The Clinical Value of a Treat-and-Extend Regimen in Neovascular Age-Related Macular Degeneration

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Introduction

Anti-VEGF therapy has revolutionized the care of patients with neovascular age-related macular degeneration (nAMD), as demonstrated by randomized clinical trials of anti-VEGF therapy given according to a fixed monthly dosing regimen in which patients achieved gains of between 6.5 and 10 letters after 2 years of therapy.1-3 “When it came to clinical practice, however, the dilemma was how to translate the outcomes of these clinical trials into the real world, where we are faced with constraints such as patient comorbidities, lack of tolerance to treatments, mobility problems, high cost of medication, limited access to treatment, and service delivery challenges,” said Dr. Arnold. “It rapidly became apparent that under-treatment was one of the major factors that prevented us from gaining the best possible outcomes in real-world practice. The question became how to maintain the efficacy obtained with the fixed schedule used in clinical trials with a decreasing burden of treatment and follow-up and how to continue this into the long term.”

Treat-and-extend is a proactive treatment approach where an injection is given at each visit, with the length of the visit interval lengthened or shortened according to an assessment of disease activity (Figure 1). The aim is to use prophylactic anti-VEGF injections to maintain an inactive choroidal neovascular (CNV) lesion at each visit. The regimen has the advantage of decreasing the burden of both injections and clinic visits compared with regimens requiring fixed monthly dosing and/or monitoring.4

Personalized treatment strategies such as treat-and-extend require assessment at each visit. Monitoring should include VA assessment, fundus examination, and other forms of imaging, most importantly OCT. Assessment of disease activity is based on continually evolving functional and imaging biomarkers including loss of VA, quantitative and qualitative assessments of markers of activity on OCT, new or persistent blood, and
leakage on fluorescein angiography. Treat-and-extend permits a personalized approach, taking into account patient factors such as disease activity, but also the state of their fellow eye, their systemic health, and their preferences,” said Dr. Arnold. The treat-and-extend regimen is now included in the European Union (EU) label for ranibizumab.

In this supplement, we will address the management of nAMD with anti-VEGF therapy, with an emphasis on the treat-and-extend regimen. We will examine the evidence for improvement in vision in patients with nAMD treated with ranibizumab on a treat-and-extend regimen, including data from the RIVAL study, and we will consider the clinical significance of this evidence and how it can be applied to clinical practice in order to optimize outcomes. Prof. Wolf will open with a description of the different regimens used in the treatment of patients with nAMD, the evolution of the ranibizumab dosing posology in Europe, and a summary of the studies currently available on treat-and-extend in nAMD. Prof. McAllister will then go into greater detail into the study design and 2-year outcomes of RIVAL, a randomized trial comparing ranibizumab and aflibercept in patients with nAMD treated according to a treat-and-extend protocol. “Finally, I will lead a discussion providing our own clinical perspectives on the treat-and-extend regimen for nAMD,” said Dr. Arnold.

Part 1
Treatment Regimens and Patient Outcomes in nAMD

Clinical trials of anti-VEGF agents for the treatment of nAMD have included both fixed (e.g. monthly, bimonthly, and quarterly) and personalized (e.g. as-needed, or prn, with monthly monitoring, observe-and-plan/observe-and-extend, wait-and-extend, and treat-and-extend) regimens. The approved dosing posology in the EU for ranibizumab for the treatment of nAMD is based on a personalized treatment schedule, although this has evolved over the past decade from the original European label from 2007 which recommended administration according to a prn regimen, with a loading phase of three mandatory monthly injections followed by monthly monitoring and reinjection in the event of a loss of VA of more than 5 letters.

Evolution of the Ranibizumab Dosing Posology

In 2011, the ranibizumab EU posology was updated to remove the strict 5-letter loss criterion for retreatment and instead recommend continuous monthly treatment until stable VA was achieved, followed by monthly monitoring with retreatment triggered by the loss of an undefined level of VA due to disease activity. The new wording of the posology also allowed for the use of the increasingly popular OCT imaging technology as a means for clinicians to determine whether VA loss was as a result of disease activity.

A further update of the posology in 2014 finally removed the requirement for any vision loss to occur before retreatment, along with the need for monthly monitoring visits. Injection is now recommended until maximum VA is achieved and/or there are no signs of disease activity, at which stage monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by VA and/or anatomical parameters. This increased flexibility means that physicians are able to treat proactively, if disease activity is present, and also to extend monitoring intervals, essentially including treat-and-extend regimens within the approved posology.

