

Initiation and maintenance of a Treat-and-Extend regimen for ranibizumab therapy in wet age-related macular degeneration: recommendations from the UK Retinal Outcomes Group

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Abstract: The treatment of neovascular (wet) age-related macular degeneration (AMD) with ranibizumab is now very well established in terms of efficacy and safety. Recent clinical trials and real-world studies have demonstrated the advantages of a Treat-and-Extend (T&E) regimen, and many hospital departments are now in the process of adopting this new regimen in favor of the pro re nata regimen for initiating and continuing ranibizumab therapy for patients with wet AMD. The comprehensive spectrum of issues related to implementation of the regimen is covered qualitatively in ten didactic topics provided by a group of clinicians with direct experience of this regimen in their department. The topics include definition, new and previously treated eyes, management of high-frequency injections, maximum extensions, discontinuing T&E, bilateral cases, clerical, audit, and patient counseling. This article aims to provide a useful resource for the implementation of the T&E regimen. A quantitative summary of the visual outcomes in key publications is also provided in this article. This article should be a valuable resource for staff training.

Keywords: ranibizumab, age-related macular degeneration, nAMD, Treat and Extend, anti-VEGF treatment

Introduction

The provision of care for patients with wet or neovascular age-related macular degeneration (nAMD) is now a major undertaking for all ophthalmology departments.^{1,2} In the UK, there are ~40,000 new cases of wet AMD each year.³ It is estimated that about 300–400 intravitreal injections per week are required for nAMD for a catchment population of 1 million (Narendran, unpublished data, 2017). The continuing challenge for health care providers is to deliver a high-quality service with sufficient capacity in the face of limited resources. It is, therefore, essential to organize the various aspects of the treatment pathway to maximize efficiency and also to optimize visual outcomes.

In the UK, following the approval of ranibizumab for nAMD by NICE in 2008 (TA155),⁴ the pro re nata (PRN) regimen was the recommended posology in which patients were reviewed every month and the decision to retreat was made at any visit when there was new or persistent lesion activity. The two main disadvantages of this regimen were the monthly review appointments and the provision of timely injections, particularly in centers that operated a two-stop injection model.⁵ These factors contributed to the much poorer visual outcomes reported by the UK real-world studies

compared with clinical trials where patient visits and retreatment intervals were not delayed.^{6–8}

Since the change of licensed posology to a Treat-and-Extend (T&E) regimen for ranibizumab therapy in 2015 in the UK and 2012 in other countries,⁹ there has been an emerging body of evidence reporting better visual outcomes with the T&E approach than with the PRN regimen in a real-world setting.^{10–14}

A multicenter observational study of 1,198 eyes treated with the T&E regimen in Australia reported mean visual acuity (VA) increasing from 56.5 letters at the initial visit to 61.8 letters at 24 months and with the average treatment interval \times weeks at 24 months. In contrast, a large UK study on eyes treated with the PRN regimen reported a mean VA gain of two letters only at 1 year with a high rate of attrition after the first year.⁷

The main feature of the T&E regimen is that the patient receives a repeat intravitreal injection at each visit but the time interval to the next visit is extended if the optical coherence tomography (OCT) scan shows a stable or an inactive lesion. This allows the hospital department to plan the number of injections required in advance and the risk of delayed treatment in the presence of an active lesion is reduced.¹⁵ The other key feature of the T&E regimen is the need for uniform evaluation of disease activity or stability. For this purpose, disease is widely considered to be active if there is new hemorrhage, or intraretinal or subretinal fluid (IRF or SRF) on fundus examination or photography,^{11,16–18} but if these surrogate signs continue to be persistent, disease stability is considered to have been achieved if there is no further morphological improvement despite continuing injections on three consecutive visits at monthly intervals.^{11,16–18}

The decision-making at each visit, therefore, concerns the interval until the next injection, rather than whether or not to reinject. This is based on the evaluation of disease activity as defined above.

The transition from a PRN regimen or the new implementation of a T&E regimen for any hospital department requires careful planning and organization.¹⁹ The aim of this article is to provide a resource that can be used by clinicians and health professionals for implementing and maintaining the T&E regimen in their hospital departments.

