMD, glaucoma, diabetic retinopathy and other eye diseases, suggesting that it is vision loss rather than a specific disease that results in CBS.

Interestingly, although not specifically commented on by the authors, it appears that patients require only what would be considered 'significant' loss of vision in one eye to experience CBS, given the significant incidence in patients with only mild visual loss in the better seeing eye. There was also no difference in the likelihood of reporting hallucinations in people aged older than 80 compared with those aged between 40 and 80 years.

More CBS was reported in females. The author suggested that this may have been due to a greater reluctance of males to report the condition. Despite the careful wording of the questioning of patients, the author suggested that the rates of CBS may be even higher than those reported as some people may have been reluctant to disclose their experiences.

Given the high proportion of CBS in people with even mild vision loss, the author recommends that health professionals need to be aware that many of their patients may be experiencing CBS, and that these people will benefit from reassurance that their experiences are not atypical and that they are not suffering from a mental health disorder.

Gordon K. *Can J Ophthalmol* 2016; 51: 3.

Effects of switching from ranibizumab to aflibercept in wet AMD

An Australian study conducted by the Fight Retinal Blindness! collaboration, reports the 12-month outcomes of switching from ranibizumab to aflibercept in wet AMD patients.

This observational study analysed data from a longitudinal online database of the 'real-world' outcomes in 384 eyes that had been treated with ranibizumab for at least 12 months prior to switching to aflibercept, although the median duration of prior ranibizumab treatment was almost 40 months. Patients were then followed for at least 12 months after switching. Eighty per cent of the eyes were graded with active neovascularisation at the time of switching, that is, these were mostly challenging or recalcitrant cases.

The mean number of injections in the first three months after the switch was 2.56, indicating that many people were given three, monthly injections at the switch. After 12 months on aflibercept, the number of eyes with active lesions had reduced from 80 per cent to 58 per cent, with most of this reduction occurring in the first two months after the switch.

At the time of switching, the median treatment interval with ranibizumab was 42 days. After 12 months on aflibercept, the median interval increased to 56 days. The net result of this was about one fewer injection per year on average for aflibercept. It is possible that the treatment interval may have increased even if patients had not switched.

Interestingly, the mean visual acuity at the time of switching (63.4 letters) did not change after 12 months (63.3 letters). As there was no control group, it is not possible to say whether vision would have been different if the patients had not switched. As a majority of patients had been treated with ranibizumab for some years, it is also likely that scar formation or geographic atrophy may have occurred in some people, limiting the potential for improvement.

A small (6.8 per cent) proportion of eyes were switched back to ranibizumab after a mean of 15 months and 10 injections of aflibercept. These eyes had typically experienced an average one-line drop in vision following the initial switch. A small number of these eyes regained their initial vision after switching back to ranibizumab, but the mean acuity in this group continued to decline, suggesting that a second switch does not confer any obvious benefit.

Despite the lack of a control group and the retrospective nature of this study, it suggests that in patients who have been treated with ranibizumab for an extended period (at least 12 months) but continue to have active lesions, there may be only a modest benefit to switching to aflibercept, in terms of slightly reducing injection frequency rather than any visual benefit.

What is not answered in this study is whether earlier switching of people who experience continually active lesions after say, six to 12 months, will provide a more meaningful benefit.

Barthelmes D et al. *BJO* 2016; online 18 March. ▲

Systemic complications of Graves' disease

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GRAVES' DISEASE is a common cause of thyrotoxicosis, accounting for 60-80 per cent of cases.[1] It is an autoimmune disorder characterised by T-cell activation, with B-cell production of immunoglobulin G (IgG) antibodies against TSH receptors (TRAb). These stimulate TSH receptors continuously, causing thyroid hormone hypersecretion and goitrous enlargement.[2]

Affected people are between 40 and 60 years but may be any age.[1] Lifetime risk is 0.5 per cent (males) and three per cent (females).[3] While exact aetiology is unknown, environmental factors appear to trigger an autoimmune response in genetically susceptible individuals. Nearly 15 per cent of patients have a first degree relative with the same condition.[4] Concordance rate between monozygotic twins is 20 per cent.[5]

Environmental factors include psychological stress, high iodine intake, postpartum status, infections and smoking.[4] It is associated with other autoimmune disorders such as diabetes mellitus type 1, Addison's disease, celiac disease, myasthenia gravis and vitiligo.[2]

Presentation can be variable. Common symptoms include easy fatigability, palpitations, weight loss with increased appetite, nervousness, insomnia, excessive sweating, diarrhoea and heat intolerance.[2] Elderly patients may experience apathy, confusion and reduced appetite.[2] It is associated with the following six systemic complications.

- **Thyrotoxic crisis or 'Thyroid Storm'**[6]

This is an accelerated thyrotoxic state, occurring in untreated or under-treated individuals. It may be precipitated by sepsis, surgery, trauma and less commonly, during labour, radiation thyroiditis or diabetic ketoacidosis. Patients typically present with fevers, agitation, tremulousness, drenching sweats, cardiac tachyarrhythmia, and congestive heart failure. Abdominal pain and vomiting may manifest early. It has high mortality if not treated quickly.

- **Cardiovascular**[7]

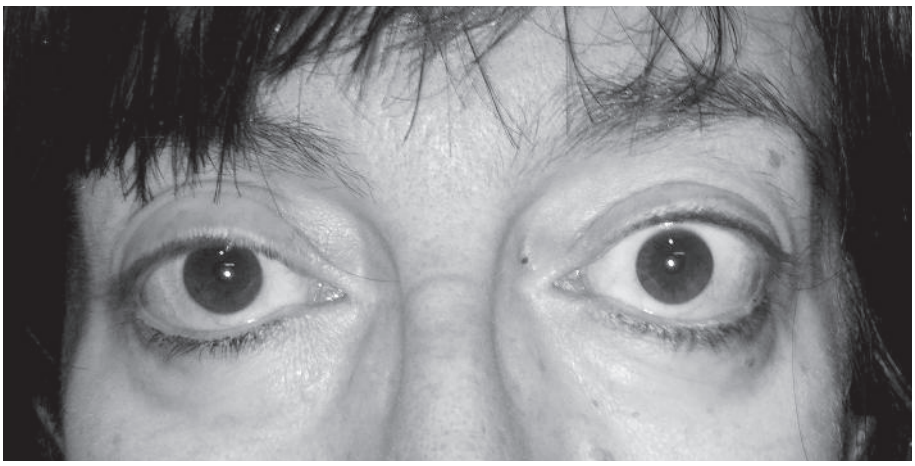
Due to increased metabolic demands of the myocardium during thyrotoxicosis, patients risk precipitating angina and myocardial infarction. Older individuals are at particular risk of cardiovascular complications. Sinus tachycardia is very common and atrial arrhythmias, especially atrial fibrillation is also common. In individuals with pre-existing cardiac conditions, congestive heart failure is a recognised complication.

- **Graves' Ophthalmopathy**[2,8]

Approximately 50 per cent of Graves' disease patients experience symptoms of ophthalmopathy which include gritty eyes, photophobia, diplopia, lacrimation and feeling of pressure behind the eye. Ocular involvement and hyperthyroidism can occur simultaneously or within 18 months of each other. Orbitopathy, a more serious ocular complication, may manifest earlier or later than hyperthyroidism. Subclinical involvement is more common, as imaging can detect extra-ocular muscles enlargement in 70 per cent of the patients with Graves' disease. Common signs are upper lid retraction, swelling, congestion of conjunctivae and proptosis. Graves' ophthalmopathy can progress into a sight-threatening disease characterised by corneal ulceration and optic nerve compression.[2]

- **Musculoskeletal system**

In longstanding cases, wasting of skeletal muscles, especially proximal groups, is well recognised.[7] Bone-related complications include



▲ Figure 1. Mild thyroid disease Image: Associate Professor Mark Roth

osteoporosis, osteopenia with increased fracture risk.[9] Thyroid acropachy is a type of finger clubbing in Graves' disease.[7] It is rare and typically presents in patients with orbitopathy and Graves' dermatopathy.[7]

- **Skin**[10]

The skin is commonly moist and hot. Palmer erythema and onycholysis are occasionally evident. Less commonly are pruritis, urticaria or hyperpigmentation. The hair is thin and there is hair loss in 40 per cent of the patients. Graves' dermatopathy is a specific feature of Graves' disease that occurs exclusively in patients who have already Graves' ophthalmopathy. Most commonly it manifests in the lower anterior part of the leg, hence called 'pretibial myxoedema'. Thickening of skin with nodularity and orange to purplish discolouration are the main features.

