

# Considerations in the management of retinal disorders

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Vision research presentations and publications explore practice considerations in the management of AMD and diabetic retinopathy.

Over the past two decades in Europe there has been a decreasing prevalence of age-related macular degeneration (AMD) and an improvement in visual acuity (VA) in choroidal neovascularisation (CNV), findings shown in a pan-European meta-analysis of prevalence data between 1990 and 2013 [1]. Study authors further observed a decreasing prevalence of late AMD after 2006, attributed in part to the implementation of anti-vascular endothelial growth factor (anti-VEGF) treatment. Nevertheless, with projections of AMD showing an almost doubling of affected persons despite a decreasing prevalence, AMD remains a significant public health challenge across Europe.

## AMD and anti-VEGF therapy

The Comparison of AMD Treatments Trials (CATT) Follow-up Study (mean 5.5 years) of long-term outcomes after initiation of anti-VEGF treatment for neovascular AMD (nAMD) reported a decrease in vision to below baseline VA at five years, with a mean change in VA of -11 letters from two years after release from the clinical trial protocol and subsequent treatment given according to best medical judgement [2]. Decreased vision was accompanied by expansion of the size of the total neovascular complex composed of neovascularisation, scarring

and atrophy, and by persistence of fluid on optical coherence tomography (OCT).

A small subset of eyes (7.1%) in this follow-up study had a VA of 20/40 or better at year five despite receiving no treatment after year two. Baseline characteristics associated with good VA at five years despite no treatment after two years included younger age, better VA, blocked fluorescence associated with the CNV lesion, absence of late AMD in the fellow eye, and no retinal pigment epithelium elevation on OCT scans [3].

Investigators noted that more frequent treatment, both in the initial two years and in later years, appears associated with better long-term outcomes, and that many patients require continuing treatment through five years and beyond.

Interestingly, a secondary analysis of the CATT data evaluated the effect of intraocular pressure (IOP)-lowering medications on treatment outcomes [4]. Concurrent use of aqueous suppressants (e.g. beta-blockers) during anti-VEGF treatment for nAMD was associated with improved visual outcomes and greater reductions in total retinal thickness on OCT after two years, compared with controls on no IOP-lowering medications. Future prospective studies are planned. Results of a prospective single-arm interventional study suggest that a supplemental regimen of topical dorzolamide-timolol twice daily may reduce central subfield thickness and subretinal fluid in nAMD eyes with persistent exudation despite anti-VEGF treatment [5].

Other clinical studies and clinician experience confirm better vision outcomes may be achieved with a more intensive scheduled anti-VEGF dosing regimen compared with as-needed treatment regimens entailing less frequent dosing. A multicentre, national electronic medical record (EMR) study compared the effectiveness of predominantly as-needed (PRN, pro re nata) ranibizumab (Lucentis, Novartis) versus continuous aflibercept

(Eylea, Bayer) therapy in treatment naïve nAMD eyes from 21 UK hospitals [6]. Fixed or treat-and-extend aflibercept treatment achieved greater VA gains from baseline at one year than PRN ranibizumab: patients receiving aflibercept (7.0 injections overall) gained 6.1 Early Treatment Diabetic Retinopathy Study (ETDRS) letters compared with an improvement of 1.6 ETDRS letters for patients treated with PRN ranibizumab (5.8 injections).

## Prevalence of PCV in Caucasians higher than previously reported, audit shows

It has been previously reported that nAMD refractory to anti-VEGF monotherapy treatment may harbor undetected polypoidal choroidal vasculopathy (PCV) and that indocyanine green angiography (ICG) imaging at baseline can help reveal polypoidal lesions [7]. Previous estimates have suggested that PCV is rare in Caucasians, accounting for only 4% of occult lesions.