Methods

The Retinal Outcomes Group (ROG) is a forum group consisting of retinal specialists from a variety of NHS hospital ophthalmology departments, whose objectives are to review contemporary issues in the field of retinal disease therapy.

Several roundtable meetings, facilitated by Novartis UK, were held by the members to identify the key aspects of the T&E regimen and the variations in practice that could be of relevance to implementation and maintenance of this regimen for their AMD services. Following these meetings, a survey questionnaire was designed to gather the views of all the group members on each aspect of T&E. Their responses were analyzed to form the basis of a descriptive report to generate a qualitative tool for implementation of T&E. To complement the qualitative tool, we also reviewed the published literature on the T&E regimen for wAMD and summarized the quantitative results on visual outcomes and duration of follow-up in a tabulated form for ease of reference.

Results

The topics and the clinicians' responses identified for the qualitative tool on T&E are provided under each subheading below.

What is T&E?

The original licensed posology for treatment of choroidal neovascularization due to AMD (nAMD) with intravitreal ranibizumab is based on the evidence from pivotal studies, which were initially based on continuous monthly therapy; subsequent studies involved monthly injections until disease stability, followed by monthly monitoring and re-commencement of injection treatment as required, ie, the PRN regimen.^{9,17,20}

The T&E posology first described by Gupta et al and Engelbert et al recommends intravitreal injections of ranibizumab at intervals of four weeks until there is no disease activity.^{16,21} Thereafter, injections are administered at longer and longer intervals, provided there is no recurrence or worsening of disease activity. If there is a worsening or recurrence, then the interval is shortened. Because each visit involves an injection regardless of the presence or absence of disease activity, the T&E regimen is a proactive regimen and has also been described as "Inject and Extend". The presence of new hemorrhage, IRF, or SRF^{11,16–18} is widely used as a surrogate biomarker for disease activity, but persistent fluid with no further morphological improvement despite continuing injections on three consecutive visits at one monthly intervals is regarded as indicative of disease stability.^{11,16–18}

T&E for unilateral injections in newly diagnosed, treatment-naïve eyes

Treatment-naïve patients are offered monthly ranibizumab until disease is inactive on OCT (no SRF/IRF) and funduscopy

or fundus color photography (no retinal hemorrhage). Initially, treatment-naïve patients receive three fixed monthly dosing and an appointment is normally offered 4 weeks after the third injection for assessment of VA and OCT improvement. This could be a face-to-face consultation or a virtual review with the use of OCT and color fundus photo. A fourth injection is administered at this visit and depending on the presence or absence of disease activity, the next review/injection is arranged for 4 or 6 weeks ideally in a one-stop clinic: virtual or face-to-face. The one-stop clinic setup is important as this ensures that the eye is treated “as is” and disease reactivation is avoided, which may occur with unwarranted additions to the treatment intervals as may result through a two-stop setup.

This standard approach is suitable for the majority of patients, although there will be a proportion of patients who would respond extremely well to treatment and may benefit from an earlier extension of the treatment interval or even placement in a PRN regimen. To identify these patients, the above pathway can be altered to include an OCT/photo on the day of the third injection with a virtual review.

Provided there are no signs of recurrence clinically or on OCT/photos or VA loss greater than five Early Treatment Diabetic Retinopathy Study letters due to active disease in future appointments/injections, the retreatment interval is sequentially increased by 2 weeks each time to a maximum interval of 12 weeks. If there is any sign of recurrence or worsening at any visit, the interval between injections is reduced by 2 weeks, or further back down to 4 weeks, depending on the clinician’s impression of the severity of the recurrence, until disease stability is reached before trying to extend again.²²

Selecting patients for T&E from those already on PRN regimen

Patients who are being treated on a PRN regimen have to be monitored every 4 weeks. Poor compliance of this strict follow-up often leads to delayed treatment of recurrences and poorer visual outcomes. The prospects of longer intervals between hospital visits and also better visual outcomes are important considerations for switching patients from the PRN regimen to the T&E regimen.