- **Reproductive system**

Women with Graves' thyrotoxicosis have anovulatory cycles, presenting with oligomenorrhea, or amenorrhea. Their fertility is reduced and they risk miscarriage during pregnancy.[6] Thyrotoxic men may suffer from low testosterone, with reduced libido and erectile dysfunction. Some men may develop gynecomastia.[2]

Diagnosis[11]

Diagnosis of Graves' disease can be made from clinical presentation associated with elevated free T3, free T4 and suppressed TSH. Presence of TRAb can be confirmatory. Radionuclide scans can differentiate Graves' from other causes of thyrotoxicosis such as toxic multinodular goitre and thyroiditis.

Treatment[3]

Choice of treatment depends on factors such as patient age, co-morbidities, presence of ophthalmopathy and patient preference. While propranolol, a beta-blocker, can be used to control the patients' symptoms, three treatments are available:

- **Anti-thyroid medication**

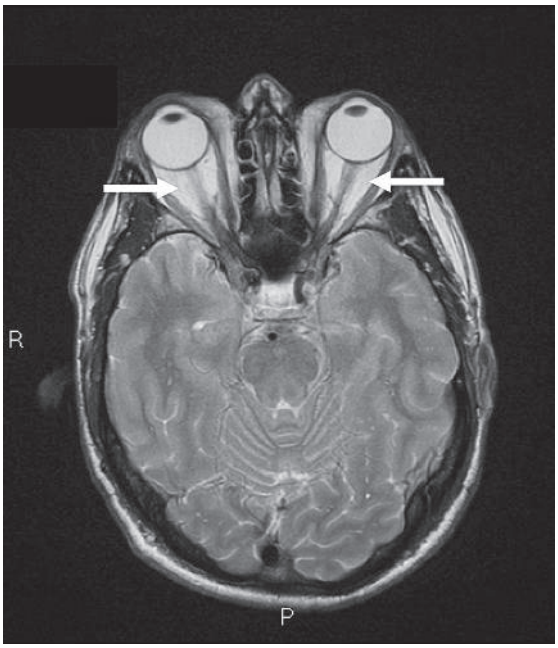
Drugs like ethimazole, carbimazole and propylthiouracil inhibit synthesis and secretion of thyroid hormones. Duration of treatment is 12 to 18 months. Remission rate is variable, but may reach 50 per cent. Side-effects include rash, arthralgia, gastrointestinal disturbance and raised liver enzymes. Agranulocytosis is a rare and serious side-effect.

- **Radioactive Iodine (RAI)**

The aim of this therapy is to destroy thyroid tissue through emitting beta particles. Remission can be achieved in 85 per cent of the patients after one year with a single dose of RAI. However, it can worsen Graves' ophthalmopathy and is contraindicated during pregnancy. It may cause irreversible treatment-related hypothyroidism.

- **Surgery**

Thyroidectomy is suitable for patients with large goitres, suspected thyroid malignancy, concomitant hyperparathyroidism or if patients prefer surgery. Potential complications include hypoparathyroidism, and recurrent laryngeal nerve injury. ▲



▲ Figure 2. MRI of the orbits, showing congestion of the retro-orbital space and enlargement of the extraocular muscles (arrows), consistent with the diagnosis of Graves' ophthalmopathy[13]

1. Weetman AP. Graves' disease. *New Eng J Med* 2000; 343: 17: 1236-1248.
2. Brent GA. Clinical practice. Graves' disease. *New Eng J Med* 2008; 358: 24: 2594-2605.
3. Burch HB, Cooper DS. Management of Graves' disease: A review. *JAMA* 2015; 314: 23: 2544-2554.
4. David G, Gardner DS. The Thyroid Gland. In: David S Cooper MPWL, MA (Oxon), MD, editor. Greenspan's Basic & Clinical Endocrinology. 9th ed: McGraw-Hill Education; 2011, p 198-206.
5. Ferri FF. Graves' Disease. Ferri's Clinical Advisor 2016. 1st ed. Philadelphia: Elsevier; 2016, p 557-558.
6. Davies TF. Hyperthyroid Disorders. In: Melmed S, Kenneth S, Polonsky P, Reed Larsen, Henry M Kronenberg, editor. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016, p 369-415.
7. Burch HB. Overview of the Clinical Manifestations of Thyrotoxicosis. In: Braverman LEC, David S, editor. Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text, 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2013, p 435-439.
8. Bahn RS. Graves' Ophthalmopathy. *New Eng J Med* 2010; 362: 8: 726-738.
9. Bauer DC, Ettinger B, Nevitt MC, Stone KL. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. *Annals Internal Med* 2001; 134: 7: 561-568.
10. Jameson JL. Disorders of the thyroid gland. In: Jameson JL, editor. Harrison's Endocrinology: McGraw-Hill Education; 2013, p 79.
11. Bahn Chair RS, Burch HB, Cooper DS et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid*: official journal of the American Thyroid Association 2011; 21: 6: 593-646.
13. Huy A Tran and Glenn EM Reeves: The influence of hepatitis C infection and interferon-α therapy on thyrotropin blocking and stimulating autoantibodies in Graves' ophthalmopathy: a case report. *Thyroid Research* 2009, 2:12 doi:10.1186/1756-6614-2-12 (Open Access)

Patients deem visual acuity worth the effort

PATIENTS with neovascular age-related macular degeneration (nAMD) were willing to opt for a higher treatment burden, which included regular intravitreal injections at short intervals and long periods of waiting, treatment and traveling, to prevent worsening of visual acuity, according to a study conducted in Germany.

The researchers conducted telephone interviews measuring patient preferences for specific levels of attributes that describe different options in the everyday intravitreal injection treatment setting.

A total of 284 patients with nAMD with a mean age of 77.4 ± 7.1 years (women: 59.9 per cent) completed the DCE interviews. Of them, 22.9 per cent had poor visual acuity, 54.9 per cent had moderate visual acuity, 14.1 per cent had good visual acuity, and visual acuity was not available for 8.1 per cent of patients.

The attribute 'change of VA' influenced overall decisions for or against treatment in 73.6 per cent of patients.

Overall, patients were willing to opt for an additional 12.7 hours of time spent for each physician visit to achieve stable visual acuity rather than worse acuity. Patients were willing to opt for an additional 21.1 hours spent for each physician visit to improve visual acuity.

The authors concluded that although the treatment burden associated with current treatment options is high, patients show a strong preference for a treatment that is likely to have a more favourable clinical outcome.

Muller S et al. Patient preferences in the treatment of neovascular age-related macular degeneration: a discrete choice experiment. *Ophthalmology* 2016; doi:10.1016/j.ophtha.2015.12.001.

Metformin recommended for diabetes

RESEARCHERS say evidence from a new meta-analysis supports current guidelines with metformin as the recommended first-line agent to treat adults with type 2 diabetes, given its beneficial effects on haemoglobin A1c, weight, and cardiovascular mortality and relative safety profile.

The analysis included over 200 randomised, controlled or observational studies, mostly short-term, published through 2015. Participants generally were overweight or obese adults with poorly controlled haemoglobin A1c levels at baseline. Among the findings are:

Cardiovascular mortality: metformin monotherapy was associated with reduced CV mortality relative to sulfonylurea monotherapy.

Haemoglobin A1c: most medications had similar effects on HbA1c; however, dipeptidyl peptidase-4 (DPP-4) inhibitors weren't as effective as metformin or sulfonylureas.

Body weight: sodium-glucose cotransporter 2 (SGLT-2) inhibitors lowered weight more than metformin, which reduced weight more than DPP-4 inhibitors.

Adverse events: sulfonylureas were associated with increased risk for severe hypoglycaemia, metformin and glucagon-like peptide-1 receptor agonists with gastrointestinal side-effects, and SGLT-2 inhibitors with genital mycotic infections.

Maruhur N et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2016; Published online 19 April 2016 doi:10.7326/M15-2650

Insights into

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RETINAL VEIN occlusion (RVO) is a global health concern which may affect men and women equally at working age. It has been estimated to affect 16.4 million people worldwide[14] and is the second most common cause of vision loss due to retinal vascular disease. While age is an important risk factor for RVO, which is more common in elderly populations, people of working age still account for one in six of RVO patients.[15] Its prevalence may also be higher in Asian and Hispanic populations.[10]

Vision loss in RVO is due to a combination of non-perfusion and macular oedema through several different mechanisms: first, vein occlusion occurs with impaired retinal blood flow leading to haemodynamic and vascular changes. The blockage also causes increased intraluminal pressure in the capillaries, with metabolic disturbance leading to increased oxidative stress and inflammation. With a reduction of retinal perfusion, non-perfusion may develop increasing the secretion of vascular endothelial grown factor (VEGF) and placental growth factor (PlGF). This results in vascular remodelling and blood-retinal barrier (BRB) breakdown which all ultimately lead to leakage and oedema.