A review of the prevalence of PCV in a Caucasian population referred to a city AMD service in Liverpool over a two-year period identified PCV in 9.1% of all nAMD patients and 22.1% of occult nAMD patients (735 cases, with 492 diagnosed with nAMD) [8]. These prevalence rates are higher than previously reported and confirm that PCV is a common type of nAMD in Caucasians. Review authors recommended that ICG should be considered at initial presentation for new patients with nAMD, particularly those with occult nAMD, so as to avoid missing this important and challenging subtype of nAMD. Of the 45 patients identified with PCV, 23 received anti-VEGF monotherapy, six received verteporfin photodynamic therapy (PDT) alone and 14 patients were managed with combined PDT and anti-VEGF therapy.

In the ongoing, 24-month, phase IV, double-masked, multicentre EVEREST II study in Asian patients with symptomatic

**“With a doubling of affected persons despite a decreasing prevalence, AMD remains a significant public health challenge across Europe.”**

macular PCV, combination PDT with ranibizumab was superior to ranibizumab monotherapy in improving VA and in achieving complete polyp regression at 12 months [9]. Another study in Asian patients with PCV evaluated the efficacy and safety of intravitreal aflibercept monotherapy compared with aflibercept plus active verteporfin PDT. Outcomes demonstrate that aflibercept monotherapy was noninferior to aflibercept plus PDT for the primary endpoint of mean change in best corrected visual acuity (BCVA) [10]. The mean change in BCVA ETDRS letter score over 52 weeks was +10.7 letters and +10.8 letters in the aflibercept monotherapy (n=157) and aflibercept plus active PDT (n=161) arms, respectively. The vast majority (85.7%) of patients in the monotherapy arm did not require additional rescue therapy with PDT and received only aflibercept every eight weeks after three initial monthly doses. Presenting the results at the 2017 ARVO annual meeting in Baltimore, USA, Professor Won Ki Lee, Seoul St Mary's Hospital, Catholic University of Korea, South Korea, commented that these data suggest that aflibercept monotherapy is an effective treatment for patients with PCV, with supplemental PDT providing no additional visual benefit.

### Optimising anti-VEGF treatment strategies for retinal disease

Professor Sebastian Wolf, University Clinic for Ophthalmology, Inselspital, University Hospital Bern, Switzerland, discussed approaches to optimising treatment strategies for chronic retinal diseases in a keynote lecture during the RCOphth 2017 Annual Congress Retina Day. The treatment regimen with anti-VEGF therapy for retinal disease should aim to maximise and stabilise visual outcomes and reduce treatment burden [11]. He added that anti-VEGF maintenance therapy using a treat-and-extend dosing regimen can help optimise long-term outcomes and lower the burden of treatment for the patient.

For patients, treat-and-extend allows

anti-VEGF treatment to be tailored according to disease severity and outcomes, while potentially minimising hospital visits as no interim monitoring visits are required. A treat-and-extend regimen provides a balance between the risk of overtreatment with fixed regimens and undertreatment associated with reactive as-needed treatment regimens, and offers the potential for less frequent severe relapses. More consistent clinic processes for every patient may also strengthen overall treatment capacity. Experience at the Bern clinic indicates that a treat-and-extend approach leads to good visual and anatomical outcomes with mean treatment intervals exceeding nine weeks. Feedback from patients shows very high acceptance of a treat-and-extend approach, added Prof Wolf.

Four key principles have been proposed as fundamental to an ideal treatment regimen for anti-VEGF management of chronic retinal disorders: maximise and maintain VA benefits for all patients; decide when to treat next, rather than whether to treat now; titrate the treatment intervals to match patients' needs; and treat at each monitoring visit [11]. Early initiation of therapy and a sufficient frequency of injections are both essential for maximising and maintaining gains in VA. A treat-and-extend regimen represents a more proactive treatment approach, with the goal of preventing disease recurrence, than treating only when there are signs of exudative disease activity. Treatment is administered at every scheduled visit. However, the interval between each visit is either increased or decreased according to the anatomic and VA status, to determine the maximum time between injections without disease recurrence, i.e. the maximum recurrence-free interval.

### Management of DMO: guidelines and debate

Guidelines for the management of diabetic macular oedema (DMO) by the European Society of Retina Specialists (EURETINA),

published in May 2017, confirm that intravitreal anti-VEGF treatment has emerged as first-line therapy for DMO, displacing laser treatment as standard of care due to clear superiority over laser in visual and anatomic outcomes [12].

