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Recent advances in age-related macular degeneration

Rasika Mohrir

Richard P Gale BSc MBChB FRCP FRCOphth MEd PhD

Professor of Ophthalmology
Hull York Medical School, University of York

Honorary Consultant Medical Ophthalmologist
York and Scarborough Teaching Hospitals NHS foundation Trust

Age-related macular degeneration (AMD) remains one of the leading causes of visual loss globally in patients over the age of 50 in the western world.[1] It has been widely stated that almost 600,000 people in UK are affected, with significant implications on quality of life, due to increased risk of falls, social isolation, mental health issues, care giver burden and mortality.

The more advanced forms of AMD are of two types, neovascular AMD (nAMD) and geographic atrophy (GA).

The introduction of anti-vascular endothelial growth factor (VEGF) treatment has revolutionised the treatment paradigm for nAMD. Many individuals can now achieve a Snellen visual acuity of around 6/12 with treatment. This has been reflected in declining rates of severe sight impartment registration and registries such as the National Ophthalmology Database (NOD).

It has been demonstrated that achieving good visual acuity (VA) is dependent upon early diagnosis, good starting VA, and timely treatment. The Early Detection of Age-Related Macular Degeneration (EDNA) and the Fibrosis, Atrophy and Subretinal Highly Reflective Material (FASBAT) studies showed the benefit of using optical coherence tomography (OCT) for early diagnosis in the second eye. Ongoing work is required to determine the likely benefit of utilising a similar strategy to enable early detection and maintenance of quality of life in first eyes.

However, despite the advances in treatment options, many ophthalmology units still struggle to achieve the recommended timeframe of treatment delivery due to the increasing burden of the disease. It has also transpired that the effectiveness of newer generation treatments for nAMD are unlikely to improve visual acuity greater than the established anti VEGF treatments. But instead, they will aim to provide increased durability by using novel mechanisms of action or higher molar doses.

In May 2022, National Institute for Health and Care Excellence (NICE) approved the use of faricimab (Vabysmo, Roche), a bispecific antibody that binds to and inhibits both VEGF-A and angiopoietin-2 (Ang-2). Clinically equivalent visual gains were found in the paired phase 3 Tenaya and Lucerne trials in which faricimab was compared with aflibercept 2mg [2,3]. Furthermore, in the faricimab arm at 48 weeks at least 79% of patients achieved a 12-week retreatment interval and 45.3% achieved 16-week retreatment interval. At an early matched phase in the study, faricimab appeared to dry the retina better than aflibercept. The faricimab retreatment criteria used in these studies was atypical 'treat and extend' posology which is used by many in the UK but a similar approach.

Aflibercept 8mg (Bayer), studied in the Phase 3 Pulsar trial, aimed to achieve longer retreatment intervals by using a higher molar concentration of aflibercept.[4] At time of writing, it is yet to be approved for use in the UK. The Pulsar study[4] demonstrated that aflibercept 8 mg, 12- and 16-week dosing regimens achieved non-inferiority in vision gains compared to the aflibercept 2mg at 8-week dosing regimen. Around 79% study patients maintained 12 weekly dosing and 76% maintained a 16 weekly treatment regime. Again, the retreatment interval was not entirely the typical treat and extend that is used by many clinicians.

Another concept being trialled is the Port Delivery System (PDS) (Roche). This implant is surgically placed via the pars plana and acts as a reservoir of a specific preparation of ranibizumab, refilled every 6 months. In the Archway study, which studied previously treated patients through to week 96, the PDS treated group had equivalent visual acuity outcomes to the monthly ranibizumab arm.

Apart from these treatment modalities, multiple new innovations such as delivery through the subretinal space, new target molecules and the use of nanoparticles are under investigation. Despite many of these novel mechanisms being further away from clinical use, there is much enthusiasm of the potential benefits they could bring. One such area, gene therapy aims to provide a sustained expression of Anti -VEGF protein with a single injection.

Ixo-Vec /ADVM-022 (Adverum Biotechnologies) and RGX-314 (Regenxbio) are utilised in clinical trials for AMD treatment. The Optic phase 1 trial[5] showed that with a single intravitreal injection of ADVM-022, there was sustained long term expression of an Aflibercept like protein for almost 24 weeks. The RGX-314 (AAV-8 associated gene therapy) expresses a ranibizumab like monoclonal antibody fragment. The Atmosphere trial[6] is

evaluating a subretinal route of administration while the Phase 2 Aaviate trial[7] aims to assess the suprachoroidal route for nAMD patients. So far efficacy data of these trials is promising.

Around eight out of 10 patients with AMD have the dry form, of which geographic atrophy is the most severe manifestation. Geographic atrophy is driven by local inflammation as seen by increased peri-lesional autofluorescence on autofluorescence imaging. In February 2023 the Food and Drug Administration (FDA) approved Pegcetacoplan (Apellis) for treatment of Geographic Atrophy. Pegcetacoplan is a cyclic peptide that inhibits Complement C3, a significant molecule in the complement cascade that is an important part of the innate immune system.

The paired Phase 3 Oaks and Derby studies demonstrated that either monthly or every other month intravitreal treatment reduced lesion growth by 22% (Oaks) and 19% (Derby) respectively compared with sham over 24 months[8]. Visual acuity remained comparable between the groups. Post hoc analysis, has demonstrated that it may be more effective in the preservation of VA in those with extrafoveal lesions. At the time of writing, European Medicines Agency (EMA) approval is being sought.

Approximately 40,000 new individuals per year developing geographic atrophy with significant challenges remain ahead. If Pegcetacoplan is approved. The NICE will have to determine whether and which individuals will be provided access and funding for treatment. In addition, greater clinical capacity would be required to take on the increased demand for treatment. Furthermore, new referral pathways will need to be developed to enable appropriate patients from the community to reach treatment.

The precursor to end-stage AMD is intermediate AMD with some treatments now commercially available. The Lightsite 3 study using the Valeda system (LumiThera) a technology that applies near infrared light in multiple treatment cycles to the retina of participants with dry AMD. Near Infrared Spectrum light (600–1000 nm) can be absorbed by mitochondrial Cytochrome C in the retinal pigment epithelium. It acts to improve cellular respiration by increasing ATP production, reducing free radicals production as well as decreasing oxidative stress. The Lightsite 3 study showed treated patients had a reduction in drusen volume, reduced risk of progression to GA and an improvement in visual acuity; however the number of participants in the trial was small.

One of the challenges relating to new agents is the increased frequency of intraocular inflammatory events as higher concentrations and more complex proteins and protein like materials are injected into the eye. As a community, we will need to be more vigilant of the extent of inflammation, its frequency, and potential consequences with these novel therapies. One recent example was the increased rates of occlusive retinal vasculitis seen with brolucizumab, a novel ant-VEGF treatment for nAMD. This complication has led to the limited use of brolucizumab. There has been small number of reports of intraocular inflammation with Pegcetacoplan.

While the complexities of managing AMD may pose challenges for healthcare systems, the progress in research and treatment options brings hope for better outcomes for those affected by the disease.

Pouya Alaghband
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