Not all patients who are on an established PRN protocol require to be switched to a T&E protocol. Those patients on PRN who are stable for more than 12 weeks should remain on the protocol, but those who have reinjection intervals of 12 weeks or less are more ideal for switching to a T&E regimen.

However, it may be useful to adopt a set of criteria for selection of those patients from the PRN cohort who can benefit most from switching to a T&E regimen. Such criteria may include the following:

1. Patients who have slowly declining VA over a period of 2–4 years due to frequent recurrences that may or may not have been retreated promptly.
2. Patients with a history of recurrences that do not respond with just one retreatment on a PRN regimen. Patients recurring less often than a 3-month interval, the typical maximum interval for T&E, and who respond well to treatment when they do recur may be candidates for continued PRN.
3. Patients with stable VA but with frequent recurrences especially with only one or two dry visits between many visits with disease activity requiring retreatment.
4. Patients with “precious eye or remaining eye” who cannot afford any delay on retreatment of any episode of recurrence.
5. Patients who have difficulty in attending for strict monthly monitoring.
6. Patients who are good responders who may not require a strict fixed dosing regimen.

Can eyes that require very frequent injections be managed on T&E regimen?

The rationale for implementing a T&E regimen for the management of nAMD patients is based on the need to achieve disease control with the lowest possible frequency of visits to eye clinics. This addresses both the issue of optimal patient experience and the need to ease capacity pressures on busy injection clinics. A sub-group of patients will require frequent treatment to maintain disease control and stabilize visual function. The T&E approach will also serve to identify these patients, and the regimen can be applied to this patient population as well. Previous reports on real-world results of the implementation of T&E regimens for nAMD have demonstrated a range in the maximum extension interval that can be achieved in order to maintain disease control.¹³ Some patients will show signs of increased disease activity when extended beyond 4-weekly retreatment intervals. In these cases, a more cautious extension strategy can be considered with increments of 1 rather than 2 weeks. Even if disease control can be achieved with 5- or 6-weekly treatment, this would still represent an improvement in patient experience and burden of care over a 4-weekly PRN regimen. Although the evidence base for this is relatively weak, it has been suggested that repeated attempts to re-challenge the extension period may

lead to visual decline. Most clinicians will not make further attempts to extend after three attempts. The optimal patient- and eye-specific retreatment interval can be determined at the first or second failed attempt not extending beyond the treatment interval when stability had last been achieved.¹³

What is the maximum extension on the T&E regimen?

The pivotal clinical trials of intravitreal anti-VEGF therapy for nAMD were 2 years in duration. They were not designed to provide evidence on the potential risk of recurrence of disease activity after cessation of anti-VEGF therapy or the impact on visual outcomes of ceasing treatment. Real-world data have provided useful insights.

Analysis of a large real-world dataset of over 2,000 eyes in the Fight Retinal Blindness! registry that received intravitreal ranibizumab for nAMD according to a T&E regimen confirmed a high rate of disease reactivation over time after disease stability had been achieved. Treatment intervals beyond 12 weeks appear to be associated with an increased risk of disease reactivation, with the risk of reactivation reaching 36.5% per visit at treatment intervals of 20 weeks.²³ This translated into an increased risk of losing ≥ 15 LogMAR letters with treatment intervals greater than 12 weeks. Therefore, in many countries and among the consultants of the ROG, the consensus is that the maximum extension should be 12 weeks.

Switching back from T&E to monitor and extend – who, when, how?

While the evidence exists that T&E regimens produce favorable VA outcomes compared with monitor and extend dosing, there remains uncertainty as to whether T&E should be continued indefinitely once longer treatment intervals have been achieved with stable disease. Doing so produces a long-term treatment burden for both the patient and the service with no finite dosing endpoint. An alternative would be to stop proactive T&E treatments at some point and instead continue monitoring with retreatment of disease reactivations as they occur.