Branch retinal vein occlusion (BRVO) can occur at different sites in the retinal vasculature but occlusions in the major superotemporal region are most common.[17] Occlusions affect a

retinal vein occlusion: mechanisms of action of aflibercept

large area and are associated with a range of complications.[18] Significant BRVO is associated with visual complications: 50 per cent of patients with BRVO have macular oedema at presentation and 20 per cent of patients with BRVO develop retinal non-perfusion, usually within the first six to 12 months of occlusion.[19]

The role of non-perfusion

Non-perfusion is an important clinical feature of central retinal vein occlusion (CRVO). Non-perfusion has been historically defined as more that 10 disc areas of retinal non-perfusion on fluorescein angiography. However, this definition has not always been consistent across different clinical trials. Up to 75 per cent of CRVO cases are non-ischaemic[20,21] and 34 per cent progress to non-perfusion within three years. Non-perfused CRVO is associated with worse visual acuity outcomes than the non-perfused type.[22,23] BRVO has a lower risk of conversion to ischaemic disease that CRVO.[24]

Non-perfusion is an indication of severity in RVO, involving a complicated cascade that gives rise to free radical production with cell death, oxidative stress, intracellular oedema and inflammation. All of this will progressively increase the levels of VEGF, PlGF and soluble cytokines interleukin (IL) 6 and 8 which lead to rupture of haematoretinal barrier and subsequent oedema.[25,26]

This is why it is important to identify ischaemic disease with the development of novel imaging techniques such a wide-field angiography and optical coherence tomography angiography. Wide-field angiography allows for detailed visualisation of retinal changes. A recent study by Prasac et al used ultra wide-field angiography to show a correlation between macular oedema and peripheral ischemia in BRVO and hemi-retinal vein occlusion (HRVO) patients.[27] Untreated non-perfusion at any location was significantly associated with macular oedema and untreated non-perfusion anterior to the globe equator was also significantly associated with macular oedema.

Peripheral non-perfusion is not the only consideration, however. Optical coherence tomography angiography can be used to show macular oedema due to perimacular capillary network remodelling with the superficial plexus showing zones of non-perfusion. Macular oedema can also be due to a decrease in macular perfusion and it is important to remember that macular perfusion also influences the visual prognosis.[25,29]

Macular oedema in RVO is also associated with other multiple factors, including increases in VEGF, PlGF and VEGF receptor 1 (VEGFR-1) levels which are expressed on endothelial cells, retinal pigment epithelium and pericytes.[30,31] It is also associated with oxidative stress in which cytokine levels are elevated, leading to blood-retinal barrier breakdown and microglial activation and inflammation.[32]

VEGF Interactions

It is known that VEGF-A interacts with VEGFR-1 and VEGFR-2, whereas PlGF binds only to VEGFR-1. The altered expression plays an important role in non-perfusion mediated retinal neovascularisation. Excessive activation of VEGFR-1 and VEGFR-2 by VEGF-A can result in pathological neovascularisation and excessive vascular permeability leading to macular oedema.[33]

RVO leads to a breakdown of retinal vasculature through pericyte loss and endothelial cell apoptosis. Vein occlusion in animal models induces immediate apoptosis of endothelial cells in occluded vessels and upstream capillaries, and also massive and delayed VEGFR-1/PlGF dependent pericyte loss from upstream capillaries.[34] This all leads to increased leakage.

One other mechanism of action in RVO is microglia activation which induces inflammatory factors L-6 that are mediated through the VEGFR-1 pathway. L-6 is strongly associated with retinal thickness in CRVO and BRVO[35] and microglia are the first inflammatory cells activated in response to retinal stress. PlGF inhibition can attenuate this inflammation.[37]

This is the pathophysiological background against which aflibercept has been bio-engineered to demonstrate strong, broad and long-lasting activity in visual impairment due to macular oedema secondary to RVO.[38] Aflibercept is the first fusion protein with innovative dual action against both VEGF and PlGF.

In summary, RVO has a complex pathophysiology with multiple contributing factors. Visual acuity decreases are mainly due to non-perfusion and macular oedema. PVO is associated with high levels of VEGF and PlGF which increase with the severity of non-perfusion. Macular oedema results from blood-retinal barrier breakdown inflammation and vascular remodelling. As a drug specifically designed to strongly bind both VEGF and PlGF, aflibercept addresses multiple factors that contribute to RVO pathogenesis.

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References available on request. Email editor Jeff Megahan j.megahan@optometry.org.au.

Management of primary open angle glaucoma

Adverse effects associated with topical treatment

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CASE REPORT

A 54-YEAR-OLD Caucasian male presented for a general eye examination, wanting to update the prescription in his 11-year-old spectacles. The patient is scheduled to see a local ophthalmologist every six months but had not done so for nine months.

The ophthalmologist had previously prescribed Travatan for the patient's primary open angle glaucoma (POAG) treatment but it had not adequately lowered the IOPs. For the following 18 months, the ophthalmologist then prescribed DuoTrav nocte; however, due to intolerable side-effects the patient had voluntarily ceased this treatment three months before presenting to update his prescription. Soon after commencing the DuoTrav treatment, the patient had been experiencing mood changes and was unable to wear his soft disposable contact lenses for more than one or two days due to discomfort.

General health was reported as good with no medications and the patient had no known family history of glaucoma, macular degeneration, diabetes or hypertension.

BCVAs were 6/9+ OD and 6/9+ OS with a distance refraction of -7.25/-1.25 x 84 OD and -7.00/-1.50 x 68 OS. Pupils, EOM movements and slit-lamp anterior examination showed no abnormal defects, and open angles were recorded.

Posterior slitlamp examination on VOLK showed an asymmetrical C/D ratio of 0.3 OD and 0.6 OS, with the macular appearing flat and clear. Perkins tonometry results were 21.5 mmHg OD, 28 mmHg OS at 11:15 am.

Humphrey Visual Field Analyzer 24-2 results of the right eye showed reliable indices, no abnormal defects, GHT within normal limits (Figure 1). The field of the left eye showed reliable indices, GHT outside normal limits and glaucomatous field changes (inferior arcuate and paracentral scotomas) (Figure 2).

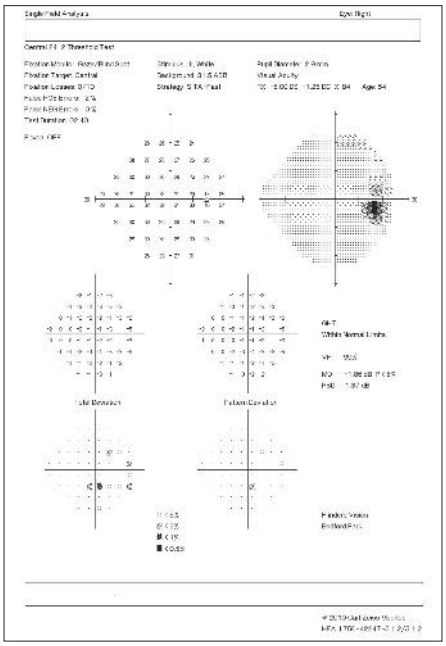
OCT optic nerve head analysis of both eyes revealed vertical C/D ratios 0.2 OD and 0.8 OS and showed OS RNFL thinning superiorly and inferiorly and OD RNFL thinning mostly superiorly (Figure 3). This patient was prescribed multifocal spectacles and was asked to return for a dilated fundus examination due to high myopia and for a better optic disc view.

Cirrus HD OCT 5- Line Raster at the next visit five days later showed no abnormalities OD and cystoid macular oedema OS (Figure 4). The patient was referred to the original ophthalmologist in regards to ceasing topical DuoTrav due to intolerable side-effects, the development of left cystoid macular oedema (CMO) and assessment for selective laser trabeculoplasty (SLT).

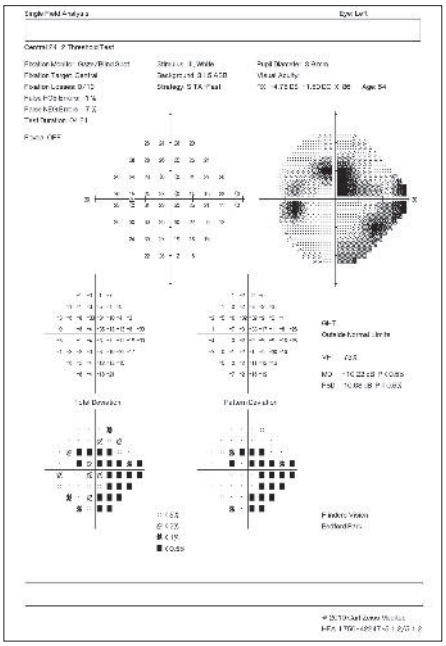
The ophthalmologist agreed that the patient was receiving some beta-blocker and prostaglandin analogue side-effects (mood changes and CMO). SLT was completed in the left eye one week later and the patient was to have a second session completed.