Development of Personalized Dosing Regimens

In clinical practice, results with prn regimens in patients with nAMD have often been disappointing. Although patients in strictly controlled clinical trials such as HARBOR and CATT achieved gains of 8.2 and 6.8 letters, respectively, at 12 months with prn dosing, real-world evidence from a large observational study performed in Germany (n = 1,729) suggests that outcomes are less impressive in practice, with initial gains in vision achieved during the upload phase of three injections not maintained for the subsequent year in which patients received a mean of 1.5 injections. It seems as though patients in the COMPASS study were undertreated in real-life conditions, probably as a result of patient burden and
logistic problems,” said Prof. Wolf. On average, vision at month 15 was slightly poorer than at baseline. In response, a number of different personalized regimens such as treat-and-extend, observe-and-plan, treat-and-observe and wait-and-extend have been developed in an attempt to improve outcomes while minimizing treatment burden. In the observe-and-extend regimen, unlike treat-and-extend, treatment is not mandatory at every clinic visit, although, like treat-and-extend, a decision on whether the visit interval should be extended or reduced is evaluated at distinct intervals.13,14

Clinical Evidence for Treat-and-Extend in nAMD

A number of prospective and retrospective studies have been performed to investigate the efficacy and safety of treat-and-extend regimens for the management of nAMD. This includes 1-year data from trials such as TREND and TREX17,18 and studies carried out by Oubraham and Toalster,20,21 (Figure 2) as well as 2- to 3-year data from the CANTREAT, RIVAL, TREX, and LUCAS studies, among others (Figure 3).16,22-30 “When comparing the results of studies using a treat-and-extend protocol, it is essential to look in detail at the treatment regimen that is used, because treat-and-extend regimens are not always the same,” said Prof. Wolf. “For example, in the TREND study, the initial loading phase comprised two injections, while in TREX it consisted of three.17,18 Likewise, in some studies the maximum extension interval is 8 weeks while in others it is 12. Nevertheless, we do have reliable clinical data for treat-and-extend regimens in nAMD up to 3 years.”

A study by Hatz and Prünte has demonstrated that a treat-and-extend regimen is associated with more stable visual gains and fewer clinic visits than treating according to a prn regimen.31 Patients with nAMD switched from a prn regimen to a treat-and-extend regimen during routine clinical practice experienced improvements in best-corrected VA (BCVA), lower intraindividual variance in BCVA, and lower mean central retinal thickness on the treat-and-extend regimen. The number of visits per month was significantly lower with the treat-and-extend regimen (Figure 4).31

Conclusions

To conclude, the treat-and-extend regimen respects the variable needs of patients and is a simple protocol generally consisting of a 2-week extension or reduction based on disease activity. The ranibizumab label permits a treat-and-extend regimen from the first year of treatment, with induction followed by management of visit intervals driven by spectral-domain OCT. In clinical practice, the treat-and-extend regimen allows patients receiving treatment for nAMD to achieve optimal outcomes even in real-world conditions. However, further long-term data on treat-and-extend in nAMD would be of value.

Part 2
New Evidence on the Treat-and-Extend Regimen: The RIVAL Study

Ian McAllister, MBBS, DM, FRANZCO, FRACS

Macular atrophy has been observed in many patients with nAMD treated with anti-VEGF agents over extended periods of time, including 98% of patients treated for a mean of 7.3 years in the SEVEN-UP study.32 Although it is possible that at least some of this atrophy is part of the underlying disease process,
The potential association between anti-VEGF treatment and the development of macular atrophy is a key area of interest that the RIVAL study aimed to address. The primary interest of this study was to determine whether or not anti-VEGF agents with different modes of action would differently affect the development of macular atrophy that we see in patients who are undergoing long-term anti-VEGF therapy," said Prof. McAllister.

**Study design**

RIVAL is the first randomized controlled trial to compare ranibizumab and aflibercept using a treat-and-extend regimen. A 24-month multicenter trial conducted in Australia, RIVAL enrolled 281 treatment-naive eyes from 281 participants with active CNV secondary to nAMD, randomizing 142 to treatment with ranibizumab 0.5 mg and 139 to aflibercept 2 mg, given according to an identical treat-and-extend regimen with three initial monthly injections and a maximum extension period of 12 weeks (Figure 5). Treatment intervals were based on disease activity, defined as a loss of VA of 5 or more letters, new retinal hemorrhage, or the presence of any intra- or subretinal fluid on OCT. If one of these criteria was present at a visit, the treatment interval was reduced by 2 weeks, while if two or more were present, the treatment interval was reduced to 4 weeks.

**Results**

A total of 80% of participants completed the 2-year study. Demographic and baseline characteristics were comparable between groups.