The current consensus is that T&E should continue for three 12-week injection intervals at which disease is stable. If attempting to transition to monitor and extend, it would be feasible to wait for 12 weeks after the last injection before the first assessment (as the patient was stable with 12-week gaps previously). Beyond that, it seems prudent to review at 4- to 6-weekly intervals initially and then progressively monitor and extend up to a maximum monitoring interval of 12 weeks.²⁴

Patient's choice should be taken into account when attempting a change from T&E to PRN monitoring. Some patients prefer a regular 12-week injection with ongoing T&E while many are keen to avoid any long-term injection treatments but are happy to remain under monitoring.

In numerous prospective studies evaluating the PRN regimen, a small subgroup of patients have been repeatedly found to require very few injections following the loading doses.^{17,20,25,26} This small subgroup of patients could be over-treated on a fixed dosing or a T&E regimen, but there are no known baseline predictive features that can be used to identify these patients. The consensus from this group is that a review of treatment response in between the third and fourth injections is useful to allow transition to monitor and extend for those with complete disease control after injection number 3.

T&E for bilateral injections

One in five patients has bilateral active disease that requires simultaneous treatment (Barthelmes et al²⁷: 28% of 1,992 patients and UK EMR user group: 16% of 11,135 patients).⁷ Treatment for bilateral disease should follow the standard treatment protocols. Treatment responses may be different in the two eyes in patients with bilateral nAMD or nAMD may occur consecutively. This causes challenges for the planning of a successful T&E regimen. There is no consensus or best clinical practice guidelines for a bilateral T&E approach.

Different options for T&E in bilateral nAMD cases are available:

1. To treat the eyes individually with the aim to synchronize both eyes (eg, treating one eye at 6 weeks and the other at 12 weeks means that a bilateral procedure can be performed every second visit, reducing the overall number of appointments)
- 2a. To treat both eyes at the same shorter T&E interval
- 2b. To compromise and treat both eyes at the longer T&E interval (especially if better seeing eye has better stability).

Each option has certain disadvantages. Individual treatment of each eye increases the number of appointments and is less convenient for the patient. If both eyes are treated at the shorter interval of the eye with the shorter T&E timing, the fellow eye will be over-treated. In many cases of bilateral nAMD, one eye may be worse than the other. It might be pragmatic to base visits according to the eye that has better visual potential and longer treatment interval. This approach reduces patient appointments but undertreats the worse eye.

In cases of bilateral nAMD, an individual approach for each patient should be discussed and the different solutions should be offered to suit the best interest of the particular patient.

Implementation and service delivery of T&E

Implementing T&E in a hospital department

The first step in planning for a T&E service is to explore the feasibility and preference of a one-stop or a two-stop service. A detailed analysis of the proposed patient pathway at each visit can then be mapped out. The following sections give an overview of these two aspects of implementation.

One-stop or two-stop

The T&E approach to nAMD management by its nature is time sensitive. A “one-stop” clinical service in which a patient has diagnostics and treatment at the same visit is, therefore, optimal to ensure the required treatment intervals are maintained.

In a “two-stop” service, patients attend for diagnostic tests at one visit and treatment at a separate visit. For a patient on T&E the risk of this approach is the potential for the time interval between these two appointments to be added to the intended treatment interval. This should not cause a problem if this interval can be consistently kept low, ie, under 1 week, but there is still a disadvantage for patients in needing to attend the clinic twice within a short period of time.

Some departments have adopted an intermediate approach that may be termed, “one-stop” for the patient but “two-stop” for the hospital. A patient undergoing T&E requires treatment at each visit; the variability is in the time interval between treatments. It is, therefore, possible to do the necessary diagnostics and treatment at the one visit for patients. At this visit patients do not need to have a consultation. The review of the patient’s disease status, degree of stability, and a decision regarding the next treatment interval can be made during a separate session, which may be in the form of a “virtual” review clinic. Patients may be contacted with their results and also periodically attend for a face-to-face consultation as necessary.

The patient pathway

High quality and safe care as well as positive patient experience are the main features of a good treatment pathway, especially for patients who attend multiple appointments throughout the year. Patients appreciate well-timed and

predictable appointments, a caring approach, and well-informed health professionals.