Diagnosis

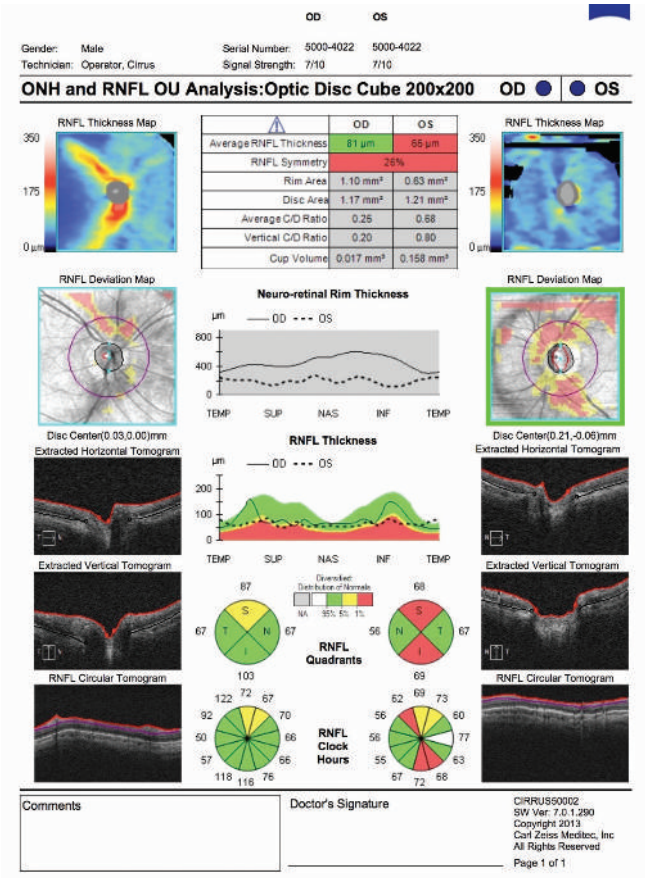
The patient was diagnosed with POAG, as he presented with elevated IOPs of 21.5 mmHg and 28 mmHg right and left, along with open anterior chamber drainage angles, high myopia, RNFL thinning on OCT and glaucomatous



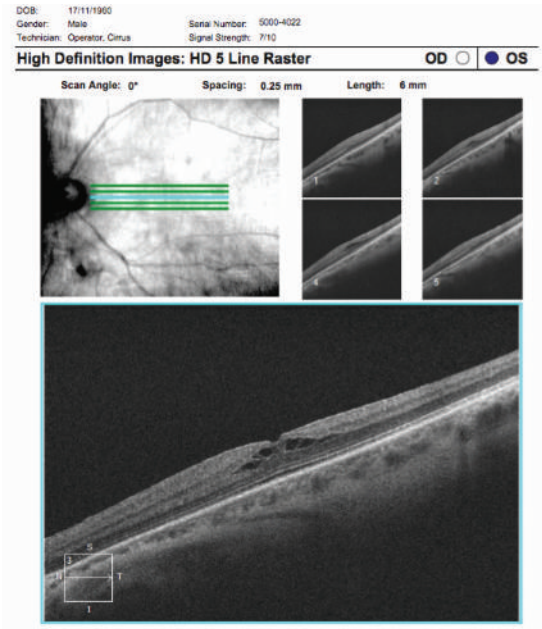
▲ Figure 1. HFA 24-2 visual field results OD: no abnormal defects



▲ Figure 2. HFA 24-2 visual field results OS: inferior arcuate and paracentral scotomas



▲ Figure 3. Cirrus OCT optic nerve head analysis OU



▲ Figure 4. Cirrus OCT HD 5 Line Raster OS showing CMO

VF defects in the left eye. The patient's mood swings could be attributed to the beta-blocker Timolol and the CMO was likely to have been caused by the prostaglandin travoprost in the DuoTrav drops that were prescribed. Contact lens intolerance is also a common side-effect from topical glaucoma medications.

POAG is often bilateral but asymmetric and it has been reported that on average, there is 50 per cent as much damage in the better eye than in the worse eye.[1]

Other differentials that were eliminated were normal tension glaucoma, ocular hypertension, primary angle closure glaucoma, pigmentary glaucoma (PG), pseudoexfoliation glaucoma, physiological cupping and thick CCTs causing higher tonometry readings.

Discussion

Reducing IOP can slow the onset and progression of glaucoma. The only factor that can be controlled in glaucoma is IOP, therefore current treatments for POAG are aimed at lowering IOP.[2,3]

The NHMRC guidelines suggest topical hypotensives as the first line of treatment for POAG and this patient was originally started on Travatan 0.004% as prostaglandin analogues (PGAs) have the highest efficacy, the most favourable side-effects and administration required only once daily. Before the patient was changed from Travatan to DuoTrav, Lumigan would have been another treatment option as there is some evidence suggesting it may be slightly more effective than the other PGAs in IOP reduction. This would have depended on how far the patient was from reaching target IOP on Travatan, as the additional IOP decrease from Lumigan is most likely to be only minor.

PGA use can result in reversible macular oedema[4] and it is believed that this patient experienced the CMO from the PGA in the DuoTrav drops, due to disruption in the blood-aqueous barrier.[5]

Although beta-blockers are also considered a first-line medical treatment by the NHMRC guidelines, they have a slightly lower efficacy compared to PGAs and usually need to be administered twice daily.[4,6] Beta-blockers require careful consideration before prescribing as systemic side-effects can occur due to the presence of beta-receptors in the heart and lungs. Depression is an associated systemic side-effect and it is believed that the patient's mood changes were due to the timolol in the DuoTrav.

Although combination glaucoma drops are considered as a second treatment choice by the NHMRC guidelines, a majority contain timolol 0.5%; therefore, changing the patient from DuoTrav to another combination drop may still have resulted in the neurological adverse effects. It is unlikely that a carbonic anhydrase inhibitor, alpha-agonist or miotic would have lowered the patient's IOP by a greater amount, therefore SLT was the next appropriate option.

Laser trabeculoplasty is the next line of treatment after topical hypotensive failure, or it can be offered as an additive to medical treatment.[4] It has been shown to be as effective as initial treatment with topical medication,

Continued page 26

Adverse effects

From page 25

with average IOP reduction rates ranging between 20 and 30 per cent.

Because the patient did not reach his target IOP with the initial Travatan 0.004%, and then experienced intolerable side-effects with DuoTrav, SLT was considered. The ophthalmologist agreed with this assessment and SLT was commenced on the left eye. Because the effects of the laser appear to diminish over time, this patient will need to be monitored closely and SLT may need to be repeated.

Surgical IOP reduction is offered when medications and/or laser therapy are unsuitable or fail.[4] Filtering surgery is an invasive procedure and therefore the risks and benefits need to be explored, and intensive proactive post-operative care is required.[7] It has been shown to have success rates of 75-90 per cent in previously unoperated eyes, and post-operative hypotensives are needed in 15-50 per cent of these patients.[4,8] Glaucoma drainage devices provide adequate long-term IOP reduction, but are usually reserved for glaucoma eyes where trabeculectomy is unsuitable or has failed. Filtering surgery may be a future option for this patient once SLT and medical therapy have failed. ▲

Older age

Family history of glaucoma: In close relatives of individuals with POAG, the prevalence is 3-6 times that of the general population.[1] There is also evidence of a small number of disease genes linked to POAG (MYOC, OPTN, WDR36).

Ethnic origin: People of African descent have been identified as having prevalence for POAG 4.3 times more than Caucasians[1]

Diabetes: The prevalence of POAG in diabetic patients has been reported to be between 1.2%-5.5%[3]

Myopia: 2-5 times higher prevalence in myopic patients[3]

High systemic blood pressure

Ocular risk factors[4]

- Raised IOP where normal IOP levels are defined as being between 10 and 21 mmHg
- Large vertical cup:disc ratio
- Vertical cup:disc ratio asymmetry (greater than 0.2)
- History of or current Drance haemorrhage: subjects with this finding are twice as likely to progress to glaucoma[5]
- Reduced central corneal thickness (CCT)[5]
- RNFL defects

▲ Table 1. Risk factors for the development of POAG

1. Quigley H. Glaucoma. *The Lancet* 2011; 377: 9774: 1367-1377.
2. Kwon Y, Fingert J, Kuehn M, Alward W. Mechanisms of disease: primary open-angle glaucoma. *New Eng J Medicine* 2009; 360: 11: 1113-1124.
3. Kass M. The Ocular Hypertension Treatment Study. *Arch Ophthalmol* 2002; 120: 6: 701.
4. NHMRC. Guidelines For the Screening, Prognosis, Diagnosis, Management and Prevention of Glaucoma. Canberra: National Health and Medical Research Council; 2010. Available at: https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp113_glaucoma_120404.pdf. [Accessed 11 January 2016].
5. Miyake L, Ibaraki N. Prostaglandins and cystoid macular oedema. *Survey Ophthalmol* 2002; 47: 1: S203-218.
6. Parrish R, Palmberg P, Sheu W. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure. *Amer J Ophthalmol* 2003; 135: 5: 688-703.
7. Kirwan JF et al. Trabeculectomy in the 21st century. *Ophthalmology* 2013; 120: 12: 2532-2539.
8. American Optometric Association. Optometric clinical practice guidelines: Care of the patients with open angle glaucoma. St Louis: American Optometric Association; 2010. Available at: http://www.aoa.org/documents/optometrists/CPG-9.pdf. [Accessed 11 January 2016].