RIVAL: Newly developed macular atrophy

- No statistical difference between ranibizumab 0.5 mg and aflibercept 2.0 mg in the proportion of patients developing new macular atrophy within the study period

Macular Atrophy

At 24 months, on the primary efficacy endpoint of mean change in square-root area of macular atrophy from baseline to month 24, there was no significant difference between ranibizumab (0.36 mm) and aflibercept (0.28 mm, \( P = .24 \)). It is interesting to consider these increases reported over 2 years in the light of data on the natural history of macular atrophy reported in the AREDS2 study, with enlargement rates of 0.29 mm and 0.28 mm per year reported for existing and emerging atrophy, respectively.33 “At this stage, the role of anti-VEGF agents in exacerbating existing macular atrophy or in the new development of macular atrophy remains unanswered, at least over a 2-year period,” said Prof. McAllister.

From baseline to month 24, the proportion of patients with macular atrophy in the RIVAL study increased from 7 to 37% for ranibizumab and from 6 to 32% for aflibercept (Figure 6).

“In terms of development of new macular atrophy within the study period, there was no statistically significant difference between ranibizumab and aflibercept,” said Prof. McAllister.

“Again, these are square-root transformed data, which decrease the dependency of macular atrophy size on the baseline macular atrophy that was present.” From baseline to month 24, 29% and 25% of patients in the ranibizumab and aflibercept groups, respectively, developed macular atrophy (\( P = .55 \); Figure 7).
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Visual and Anatomical Outcomes

BCVA gains were seen in both study arms, despite a relatively high baseline BCVA. At 24 months, patients in the ranibizumab arm had achieved a mean 6.6 letter improvement in vision, compared with 4.6 letters in the aflibercept arm (least-square means; \( P = .15 \); Figure 8). Similar proportions of patients in each study arm achieved gains of at least 15 letters from baseline to month 24 (25% and 19% for ranibizumab and aflibercept, respectively; \( P = .21 \)), and there was no statistical difference between the arms in terms of mean change in central subfield thickness from baseline to month 24 \( (P = .23) \). There were also no observed differences in terms of the proportions of patients with no intra- or subretinal fluid at month 24 (57% and 61% for ranibizumab and aflibercept, respectively; \( P = .62 \)).

Injections

These visual outcomes were achieved with similar mean numbers of injections, distribution of maximum injection intervals, and mean injection intervals over 24 months (Figure 9). “Over the 24-month study period, using an identical treat-and-extend protocol, a mean of 17.7 injections was required for ranibizumab and 17 for aflibercept,” said Prof McAllister. “The maximum injection intervals are again virtually identical between arms, so these two agents allowed both sets of patients to extend out to a very similar maximum treatment interval over the study period. In addition, the mean injection intervals were identical at 6.1 weeks.”

Plasma VEGF

Plasma VEGF concentrations were measured 1 week after the second and third mandatory injections. A statistically significant difference was observed between ranibizumab and aflibercept (Figure 10). “This analysis was performed using a mixed model, adjusting for baseline VEGF concentration, and it reveals highly significant differences in circulating plasma VEGF at 1 week after injection at both week 5 and week 9,” said Prof. McAllister. “The reduction in VEGF concentration in the aflibercept arm is obviously a concern, with the potential for a greater risk of arterial thrombotic events.”

Safety

Arterial thromboembolic events (ATEs) were reported in 7.8% of patients in the ranibizumab arm and 5% of patients in the aflibercept arm. The most common ATE was non-fatal stroke, occurring in 4.3% of patients given ranibizumab and 2.9% of patients given aflibercept. “Although the plasma VEGF results show significant differences between study arms, these aren’t reflected in any imbalances in vascular-type adverse events during the 2-year study period,” said Prof. McAllister.

Conclusions

RIVAL is the first prospective randomized, controlled trial to compare ranibizumab 0.5 mg and aflibercept 2 mg using a treat-and-extend regimen. The study found no statistical difference between ranibizumab and aflibercept in terms of the development of macular atrophy in patients with nAMD treated over 24 months. Ranibizumab and aflibercept required similar number of injections and achieved similar VA outcomes and retinal thickness improvements over 24 months, with comparable safety results. However, further studies are required to investigate the long-term effects of anti-VEGF therapy on the development of macular atrophy.

“The study found no statistical difference between ranibizumab and aflibercept in terms of the development of macular atrophy in patients with nAMD treated over 24 months. Ranibizumab and aflibercept required similar number of injections and achieved similar VA outcomes and retinal thickness improvements over 24 months...”

- Ian McAllister, MBBS, DM, FRANZCO, FRACS
Part 3
Clinical Perspectives on Treat-and-Extend

Dr. Arnold leads a discussion about the clinical management of patients with nAMD treated with anti-VEGF therapy given according to a treat-and-extend regimen.

What are the clinical implications of the outcomes of the RIVAL study in terms of the primary endpoint of geographic atrophy?