The typical T&E session for nAMD patients after the initialization of treatment is made of two components: examination and treatment. If these are delivered on the same day, ie, one-stop model, examination consists of standard VA assessment using the ETDRS chart and macular OCT imaging performed by a health care assistant or technician followed by slit lamp examination by an appropriately trained medical or non-medical ophthalmic health care professional clinician. Patients then proceed to treatment at the same visit if not contraindicated.

In a “two-stop for the hospital/one stop for the patient” virtual review model, slit lamp examination is not done but additional fundus photography of the macula may be required to document features not as easily identifiable on OCT such as retinal or subretinal hemorrhage. In this model, a good practice is to document patients’ subjective vision, and ocular and systemic complaints at the time of doing the VA. Following diagnostic tests, the patient proceeds to receive further intravitreal injection (unless contraindicated). The next appointment is either planned at the time of examination or determined later by grading clinician depending on the service model.

It is our opinion that the patient pathway on the day of the appointment should take no more than 1.5 hours from start to finish regardless of the type of clinic they are attending, whether clinician-led or virtual clinic, and sufficient resource should be provided to achieve this.

It is vitally important that the implementation process is led by a retinal specialist and through the development of agreed departmental policies. Ideally, a set of local governance-committee approved Standard Operating Procedures (SOPs) manuals should be produced and archived for referencing by all team members. Patient information leaflets are required. Also, an agreed plan for regular audit and the performance indicators may also be declared a priori in the departmental SOP manuals.

All personnel in the AMD service, including doctors, nurses, allied health care professionals, photographers in fast track clinics, follow-up clinics, and injection clinics, need to be informed about the change of regimen from PRN to T&E.

Once implemented, it is important to focus on additional factors that can influence the patients’ adherence to the treatment program. Although virtual clinics help reduce the burden on capacity and workforce in the short term, it is important to maintain good clinician–patient relationship

with a proportion of visits being face-to-face. This will enable the clinician to emphasize the importance of compliance to the patient in person and also address issues that are difficult to do so in a virtual setting.

How to audit the T&E regimen within a service

A consensus regarding a standardized set of minimum outcome measures for nAMD is required for health care professionals to assess their performance objectively and compare it with others to drive improvements in clinical practice. Such a standardized outcome set might also help patients to make well-informed decisions about their treatment and allow commissioners to understand the quality and value of care that they are funding. Real-world registries could potentially be linked to other databases to determine systemic safety and genetic predictors of treatment response.⁶

Recommendations from a working group of international experts in AMD outcomes registry development and patient advocates were facilitated by the International Consortium for Health Outcomes Measurement (ICHOM).²⁸ A modified Delphi technique was employed to drive consensus decisions. Potential outcomes were identified through a review of outcomes collected by existing registries and reported in major clinical trials. Outcomes were refined by the working group and selected based on impact to patients, relationship to good clinical care, and feasibility of measurement in routine clinical practice. The recommendations from the UK ROG for auditing the T&E regimen within your service build on these ICHOM guidelines, and include:

VA outcomes:

1. Baseline VA on initiation of intravitreal anti-VEGF therapy
2. VA after three loading doses of intravitreal anti-VEGF therapy (this is likely to be close to the best achievable VA for that eye; response does depend upon stratification of baseline vision, a service with a relatively low baseline VA might expect a higher gain in VA at month 3)
3. Change in VA from post-loading dose to end of the first year and change in VA during each 12-month period annually thereafter (this defines how well the unit maintains VA in treated eyes, does depend on co-morbidities within the patient cohort). The mean change in VA with SD and proportion of eyes with gain or loss of 15 letters in vision should be recorded.

Disease activity outcomes:

4. Percentage of visits where the eye develops new disease activity (presence of IRF or subretinal fluid or hemorrhage that is attributable to activity of neovascular lesion

as determined by the treating clinician – this allows a fluid index to be calculated)

5. Number of intravitreal anti-VEGF injections per year
- Patient-reported outcomes:
6. Patient-reported outcome measures at baseline and annually (eg, brief impact of vision impairment questionnaire as recommended by ICHOM).
- Ocular safety outcome:
7. Endophthalmitis rate.
- Service delivery:
8. Measurement of referral to treatment times (NICE Technology Appraisal guidelines recommend for 2 weeks)²⁹
 9. Percentage of injections and/or assessment appointments delivered on time (where delays are only included if due to service issues and not patient DNAs [Do not Attend])
 10. Measurement of patient UTAs (Unable to Attend) and DNAs (these will influence the VA outcomes for the patient).