TOPICAL HYPOTENSIVES

Prostaglandin analogues
- NHMRC first choice, efficacy 25-30%
- Latanoprost (Xalatan) 0.005%
- Travoprost (Travatan) 0.004%
- Bimatoprost (Lumigan) 0.03%

Beta-blockers
- NHMRC first choice, efficacy 20-25%
- Timolol (Tenopt, Timoptol) 0.25%, 0.5%, 0.1%
- Betaxolol (Betoptic, Betoquin) 0.25%, 0.5%
- Levobunolol 0.25%

Combination
- NHMRC second choice, efficacy 25-30%
- Brimonidine 0.2%/Timolol 0.5% (Combigan)
- Dorzolamide 2%/Timolol 0.5% (Cosopt)
- Travoprost 0.004%/Timolol 0.5% (DuoTrav)
- Latanoprost 0.005%/Timolol 0.5% (Xalacom)
- Bimatoprost 0.03%/Timolol 0.5% (Ganfort)
- Brinzolamide 1%/Timolol 0.5% (Azarga)
- Brinzolamide 1%/Brimonidine 0.2% (Simbrinza)

CAIs
- NHMRC second choice, efficacy 15-20%
- Dorzolamide (Trusopt) 2%
- Brinzolamide (Azopt) 1%
- Systemic acetazolamide 250 mg

Alpha-agonists
- NHMRC second choice, efficacy 20-25%
- Brimonidine (Alphagan) 0.2%
- Apraclonidine 0.5%

Miotics
- NHMRC third choice, efficacy 20-25%
- Pilocarpine 1%, 2%
- Carbachol 1.5%, 3%

LASER
- Argon laser trabeculoplasty (ALT)
- Selective laser trabeculoplasty (SLT)

SURGERY
- Filtering surgery (trabeculectomy)
- Drainage implants

▲ Table 2. Treatment options in Australia for POAG

Normal tension glaucoma

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CASE REPORT

A 79-YEAR-OLD Caucasian female presented for annual review in July 2015. Since her initial presentation in 2009, she had been monitored annually as a suspect for normal tension glaucoma (NTG) due to cup-to-disc ratios of 0.70 and 0.75, and IOPs of 12 mmHg and 14 mmHg, right and left, respectively.

These readings had remained unchanged between 2009 and 2014. OCT had been performed at each visit and showed no evidence of thinning of the retinal nerve fibre layer (RNFL). The patient was not taking any medications but she was symptomatic of Raynaud's phenomenon. In addition to peripheral vasospasm, her rural location and advancing age are relevant risk factors to her development of NTG.[1]

Examination July 2015

Best corrected visual acuity (BCVA), OD: 6/7.5-, OS: 6/7.5+.

IOP Perkins 9:30 am, OD: 13 mmHg, OS: 14 mmHg.

Central corneal thickness (CCT), OD: 520 µm, OS: 522 µm.

Pupils PERRL, no RAPD.

Slitlamp examination revealed a clear and quiet anterior chamber with open angles. No pigment, inflammatory cells, pseudoexfoliative material, neovascularisation or other signs of secondary glaucoma were present OU. Mild nuclear and cortical cataract was present in each eye (graded LOCS III NO2 NC3 C2 P0.1 OU). A dilated fundus examination revealed OD C/D 0.70, OS C/D 0.75 with an inferior temporal disc haemorrhage in the left eye.

The patient had no known history of disc haemorrhages. No abnormalities were present at the macula or peripheral retina OU. The OCT showed no decrease in RNFL thickness compared with previous scans; it was in the normal range circumferentially, and showed acceptable symmetry (Figures 1 and 2).

Examination August 2015

The patient returned for repeated IOP measurement and automated perimetry. IOP was 14 mmHg OU (Perkins 11:20 am). The right eye had an inferior nasal step (Figure 3), though given the extended nasal field area measured by Matrix automated perimetry, it is possible that this was caused by a nose defect and thus repeated perimetry to establish consistency would be useful. The left VF was full (Figure 4), with no evidence of glaucomatous defects or otherwise. The reliability indices were excellent bilaterally.

Diagnosis

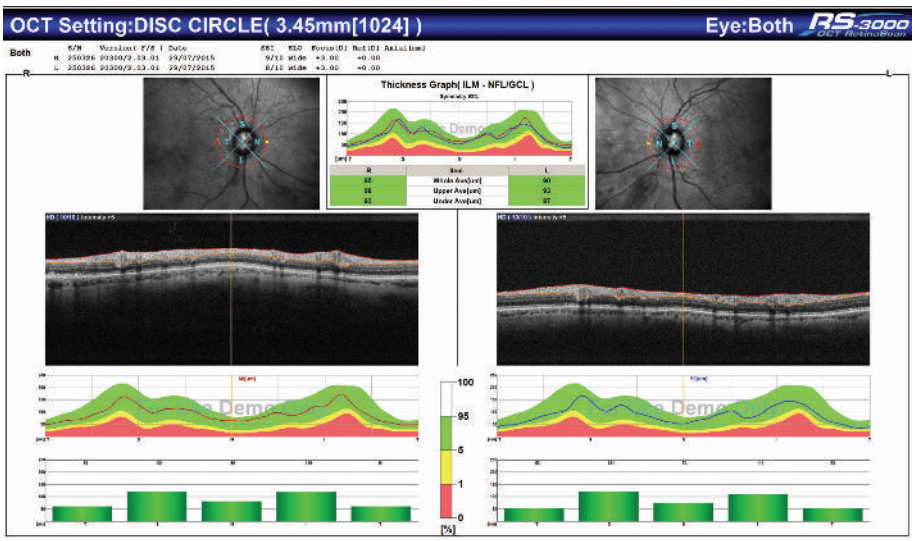
A diagnosis of NTG was made, based on the appearance of the optic nerves; in particular, the left disc haemorrhage.

Reasonable differential diagnoses include POAG, pseudo-glaucoma (that is, large physiological cup) and pigmentary glaucoma. Pachymetry is crucial in the diagnosis of NTG, as underestimation of IOP due to low CCT may cause POAG to be incorrectly diagnosed as NTG.

Low CCT is also a risk factor for NTG, with CCT being lower in NTG than in POAG.[2] Similarly, repeated baseline tonometry is essential to differentiate POAG from NTG. Establishing a comprehensive baseline range of diurnal IOP measurements is required to form an accurate baseline that accounts for diurnal variation.

Other causes of optic disc haemorrhages must also be considered. These include diabetic papillopathy, ischaemic optic neuropathies and localised retinal branch vein occlusion.[3] However, in the absence of disc oedema, retinal abnormalities and

Continued page 28



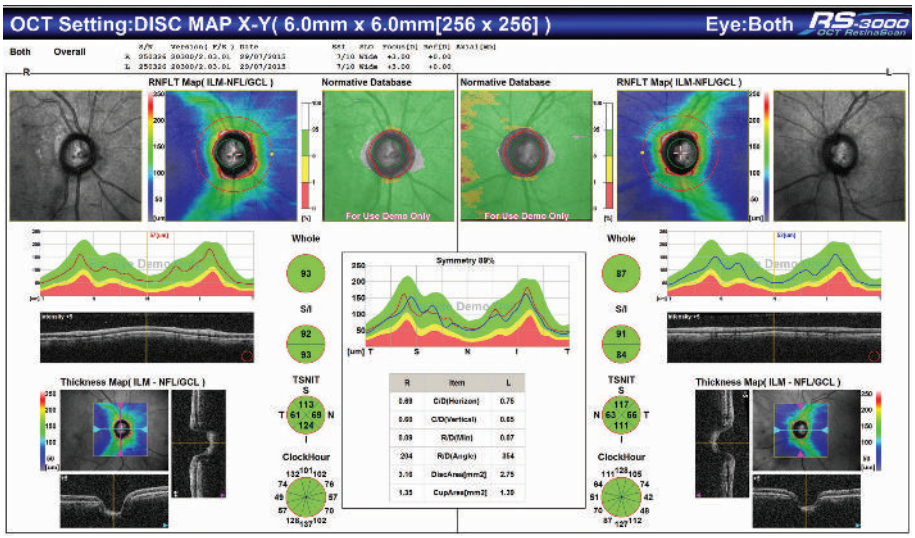
▲ Figure 1. Disc circle (Nidek RS-3000 OCT)

Normal tension glaucoma

From page 27

retinal vascular changes, these causes were unlikely.

Disc haemorrhages can also occur in association with posterior vitreous detachment, but dilated fundus examination revealed no sign of this, and the patient had not experienced any flash or floater symptoms. Given her five-year history as a NTG suspect and in the absence of other ocular signs, the disc haemorrhage seems most likely to be associated with glaucoma.