Prof. McAllister: This study shows that the different modalities for VEGF suppression within the eye do not appear to have different effects on macular atrophy development, but the actual role of VEGF suppression on macular atrophy is not yet answered. This is something that is worthy of further study, especially as longer-acting agents, which will suppress VEGF in the eye for a longer period of time, become available.

Dr. Arnold: It’s certainly useful to have studies such as this to give us more detail about the atrophy risk, especially since the imaging, detection, and quantification of atrophy has progressed since early results such as those from the CATT study, which were based on color photographs alone. In contrast, the recent RIVAL study used autofluorescence and other types of multimodal imaging.

In your clinical practice, do you see similar outcomes to those of the RIVAL study in terms of comparative vision gains and injection frequency between ranibizumab and aflibercept?

Prof. McAllister: For most patients I do not see any differentiation between these two agents, in terms of VA gains, injection frequency, or reduction of central subfoveal thickness. My impression over a number of years of having used both of these agents frequently is that they are both equally efficacious. Switching between agents is an interesting point, and with both agents there is possibly some element of tachyphylaxis, where one agent sometimes seems to become less effective after being used for a significant period of time, and the patient responds better when switched to another agent. I have observed tachyphylaxis both when patients have been switched from ranibizumab to aflibercept and when patients have been switched back from aflibercept to ranibizumab.

Prof. Wolf: In terms of injection frequency, there seem to be other factors influencing the duration of treatment effects other than just the agent used. In my previous experience I noticed a trend towards longer duration of action for aflibercept, but it seems that this effect is less pronounced in a large number of patients.

Are differences in systemic VEGF suppression between anti-VEGF agents relevant to clinical practice?

Prof. McAllister: It is a concern, as systemic VEGF suppression has been linked to the likelihood of ATEs. In the RIVAL study, the degree of systemic plasma VEGF suppression that occurred with aflibercept compared with ranibizumab surprised me. Based on these data, I would be more wary of using aflibercept to treat someone who has had a recent myocardial infarction, stroke, or some other significant vascular event.

Prof. Wolf: While we see that there is apparently a clear difference in systemic VEGF suppression, we do not have clear data that this has clinical relevance. However, as Prof. McAllister pointed out, if you have patients at higher risk for stroke or heart disease, choosing the right agent might help with reducing that risk.

What is your preferred regimen for managing people with nAMD?

Prof. Wolf: The treat-and-extend regimen has recently gained a lot of acceptance and popularity here in Europe among physicians treating nAMD patients, because it offers controlled treatment effects and avoids uncertainty for the patients as to whether they will receive an injection or have only a monitoring visit.

Prof. McAllister: I treat almost all of my nAMD patients with a treat-and-extend regimen as I think it has a number of advantages. The injection load is less, and the regimen allows disease activity to dictate how frequent the injections need to be. Studies like RIVAL show that treat-and-extend is equally as effective as, if not more effective than, prn and other fixed dosing regimens. Also, in my experience, patients prefer it because their visit intervals can be extended more, and because they know that they’re going to get an injection every time they come in so there’s no disappointment or shock that they need an injection when they weren’t expecting it.

Dr. Arnold: Treat-and-extend has become very popular in Australia, and it is certainly my personal preference for managing patients with nAMD. One of the chief advantages of treat-and-extend is that a large proportion of people will only require a low treatment frequency which is more manageable in the long term; this is important since sustained treatment is required to prevent recurrences and maintain early vision gains beyond 5 and 10 years.
Conclusions: Jennifer Arnold, MBBS, FRANZCO

To conclude, evidence shows that patients with nAMD have variable retreatment needs, and VA gains can be maintained for some patients with fewer than average injections. The treat-and-extend regimen aims to continue regular therapy to maintain an inactive CNV and considers the variable treatment needs of patients, allowing for a tailored follow-up schedule. Ranibizumab given according to a treat-and-extend regimen has been proven to be an effective approach both in real-world practice and in randomized controlled trials. The most recent clinical evidence from RIVAL shows that a treat-and-extend approach with ranibizumab offers excellent visual outcomes and improved clinic efficiency.

In practical terms, how do you implement a treat-and-extend protocol in your patients?

Prof. Wolf: I adhere very strongly to the posology, namely, to extend the treatment interval based on spectral-domain OCT findings after an initial phase of three injections. After recurrence or detection of disease activity, I reduce the treatment interval by 2 weeks and monitor to determine if the patient stays at this interval. I do not cease treatment in patients that are able to extend to 12-week intervals, as I don’t believe there are robust data available to demonstrate that these patients do not need any further injections.

Prof. McAllister: This is important because, for patients with nAMD that do get a recurrence or reactivation of their disease that is untreated for any significant period of time, their vision simply cannot be recovered back to what it was prior to that event happening.
