What Is the Best Neovascular Age-related Macular Degeneration Treatment Regime for 2016?

Richard P Gale¹ and Reema Gupta²

1. Consultant Medical Ophthalmologist and Honorary Senior Clinical Lecturer, Academic Unit of Ophthalmology, York Hospital, York, UK;
2. Clinical Research Fellow, Academic Unit of Ophthalmology, York Hospital, York, UK

Abstract
The management of neovascular age-related macular degeneration (nvAMD) has evolved significantly over the last few years with a significant step forward being taken with the advent of intravitreal therapy. Many different treatment regimens can be used, and the goal of treatment is shifting away from just salvaging vision to include reducing treatment burden on patients, carers and healthcare systems. This editorial discusses the common treatment regimens and proposes a pragmatic way of treating patients in three steps: (1) initiating a treatment, (2) finding the appropriate re-treatment interval and (3) fixing the re-treatment interval.

Keywords
AMD, neovascular AMD, anti-VEGF, posology

Disclosures: Richard P Gale has received consultancy, lecture fees, local Principles Investigator and/or research grants from Novartis and Bayer. Reema Gupta has nothing to declare in relation to this article. No funding was received in the publication of this article.

Open Access: This article is published under the Creative Commons Attribution Noncommercial License, which permits any non-commercial use, distribution, adaptation and reproduction provided the original author(s) and source are given appropriate credit.

Received: 30 October 2015 Published online: 21 December 2015 Citation: European Ophthalmic Review, 2015;9(2):157–8

Correspondence: Richard P Gale, Consultant Medical Ophthalmologist and Honorary Senior Clinical Lecturer, Academic Unit of Ophthalmology, York Hospital, Wigginton Road, York, YO31 8HE York, UK. E: richard.gale@york.nhs.uk

Age-related macular degeneration (AMD) is the leading cause of central visual loss and legal blindness in patients over the age of 65 years.¹² The exudative or neovascular form of AMD accounts for over 90 % of the cases with severe visual loss.³

AMD is a highly complex disease with demographic, environmental and genetic risk factors. The pathogenesis of AMD lesions remains largely unclear and current evidence suggests that AMD results from genetic predisposition and a combination of metabolic and inflammatory insult to photoreceptors and retinal pigment epithelium (RPE).⁴

The Seven Year Update of Macular Degeneration Patients (SEVEN-UP) study helped elucidate the challenges of long-term management of neovascular AMD (nvAMD), in particular that it is a chronic disease and that the patients remain at risk of vision loss many years after the treatment.⁵

There is a need to find the best treatment regime for nvAMD that optimises visual outcomes and safety while minimising burden to patients, carers and healthcare providers (see Table 1). This editorial focuses on the pros and cons of current nvAMD treatment regimens and proposes a regimen appropriate for 2016.

Studies directly comparing treatment regimens are often complicated by the usage of different drugs, a retrospective nature, single-arm design or cross-study comparison, so interpretation can be difficult.

Currently Available Regimens for Neovascular Age-related Macular Degeneration
Regimens can be divided into an initiation and a stability/maintenance phase.

Many studies used three initiation injections, on a monthly basis, to commence treatment.⁶⁷ This remains a pragmatic way of commencing therapy as the majority of patients in a one dose plus re-treatment-as-necessary regimen still required three doses to achieve a similar good outcome.⁸

Once maximum control of activity and visual gain is achieved, ongoing disease suppression is required. The different approaches for managing this stability/maintenance phase can be considered as either ‘reactive’ or ‘proactive’ regimens. In the reactive form, treatment is given on a pro re nata (prn) basis whenever there are signs of activity and can be either ‘tolerant’ of a degree of disease activity or ‘intolerant’ of any signs activity. Disease activity is judged by taking a composite view of new symptoms, reduced measured visual acuity, dynamic evaluation with fluorescein angiography and most important morphology on optical coherence tomography (OCT). Intraretinal fluid and cysts, subretinal fluid and sometimes change in pigment epithelial detachment height are also considered.

In the proactive form, treatment is given in a continuous manner, ideally before disease activity manifests. Proactive regimens can be further subdivided into ‘fixed’ or ‘variable’ form.
The safety and efficacy of a flexible dosing regimen of ranibizumab in an nAMD study (Safety Assessment of Intravitreous Lucentis for AMD [SAILOR] study) had re-treatment criteria that tolerated a degree in an nvAMD study (Safety Assessment of Intravitreous Bevacizumab for Neovascular Age-related Macular Degeneration (SUSTAIN study)) that allowed patients to be re-treated as-needed. This is in contrast to the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody for the Treatment of Neovascular AMD) study which used a fixed monthly regimen. The NCTA trial has shown promising results in its first year. The improvement in visual acuity in both treatment groups, ranibizumab or bevacizumab, using a T&E protocol was comparable with visual acuity results in the monthly treatment groups of the CAT, while reducing patient visits. Open-label design studies have suggested an impact on reducing overall cost. It may be feared that this type of regime is complex to manage in a high-volume service.

### Variable Regimes

A treat-and-extend (T&E) strategy aims to individualise the needs of an eye following initiation of a treatment. The patient receives an injection at each visit with the results of the assessment of disease activity determining the interval to the next visit. If inactive, the interval is extended by 1 or 2 weeks; if active, the interval is decreased.

While there no large prospective trials comparing T&E with other dosing regimes have yet been reported, the Lucentis Compared to Avastin Study (LUCAS) trial has shown promising results in its first year. The improvement in visual acuity in both treatment groups, ranibizumab or bevacizumab, using a T&E protocol was comparable with visual acuity results in the monthly treatment groups of the CAT, while reducing patient visits. Open-label design studies have suggested an impact on reducing overall cost. It may be feared that this type of regime is complex to manage in a high-volume service.

### Is There a Perfect Regimen for Neovascular Age-related Macular Degeneration in 2016?

Unfortunately, there is no single perfect regime for all nAMD patients and a regimen may need to be selected to best suit an individual depending upon disease progression and impact on lifestyle and healthcare systems. Available evidence suggests that individualised treatment plans provide a reasonable alternative to the monthly injection protocols. Among these, the T&E protocol seems to be increasingly favoured.

A proposed pragmatic regime to treat patients in 2016 is to initiate with three injections on a monthly basis and then find the appropriate re-treatment interval by using a T&E-style pathway. Once an interval in recognised then fix at an interval during which there is disease control for 6–12 months before reviewing the need to modify it. It is necessary to be alert to any significant increase in activity that could occur during this period. The new UK MATE study (treatment with aflibercept: a pilot, 24-month, multicentre randomised controlled trial comparing standard of care with an individualised T&E regimen) using this type of regime will inform us in 2017 to 2019.

### Conclusion

In the last decade, there have been numerous advances and breakthroughs in the management of nAMD. Despite years of trials, the optimal treatment strategy has not yet been defined and treatment decisions should be based on an in-depth discussion between the patient and physician.