As indicated earlier, we recommend the use of distance LogMAR charts (eg, ETDRS charts) for VA measurements. Rates of loss to follow-up should be recorded as attrition bias can skew results.⁶ We would urge real-world data collection platforms such as Medisoft, OpenEyes, and Fight Retinal Blindness! to ensure these data can be easily recorded and self-audited within units.

Essential information for patient counseling

What does your patient need to know? During the initial consultation with your patient, it is important to help them understand their condition, therapy, and management options. Discussions will need to be tailored to the individual and ensure that there is opportunity for them to ask questions.

Explain why they are receiving anti-VEGF therapy

Describe the disease, emphasizing the chronic nature of nAMD, the requirement for long-term therapy and monitoring and the rationale for choosing a particular anti-VEGF treatment, such as ranibizumab, as the therapy for nAMD⁹ and the side effects that may occur.^{4,30–32} There should also be a discussion on the risk of the second healthy eye developing the disease.³³ In addition, the patient should be made aware of the co-existence of dry AMD in wet AMD eyes and the challenging, untreatable nature of this part of the disease.

Discuss the treatment plan

The number of injections each patient receives will depend on the extent of their disease and what the retinal specialist considers the optimum management plan for the patient.^{4,9}

Include a brief discussion of what happens during and after a typical injection appointment, mentioning the vision test, eye scan, and subsequent injection schedule. Highlight the significance of what the T&E schedule offers the patient, how it can provide flexibility and reduce the number of visits without a loss of efficacy.³² Reinforce the importance of adhering to the dosing schedule and attending their planned injection appointments, and the possibility of an endpoint to treatment but that in the vast majority of patients discontinuation of therapy and monitoring cannot be achieved and lifelong injections and monitoring at less and less frequent intervals may be necessary.

Support beyond the consultation

At the end of the consultation, direct the patient to any additional support services and specific patient materials offered by the hospital or patient groups/societies, eg, NICE guidelines,²⁹ patient support groups, Macular Society patient leaflets. The patient should also be counseled regarding smoking cessation, self-monitoring of both eyes for wet AMD recurrence, impact of depression, LVA and CVI status and, where applicable, the timing of cataract surgery.

Discussion and conclusion

For hospital departments that are using a PRN regimen but are considering implementing or introducing the T&E regimen into their departmental AMD protocols, it can be a daunting task with possibly hundreds of appointments already booked in advance for PRN visits at any one time. The information gathered from our round table discussion and questionnaire survey represented the experience from retinal specialists

from 13 UK sites of varying sizes. In this article, we have provided a packaged resource that may be helpful for implementing this new regimen for nAMD services. Although we have attempted to break down the process of transitioning to T&E into small sections and provided detailed information on the basic principles of each aspect, it is inevitable that there will be local factors that may arise that are unique to individual hospital departments. In these situations, we feel that individual clinicians can still find the basic principles that are outlined here as a helpful initial aid to developing bespoke solutions for any unique situations. Health professionals may also wish to update their core knowledge on the current status of the published literature on the T&E regimen in nAMD. A detailed review of these publications is beyond the scope of this article but we have provided a convenient summary in Table 1 of the 15 key publications^{10,11,16,32,34–37,39,41–46} in this field. However, it is worth highlighting that a recent systematic review on T&E in nAMD by Rufai et al analyzed the outcomes of 748 eyes from nine studies and found mean VA gain of 8.92 letters with a mean of 8.60 injection at 1 year.¹³ The authors concluded that the T&E regimen “delivered visual outcomes superior to PRN and approaches similar efficacy to monthly injections”.

In this exercise, we have also included a section on clinical audit. The landscape of nAMD therapy is still changing and evolving with ever increasing demands for services and also increasing pressures on resources. It is vital that we continue to develop robust tools for audit and ensure that we use relevant outcome measures and collect data on representative population samples to generate meaningful evidence to support the long-term use of the T&E regimen for AMD.