▲ Figure 2. Disc map (Nidek RS-3000 OCT)

Management

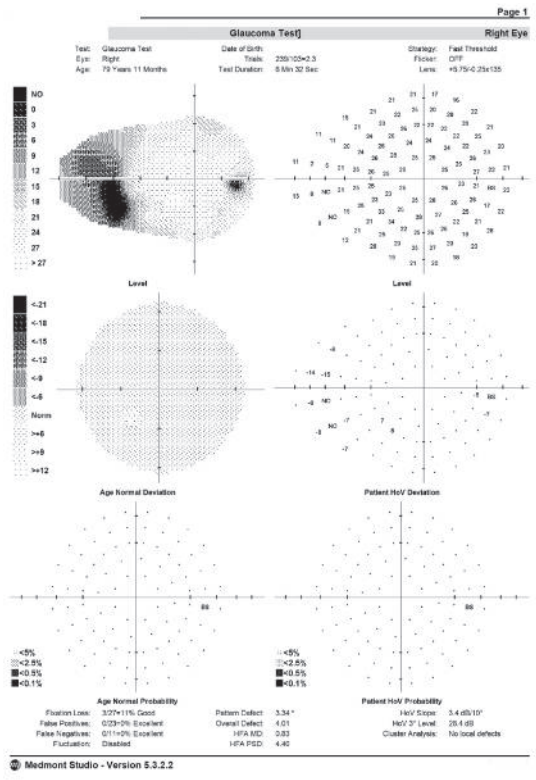
The patient was initiated on latanoprost 0.005% (Xalatan) nocte OU with the aim of achieving 30 per cent reduction in IOP and therefore, target pressures were set at 9.8 mmHg OU.

At the four-week review, IOP was measured as 8 mmHg OU (Perkins 10:00 am). The medical therapy was deemed to be successful.

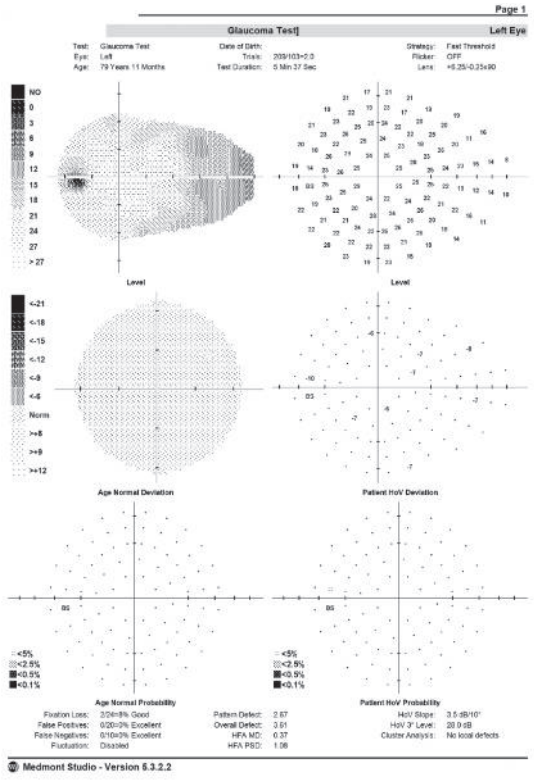
Discussion

The rate of progression in cases of untreated NTG is highly variable.[4,5] Some cases progress within a few months; however, about half show no progression within five years. About one-third of patients with untreated NTG will show localised progression (defined by a VF loss of at least 10 dB deterioration from baseline) within three years.[4]

Some cases never progress, while others demonstrate episodic failure.[6] For this reason and given that the average rate of deterioration is slow, clinicians may not need to initiate



▲ Figure 3. Visual field test, right eye (Medmont M700 Automated Perimeter)



▲ Figure 4. Visual field test, left eye (Medmont M700 Automated Perimeter)

treatment immediately.[4] The urgency and aggressiveness of therapeutic management in NTG should be decided on an individual basis, with consideration of the stage of the disease at presentation and the expected untreated trajectory for the individual.[5]

Risk factors that can act as prognostic indicators for progression of NTG are migraine, female gender and disc haemorrhage at diagnosis.[5] An optic disc haemorrhage is one of the most important risk factors for development and progression of glaucomatous VF deterioration.[7]

Optic disc haemorrhages are reported more frequently in NTG but are also observed in uncontrolled POAG, as they represent an active disease process.[7,8] Despite this, one study reported that of 23 patients with disc haemorrhages observed at the time of initial presentation, the course of the 11 subjects treated to lower the IOP was not statistically better than that of the 12 patients who were left untreated.[5,7] Evidence also suggests that recurrent disc haemorrhages show significantly more progressive VF loss compared with disc haemorrhages that were not observed to be recurrent.[7]

Although the presence of a disc haemorrhage suggests active glaucomatous disease, the appearance of the OCT and VF and a five-year history of annual monitoring without progression suggests that this particular individual has a slow rate of progression. This provides the managing clinician with the latitude to closely monitor the patient for evidence of progression without necessitating immediate treatment.

This is especially valid, given that this patient is 79 years old. A younger patient typically requires more aggressive treatment, as glaucomatous visual loss is more likely to occur in their lifetime.[1] Conversely, for an elderly patient, the decline in quality of life associated with use of medical therapy may outweigh the decline in quality of life associated with gradual visual deterioration, considering the financial expense of medications, the need to use them every day, physical ability to administer the drops and the adverse effects associated with their use.[9]

The need to preserve vision and the urgency to commence medical therapy may be more vital in patients with co-morbidity. For example, it may be reasonable to commence treatment sooner in a patient with macular degeneration, which is likely to impact central vision and therefore, preserving peripheral vision may be of higher importance. This patient did not have any relevant co-morbidity that would skew the risk-to-benefit analysis towards earlier or more aggressive treatment.

Given that this patient has not demonstrated progression throughout years of monitoring, and in light of the individual factors discussed above, a period of observation would have been a reasonable alternative management protocol.[8] If progression were observed, initiation of topical latanoprost would be sensible. A uniocular trial to determine if the treated eye fares better than the untreated eye should also be considered.[1,8]

As this patient has been diagnosed with NTG and initiated on medical therapy, she should be monitored every four to six months for the first two years to establish if the VF loss is progressing; stabilisation would warrant reduced review frequency.[1] ▲

1. NHMRC Guidelines for the screening, prognosis, diagnosis, management and prevention of glaucoma 2010. Australian Government, National Health and Medical Research Council. Commonwealth of Australia 2010.
2. Bowling B, Kanski JJ. Kanski's Clinical Ophthalmology. Edinburgh: Elsevier, 2015.
3. Kanski J, Nischal K, Milewski S. Ophthalmology. London: Mosby, 1999.
4. Collaborative Normal-Tension Glaucoma Study Group. Natural history of normal-tension glaucoma. *Ophthalmology* 2001; 108: 2: 247-253.
5. Anderson D, Drance S, Schulzer M. Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. *Am J Ophthalmol* 2003; 136: 5: 820-829.
6. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol* 1998; 126: 4: 487-497.
7. Suh M, Park K. Pathogenesis and clinical implications of optic disk hemorrhage in glaucoma. *Surv Ophthalmol* 2014; 59: 1: 19-29.
8. Anderson D. Normal-tension glaucoma (low-tension glaucoma). *Indian J Ophthalmol* 2011; 59: 7: 97.
9. Guedes R. Quality of life and glaucoma. *Revista Brasileira de Oftalmologia* 2015; 74: 3.

Diabetes on list of unusual associations related to IOP

IN THE LARGEST study of associations of intraocular pressure with demographic and systemic factors to date, researchers have demonstrated previously unknown differential associations. Among them are self-reported diabetes, mixed ethnicity and height.

Researchers explored associations within various physical and demographic factors for Goldmann-correlated IOP and corneal-compensated IOP. Systolic blood pressure and refractive error were found to be the strongest factors influencing both.

The study included 110,573 participants from the Biobank British cohort. Mean patient age was 57 years, with 54 per cent women and 90 per cent Caucasian. Participants underwent IOP readings on each eye using the Ocular Response Analyzer (Reichert) noncontact tonometer.

The mean Goldmann-correlated IOP (IOPg) was 15.72 mmHg, and the mean corneal-compensated IOP (IOPcc) was 15.95 mmHg. Both IOPg and IOPcc were significantly associated with older age, male sex, higher systolic blood pressure, faster heart rate, greater myopia, self-reported glaucoma and colder season, according to the study.

Researchers found the following variables had different directions of association with IOPg and IOPcc: height (-0.77 mmHg/m IOPg; 1.03 mmHg/m IOPcc), smoking (0.19 mmHg IOPg, -0.35 mmHg IOPcc), self-reported diabetes (0.41 mmHg IOPg, -0.05 mmHg IOPcc) and African American ethnicity (-0.80 mmHg IOPg, 0.77 mmHg IOPcc). Among those of mixed ethnicities, the increase in IOPg and IOPcc was the greatest, followed by African Americans and Caucasians.