Relative indications for laser treatment include the vasogenic subform of DMO, eyes affected by DMO with central retinal thickness less than 300µm or eyes with persisting vitreomacular adhesion. Subthreshold grid laser treatment can also be of help in eyes with higher VA affected by early diffuse DMO. Steroids maintain a role in the management of chronically persistent DMO and pseudophakic patients are preferred for the use of steroids due to the high risk for cataract progression.

EURETINA guidelines recommend effective coordinated management of systemic diabetic disease [12]. Ophthalmologists have an important responsibility to instruct the patient about the need to have the diabetic control consolidated. Findings from the National Diabetes Audit regarding attainment of key treatment targets are shown in Table 1. Younger people with type 1 or type 2 and other diabetes are less likely to achieve all three treatment targets than their older counterparts, primarily due to poorer glucose and cholesterol control in those aged under 65 years.

The role of combination therapy for DMO was explored in a debate during the RCOphth 2017 Annual Congress Retina Day. Ben Burton, James Paget University Hospital, Great Yarmouth, argued that it not yet known what the 'best' treatment of DMO is, but all that can be said with certainty is that no single therapy on its own is the best therapy. The pathophysiology of DMO is complex. Retinal vascular leakage in DMO is contributed to by VEGF upregulation as well as non-VEGF-dependent inflammatory pathways, so that chronic subclinical inflammation is important in the pathogenesis of diabetic retinopathy [13]. Mr Burton argued that the best therapy currently available is

**Table 1: National Diabetes Audit 2015-2016: percentage of diabetes patients (total registrations 2.7m) attaining NICE-defined treatment targets for glucose control, blood pressure and blood cholesterol in England and Wales.**

	Type 1 Diabetes	Type 2 Diabetes and other
HbA1c ≤58 mmol/mol (≤7.5%)	29.2%	65.7%
Blood pressure ≤140/80	74.2%	73.6%
Cholesterol <5 mmol/L	70.8%	77.1%
<b>Meeting all three treatment targets</b>	<b>18.1%</b>	<b>40.2%</b>

Abbreviations: National Institute for Health and Care Excellence, NICE; Haemoglobin A1c, HbA1c.

Source: Adapted from: National Diabetes Audit. Report 1: Care processes and treatment targets, 2015-2016. Published by NHS Digital. Copyright 2017, the Healthcare Quality Improvement Partnership, National Diabetes Audit.

likely to include medications to combat systemic features and intravitreal anti-VEGF injections, perhaps in combination with long-acting steroids or laser and possibly new modalities such as polyphotonics light mask and micropulse laser.

Christopher Brand, The Royal Hallamshire Hospital, Sheffield, spoke against the motion that combination therapy is the best treatment for DMO, suggesting that laser treatment is obsolete as a first-line treatment for central-involved DMO in the current era of intravitreal anti-VEGF therapy. In the Diabetic Retinopathy Clinical Research network (DRCR.net) Protocol I study in DMO, at year one and two, ranibizumab treatment resulted in significantly more eyes with a BCVA gain of  $\geq 15$  letters than sham + laser [14]. Most eyes receiving ranibizumab and either prompt or deferred laser maintained the vision gains obtained during the first year through five years with little additional treatment after three years [15]. Three-year results from the VISTA DME and VIVID DME phase III trials comparing the efficacy of aflibercept with macular laser photocoagulation for DMO show a mean BCVA improvement from baseline to week 148 of 10.5 to 11.7 letters for patients treated with aflibercept every eight weeks after five monthly doses compared with a gain of between 1.4 and 1.6 letters for laser control [16].

Anti-VEGF monotherapy treatment improves vision, stops patients losing vision, reduces macular oedema, and allows more patients to maintain or attain driving-vision standard, explained Mr Brand. Anti-VEGF drugs are effective at improving vision in people with DMO with three to four in every 10 people likely to experience an improvement of three or more lines of VA at one year [17].

