Editorial

Anti-VEGF Therapy: Proactive or Reactive?

One of the greatest breakthroughs in ophthalmology occurred only ten years ago following the first publication of the use of intravitreal bevacizumab to treat choroidal neovascularisation.[1] Since then the use of anti-VEGF agents bevacizumab, ranibizumab and aflibercept has spread on a massive scale throughout the world and patients are benefiting from sight-saving therapy for diseases which previously had limited or no effective therapy.

For most patients commencing anti-VEGF therapy the treatment course can last many years and maintaining the early benefit gained from treatment is a challenge for clinicians. Some patients may discontinue therapy due to lack of effect, progression of untreatable aspects of the disease such as atrophy and ischaemia or other systemic problems may prevent ability to attend for treatment. However, for many there may be an initial positive treatment benefit which is lost over time. The reasons for this may naturally reflect the differences in patient response when compared to clinical trials but real world data is emerging indicating response may also be variable depending on treatment approach.

The landmark studies of ranibizumab (ANCHOR, MARINA) in wet AMD showed mean gain in vision maintained for two years on monthly treatment. When monthly treatment was discontinued and a more reactive clinician guided approach of review and treatment as required was used, over the subsequent two years (HORIZON study) there was a gradual reduction in mean vision gain. This trend continued in the further long term follow-up (SEVEN-UP) study.[2] The landmark studies of Aflibercept (VIEW) also showed good maintenance of vision gain using a proactive treatment approach in the first year; monthly treatment for three months followed by bi-monthly and in the second year a prn approach being used but capped so that treatment was given at twelve weeks even if the patient was stable and not strictly needing a treatment according to the prn approach.[3]

In routine clinical practice a reactive clinical approach is commonly used to try and limit the number of intravitreal injections used for an individual patient whilst trying to maintain treatment effect. This has partly been driven by cost and capacity. Although it is possible to achieve good visual results from a prn approach as shown in the CATT study which compared prn bevacizumab and ranibizumab with monthly treatment, this was achieved through tight monthly monitoring, a very low retreatment threshold and a relatively high number of treatments in the prn arms.[4]

Longer term results of anti-VEGF treatments for wet AMD in real world clinical practice using a prn approach appear to be showing that this approach can lead to a gradual loss of treatment effect in the longer term. The UK EMR study of 12951 eyes receiving 92976 injections showed an initial visual again after a loading dose of three injections but then a gradual reduction of visual acuity to below baseline over the course of three years[5]. This was also shown in a cross-country comparison in the international AURA study in which the UK fared better but had the highest overall number of injections and patient visits.[6] In contrast a proactive approach using Aflibercept using a fixed dosing treatment protocol as in the VIEW studies showed good results in routine clinical practice.[7]

These trends towards lack of maintenance of efficacy in routine clinical practice with a reactive approach could be explained by the damaging effect of the underlying disease process. A study measuring aqueous VEGF levels showed that VEGF suppression is lost before detectable recurrence of disease on OCT scan and this precedes visual acuity loss. At any time that recurrence is detected at a routine review appointment the disease will inevitably have been active for a variable period of time during which damage may have been occurring which could affect response to treatment and future visual outcomes.

A treatment approach which attempts to take a more proactive approach and tailor the treatment to the response of an individual patient is the concept called "treat and extend" (TAE). This approach already very popular in the US and Australia and evidence is building for its efficacy in the clinical trial setting and real world clinical practice. This approach involves commencing treatment using a fixed monthly

dosing approach until a dry retina or disease stability is achieved. The treatment is then continued and the review interval is extended sequentially at each visit in up to 12 weeks if there is disease stability. If signs of disease activity increase, the treatment interval is reduced. All visits therefore become treatment visits and vary not in deciding whether treatment is required but at what interval to review the patient.

The LUCAS study compared bevacizumab and ranibizumab for wet AMD patients using a TAE approached and showed increase in best-corrected visual acuity VA of 7.9 and 8.2 letters, respectively, after 1 year of treatment.[8] Real world data has been published in an Australian study reviewing results from 1198 eyes of 1101 patients treated according to a TAE approach. Mean visual acuity improved by 6.5 letters in the first year and was maintained at 5.3 in the second year with an overall mean of 13.0 injections over two years and 14.8 clinic visits.[9]

Potential criticisms of this approach include the possibility of over-treating a dry retina, an increased risk of atrophy, greater cost and need for exit criteria. At present the evidence for atrophy risk is inconclusive and has to be weighed against the risk to the eye of damage from repeated recurrent disease. Although on average more treatments may seem to be required in the first year, the treatment number in reported studies is comparable with patients managed more intensively using a prn approach without the need for intervening monitoring visits.

Over-treatment can be minimised by excluding particularly good responders. In the SUSTAIN study which used a prn approach, approximately 20% of patients did not require an injection after the first three treatments[10]. Patients responding so well to treatment could therefore be excluded from the TAE approach and continued prn if needing infrequent treatment but if disease recurrence occurs within a three month timescale, treat and extend could be implemented for patients from that point. Exit could be an option when a patient has been extended up to a 12 week interval and remains dry at 2 – 3 consecutive visits although in patients with a high risk from recurrent disease e.g. those on treatment in their better eye long term treatment may be preferred to the risking recurrent disease. Implementing TAE also requires a modification of staff and patient psychology and expectations need to be set so a patient expects treatment at each visit and discontinuing treatment is not perceived to be a success and continuing treatment a failure.

The TAE approach has been reported most for wet AMD patients. Data is limited for retinal vein occlusion. For diabetic macular oedema there appears to be less detriment from allowing fluid to recur for a period and long term results from a prn approach used in DRCR.net study protocol[11] and RESTORE study[12] show an average reduction in injection requirement year on year to very low levels after the second year from initiating treatment. In the first two years though a TAE approach may help manage capacity by reducing monitoring visit requirements as shown in the RETAIN study.[13]

Although particularly good responders requiring few treatments may be seen in all disease types treated with anti-VEGF therapy in the majority of cases chronic disease requires long term therapy and a proactive approach makes sense to achieve the best long term outcomes for patients.

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