Chan PY et al. Associations with intraocular pressure in a large cohort. *Ophthalmology* 2015; doi:http://dx.doi.org/10.1016/j.ophtha.2015.11.031.

Present and future treatment for age-related macular degeneration

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AGE-RELATED macular degeneration (AMD) is the leading cause of severe, irreversible vision loss in people over the age of 70 years in Australia.[1] There are two late forms of AMD in which vision is threatened: neovascular AMD (nAMD) (wet) and geographic atrophy (GA) (dry). Anti-vascular endothelial growth factor (VEGF) has revolutionised the treatment for nAMD. The two currently approved anti-VEGF treatments for nAMD are Lucentis (ranibizumab) and Eylea (aflibercept). Avastin (bevacizumab) is used off-label for the same indication.

The future treatment of nAMD focuses on the development of newer drugs with more ubiquitous blocking actions or with longer duration of action, thereby decreasing the frequency of the injections required. There is as yet no proven treatment for GA; however, several pharmaceutical studies are underway to determine the efficacy of possible treatments.

Neovascular AMD (wet AMD)

In patients who develop nAMD (Figure 1), there is often but not always a sudden blurring or distortion of vision. nAMD contributes to about 10 per cent of all AMD cases and had accounted for 90 per cent of severe vision loss from AMD prior to the era of anti-VEGF agents.[2]

To understand the mechanism by which anti-VEGF agents work in nAMD, it is useful to briefly review the current understanding of the aetiology of choroidal neovascular membranes (CNV). Abnormal blood vessels originate in the choroid which lies below the retina and supplies nutrients and oxygen to the outer retina. The pathological proliferation, migration and invasion of choroidal vessels, through Bruch's membrane, into the subretinal space are driven by a complex signal pathway.

VEGF is a key signalling molecule in the initiation of angiogenesis, and is produced by the retinal pigment epithelial (RPE) cells and acts on the endothelial cells. VEGF also increases permeability of the vessels so that the abnormal vessels bleed and leak fluid intraretinally and into the subretinal space, resulting in damage to retinal cells and long-term scarring. Anti-VEGF agents block the actions of circulating VEGFs, thereby reducing the stimulus for abnormal blood vessel growth.

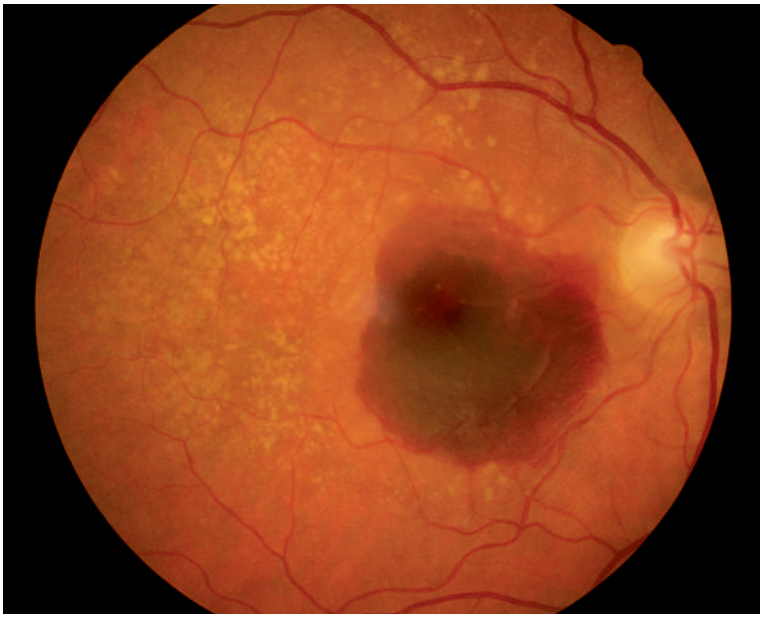
Ranibizumab (Lucentis)

Ranibizumab is an anti-VEGF agent designed for ocular use. It is a fragment of the monoclonal antibody fragment acting on VEGF-A, the most potent VEGF isoform in the pathogenesis of AMD. The landmark ANCHOR and MARINA studies showed that fewer subjects in the ranibizumab group had vision loss from baseline compared to the sham control group (90-95 per cent vs 60 per cent, respectively).[3,4]

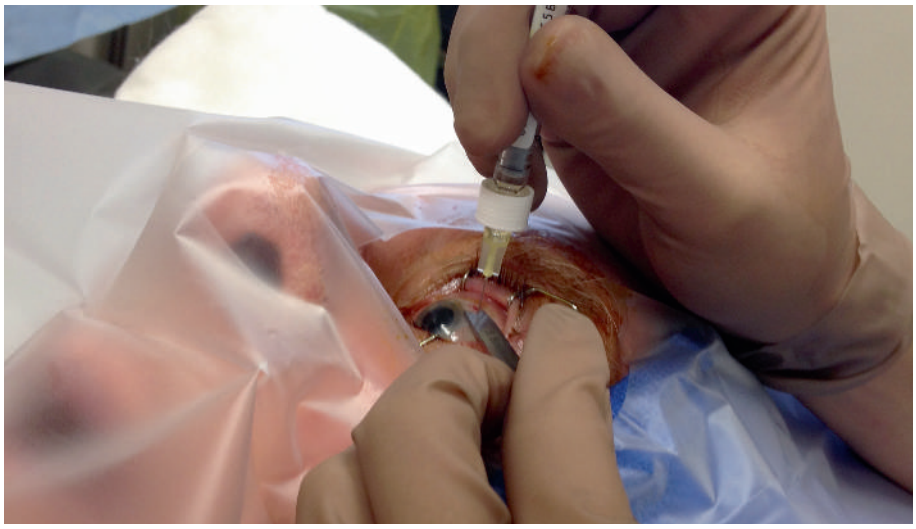
A significantly smaller number of patients in the ranibizumab group had severe vision loss comparing to the sham control group (one per cent vs 15 per cent). More people in the ranibizumab group gained vision compared to the sham control group (25-40 per cent vs six per cent, respectively). On average, the ranibizumab treatment group gained 7-11 letters of vision, while the control group lost an average of 10 letters. This translated to functional improvements for patients and improved quality of life.

Aflibercept (Eylea)

Aflibercept is a fusion protein that imitates VEGF receptors. It binds with high affinity with multiple agents in the VEGF family such as VEGF-A,



▲ **Figure 1.** Neovascular AMD with subretinal blood



▲ **Figure 2**. A patient receiving an intravitreal injection

VEGF-B and placental growth factors. It consequently inhibits activation of the receptors and stops the undesired effects of angiogenesis. The evidence for its use in AMD is from the VIEW1 and VIEW2 studies. These studies demonstrated that with two doses (0.5 mg and 2 mg) and a two-dosing regimen (four-weekly or eight-weekly), each treatment arm was not inferior to monthly ranibizumab.[5]

Bevacizumab (Avastin)

Bevacizumab is a full-size monoclonal antibody which binds to VEGF. It was designed to stop angiogenesis in various cancers. Although it was not specifically designed for the eye and its use is off-label, it is effective in the eye. The CATT study was a head to head comparison of ranibizumab and bevacizumab.[6] With the same treatment regimen, bevacizumab was not inferior to ranibizumab for nAMD treatment. When unsubsidised, bevacizumab is less expensive than other anti-VEGF agents and as such is offered alongside the approved therapeutic agents.

Methods of administration and risks

All the anti-VEGF agents are administered as an injection into the vitreous under an aseptic technique (Figure 2). It is a 15-minute procedure commonly performed in treatment rooms or the ophthalmologist's rooms. Topical ± subconjunctival anaesthesia is used at the time of injection to reduce discomfort. After the injection, it is common for the patient to have some ocular discomfort, conjunctival haemorrhage and vitreous floaters. The risk of endophthalmitis, non-infectious uveitis, retinal tear and cataract are rare but can be devastating for the long-term health of the eye.

Treatment protocols

As we become more familiar with the use of anti-VEGF medications, clinicians have tried to individualise the dosing schedule based on treatment responses. Common treatment protocols practised include:

- strict monthly treatment
- treat as required (PRN)
- treat and extend.[7]

The strict monthly treatment schedule is based on initial pharmaceutical studies in which patients were injected every month regardless of their response to the treatment. No active management decision needed to be made in this approach as all patients received the same treatment schedule.

Treat as required is an alternative treatment protocol. In the setting, after initial disease stabilisation, the patient is reviewed every month to check for disease activity and is injected only when there is clinical or OCT evidence of disease activity.[8] If no disease activity is noted, the patient is not injected and is reviewed again in another month. This protocol usually results in more visits but fewer injections than the treat and extend protocols.