That said, in real-world clinical practice people in need of antiangiogenic treatment may often be undertreated or not monitored at regular intervals. The UK AMD and DR EMR Users Group evaluated baseline characteristics and outcomes from a multicentre database of eyes treated with intravitreal ranibizumab for DMO (12,989 clinic visits at baseline and follow-up for 3103 eyes) [18]. For eyes followed for at least two years, mean VA letter score was 51.1 at baseline, 54.2 at one year and 52.5 at two years, respectively. Eyes followed for at least six months received a mean of 3.3 injections in one year. The proportion of eyes with a VA better than or equal to 6/12 ( $\geq 72$  letters) increased from 25% at baseline to 33% at one year for treatment naïve eyes.

The DRCR.net acknowledges the need for alternative or additional treatments that will improve vision by reducing retinal oedema in eyes with persistent DMO

following previous anti-VEGF therapy. Intravitreal steroid therapy is not as efficacious as anti-VEGF therapy in eyes with central-involved DMO overall, but has been shown to have a positive effect for DMO in some eyes and might add benefit in eyes that are already receiving anti-VEGF therapy with recalcitrant or insufficiently responsive oedema.

Khan et al. reported results of a meta-analysis assessing the short-term efficacy of sustained-release dexamethasone implant (Ozurdex, Allergan) for DMO refractory to anti-VEGF therapy, showing significant mean improvement in VA in patients with recalcitrant DMO [19]. The authors recommended that clinicians should have a multimodality approach to treating DMO and be aware of this treatment option in those who have a suboptimal response to anti-VEGF therapy.

Results from across 14 UK clinical sites show that intravitreal fluocinolone acetonide (Iluvien, Alimera Sciences) is a useful treatment option for patients with chronic DMO that have not responded adequately to prior DMO therapies (345 eyes with a mean follow-up of 428 days) [20]. Mean best-recorded VA increased from 51.9 letters at baseline to 57.2 letters at 24 months (n=53). Fluocinolone implant treatment was associated with sustained or improved vision for 86.7% of patients at 24 months and 20.8% achieved a  $\geq 15$  letter improvement from baseline. Approximately one-third of patients (35.7%) received additional treatments for DMO post fluocinolone acetonide injection.

### Alternative potential approaches for proliferative diabetic retinopathy

Proliferative diabetic retinopathy (PDR) is a leading cause of blindness if left untreated. While panretinal photocoagulation (PRP) has been the time-tested standard of care for PDR for over four decades, emerging evidence suggests that intravitreal anti-VEGF agents could potentially be of value as a reasonable treatment alternative for patients with PDR without vision-impairing DMO.

Trial outcomes show that ranibizumab for PDR is at least as good as (noninferior to) PRP for mean VA change at two years, representing an effective treatment alternative to PRP for PDR [21]. Visual field loss was worse in the PRP group, while vitrectomy was more common and DMO developed more frequently in the PRP group. In April 2017, the United States Food and Drug Administration (FDA) approved ranibizumab 0.3mg for the monthly treatment of DR without DMO, based on an analysis of the DRCR.net Protocol S study.

Conducted in the UK, an investigator-initiated, randomised, non-inferiority study evaluated the clinical efficacy of intravitreal aflibercept versus PRP for BCVA in patients with active PDR and no baseline DMO (n=232). One-year results from the CLARITY study demonstrate that aflibercept was noninferior and superior to PRP, with a mean BCVA difference of 3.9 and 4.0 letters in the modified intention-to-treat population and per-protocol population, respectively [22]. There was less chance of incident vitreous haemorrhage or new-onset DMO with aflibercept therapy. Other DR assessments show that 64% of aflibercept-treated patients had 'total regression' compared with 34% of patients treated with PRP (P<0.0001). Mean number of aflibercept injections over 52 weeks was 4.4, with a mean of 1.4 treatments required during the 40-week post-loading phase; supplemental PRP was rarely required (1%).

Investigators concluded that visual outcomes in patients with PDR treated with intravitreal aflibercept are superior to PRP over one year, with fewer vision-related adverse events. Longer follow-up studies are required to determine whether the observed anti-VEGF treatment effects at one year are sustained over subsequent years.

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