Treat and extend is widely practised in Australia. The principle of this treatment protocol involves initial monthly treatment with anti-VEGF agents until there is no further improvement in the patient's vision and no signs of activity are noted: fresh haemorrhage, or intraretinal or subretinal fluid as determined on high resolution optical coherence tomography (OCT). The treatment interval is then extended by 1-2 weeks each visit. At each visit, the clinical and OCT signs of disease activity are monitored. If there is a recurrence of disease activity, the treatment interval is then shortened.

Over time we can individualise treatment and achieve an optimal treatment interval for each patient depending on their response to the administered drug. The treat and extend protocol reduces the number of visits compared to a monthly visit schedule. One can consider the treat and extend protocol as proactive, aiming to prevent the eye from reactivating, and the PRN protocol as reactive, with people receiving an injection only when the disease is active.

Future treatment for neovascular AMD

The new treatments under investigation for nAMD falls under two objectives: either to increase the duration between treatments or to have more effective treatments, which translates to more visual gains for the patient. Below are some of the studies underway in nAMD.

- **HAWK study (Alcon)**

The phase 3 study is investigating RTH258, a single chain antibody fragment, comparing its efficacy to aflibercept. RTH258 binds to VEGF-A with high affinity. The aim is to have a longer duration of action with three-monthly interval treatments, thus reducing the treatment burden.

- **Fovista study (Ophthotech)**

The phase 3 study is investigating an anti-platelet-derived growth factor (anti-PDGF). It targets another signal in the pathway of angiogenesis. With the promise of synergistic action by combining with an existing anti-VEGF

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Present and future treatment for AMD

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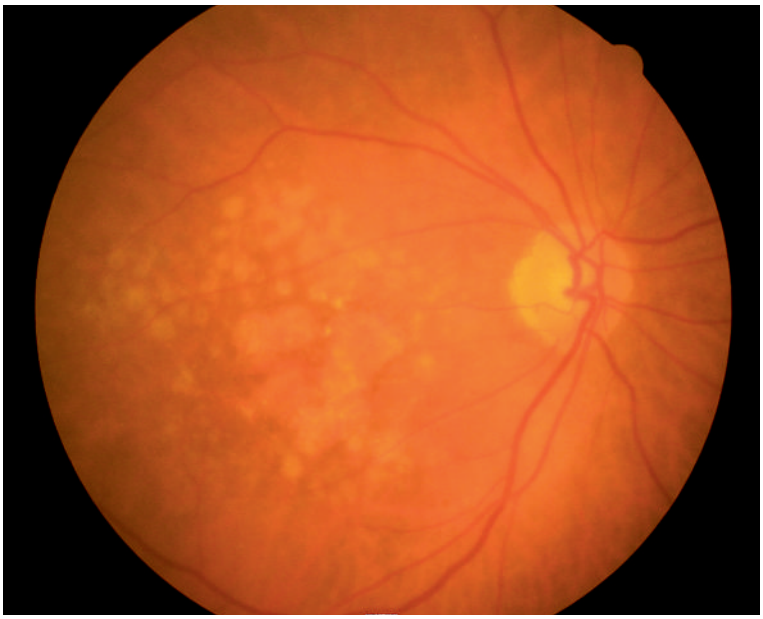
agents, it promises to increase visual gain compared to the use of anti-VEGF agent alone.

- **Sequoia study (Allergan)**

The phase 3 trial is investigating abicipar, which is another antibody that binds to VEGF-A. It claims that with its small size, high potency and long intravitreal half-life, it would result in less frequent injections than ranibizumab.



▲ **Figure 3**. Advanced geographic atrophy

Geographic atrophy

Geographic atrophy (Figure 3), although having a slower onset than nAMD, is still associated with significant and permanent vision loss. It is four times more common than nAMD in people over the age of 85 years.[9] Clinically, it is identified as areas of macular depigmentation with underlying choroidal vessels visible. Histologically, it corresponds to atrophy of RPE and photoreceptors. These changes often initially start in the peri-foveal region and as the disease advances it encroaches on the fovea, and the patient experiences central vision loss.

There is currently no available treatment to slow the progression of GA; however, new treatments are starting to be investigated. The end goal of these ongoing studies is to measure a decrease in the rate of growth of GA compared to the control subjects. To reliably measure the area of GA and document change, only patients with reasonably large areas of GA qualify for enrolment.

- **Lampalizumab (Hoffmann-La Roche)**

This is a phase 3 study of lampalizumab, a drug that acts to inhibit the complement pathway. It is also administrated in the form of intravitreal injections, the end point is to assess its effectiveness in slowing GA progression.

- **BEACON study (Allergan)**

This is a phase 2 study of brimonidine, a selective alpha-2-adrenergic agonist currently used as topical therapy for glaucoma. It is postulated to have neuroprotective properties via the activation of the alpha-2-adrenoceptor and inhibiting apoptosis, thereby slowing the progression of GA.

- **FILLY study (Apellis Pharmaceuticals)**

The phase 2 study is investigating APL-2 therapy which acts to inhibit the complement pathway. It is under trial for its safety and effectiveness in stabilising the size of GA. The subjects receive the injection every four to eight weeks.

Conclusion

There has been a revolution in the treatment outcomes for people with nAMD. In the past 10 years, the anti-VEGF treatments have more than halved the rates of blindness from this complication.[10] For the first time in the treatment history of nAMD, improvement in vision is a possibility. The future of nAMD treatment holds promise of agents that work more effectively to improve vision and have potentially longer duration of action. For GA, multiple new agents are already in phase 2 or 3 studies with the aim of slowing the progression of GA. ▲

1. Wang JJ, Foran S, Mitchell P. Age-specific prevalence and causes of bilateral and unilateral visual impairment in older Australians: the Blue Mountains Eye Study. *Clin Exp Ophthalmol* 2000; 28: 4: 268-273.
2. Bressler NM, Bressler SB, Fine SL. Age-related macular degeneration. *Surv Ophthalmol* 1988; 32: 6: 375-413.
3. Brown DM, Michels M, Kaiser PK et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology* 2009; 116: 1: 57-65.e5.
4. Rosenfeld PJ, Brown DM, Heier JS et al. Ranibizumab for neovascular age-related macular degeneration. *New Eng J Med* 2006; 355: 14: 1419-1431.
5. Heier JS, Brown DM, Chong V et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012; 119: 12: 2537-2548.
6. Martin DF, Maguire MG, Ying GS et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *New Eng J Med* 2011; 364: 20: 1897-1908.
7. Abedi F, Wickremasinghe S, Islam AF et al. Anti-VEGF treatment in neovascular age-related macular degeneration: a treat-and-extend protocol over 2 years. *Retina* 2014; 34: 8: 1531-1538.
8. Lalwani GA, Rosenfeld PJ, Fung AE et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol* 2009; 148: 1: 43-58.e1.
9. Klein R, Klein BE, Knudtson MD et al. Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology* 2007; 114: 2: 253-262.
10. Buckle M, Lee A, Mohamed Q et al. Prevalence and incidence of blindness and other degrees of sight impairment in patients treated for neovascular age-related macular degeneration in a well-defined region of the United Kingdom. *Eye* (London, England) 2015; 29: 3: 403-408.

Dive into the detail

PBS Information: Authority required for the treatment of wet age-related macular degeneration, diabetic macular oedema and central retinal vein occlusion. Refer to PBS schedule for full Authority Required information.
EYLEA is not listed on the PBS for branch retinal vein occlusion and myopic choroidal neovascularisation.

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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); visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)*; diabetic macular oedema (DME), visual impairment due to myopic choroidal neovascularisation (myopic CNV)*. **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, myopic CNV: no experience in the treatment of non-Asian patients, previous treatment for myopic CNV and extrafoveal lesions*); see full PI for effects on fertility, pregnancy, lactation, effects on ability to drive or use machines. **ADVERSE EFFECTS:** Very common: visual acuity reduced*, conjunctival haemorrhage, eye pain. Common: retinal pigment epithelial tear, detachment of retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract, cataract cortical, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, 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*:** 2 mg aflibercept (equivalent to injection volume of 50 µL). EYLEA is for intravitreal injection only. The interval between doses injected into the same eye should not be shorter than one month. Advice on treatment initiation and maintenance of therapy specific to each patient population is described in the section below. 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 BRVO:* 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. *For myopic CNV:* EYLEA treatment is initiated with one injection of 2 mg aflibercept (equivalent to 50 µL). Additional doses should be administered only if visual and/or anatomic outcomes indicate that the disease persists. Recurrences are treated like a new manifestation of the disease. **DATE OF PREPARATION:** Based on PI dated April 2016. Approved PI available at http://www.bayerresources.com.au/resources/uploads/PI/file10294.pdf or upon request from Bayer Australia Ltd, ABN 22 000 138 714, 875 Pacific Highway, Pymble NSW 2073.

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