Table 1 Publications providing evidence for the use of ranibizumab in a T&E regimen for wAMD

Study	Population	Intervention	Outcomes	Topline results	Study duration
RCT studies					
Berg et al 2016 ³⁹ (LUCAS)	People with previously untreated AMD (n=441)	Ranibizumab Bevacizumab	Mean change in VA at 2 years	+6.6 letters at year 2 in ranibizumab group	24 months
Wykoff et al 2015 ¹¹ (TRES)	People with treatment-naïve wAMD (n=20)	Ranibizumab	Mean BCVA change from baseline	+10.5 letters at year 1	12 months
Silva et al 2018 ³² (TREND)	People with treatment-naïve wAMD (n=323)	Ranibizumab	Change in BCVA from baseline	+6.2 letters at year 1	12 months
Non-RCT studies					
Abedi et al 2014 ⁴²	People with CNV due to AMD (n=120 at 12 months and 101 at 24 months)	Ranibizumab Becavizumab	% losing <15 letters and change in BCVA	97.5% and 95% lost <15 letters at 12 and 24 months, +9.5 and +8 letters at 12 and 24 months	24 months
Toalster et al 2013 ³⁴	People with CNV due to AMD (n=45)	Ranibizumab	Change in BCVA	+7 letters at month 12 (P=0.008)	12 months
Arnold et al 2015 ⁴¹	People with CNV due to AMD (n=1,011)	Ranibizumab Aflibercept Becavizumab	Change in BCVA	+5.3 letters at 24 months	24 months

(Continued)

Table 1 (Continued)

Study	Population	Intervention	Outcomes	Topline results	Study duration
Calvo et al 2014 ⁴³	People with CNV due to AMD (n=30 for PRN and n=30 for TREX)	Ranibizumab PRN and TREX	Change in BCVA of PRN vs TREX	No significant difference in BCVA change between groups ($P>0.05$)	36 months
Chen et al 2016 ⁴⁴	People with CNV due to AMD (n=79)	Ranibizumab	Change in BCVA after induction and extension phases	+8.4 letters during the induction ($P<0.001$) with maintenance over TREX phase ($P=0.81$)	
Gupta et al 2010 ¹⁶	People with CNV due to AMD (n=92)	Ranibizumab	Change in Snellen VA	Significant improvement at 1 year ($P<0.001$) and 2 years ($P=0.002$) follow-up	24 months
Hatz and Prunte 2016 ³⁷	People with CNV due to AMD (n=70 for PRN and n=70 for TREX)	Ranibizumab PRN and TREX	Change in BCVA of PRN vs TREX	+0.18 for TREX vs +0.07 for PRN at month 12 ($P=0.001$)	12 months
Mrejen et al 2015 ⁴⁵	People with CNV due to AMD (n=185)	Ranibizumab Aflibercept Bevacizumab	Change in BCVA	-0.1245 logMAR at 18 months, -0.1061, -0.0896, and -0.0782 logMAR at 3, 4, and 5 years	72 months
Oubraham et al 2011 ³⁶	People with CNV due to AMD (n=52 for PRN and n=38 for TREX)	Ranibizumab	Change in BCVA of PRN vs TREX	+10.8 letters for TREX vs +2.3 for PRN at month 12 ($P=0.036$)	12 months
Rayess et al 2015 ³⁵	People with CNV due to AMD (n=189)	Ranibizumab Becavizumab	Change in BCVA	+11.6 letters at year 1, +10.7 at year two and +13.6 at year 3	36 months
Vardarinos et al 2017 ¹⁰	People with CNV due to AMD (n=54 people at 12 months and n=45 people at 24 months)	Ranibizumab	Change in BCVA at 12 and 24 months	+8.3 letters at month 12 ($P<0.001$) and +5.2 letters at month 24 ($P=0.007$)	24 months
Gillies et al 2015 ^{46,a}	People with AMD (n=1,043)	Ranibizumab Becavizumab Aflibercept	Change in mean VA	+6.3 letters at month 6, remained above baseline for 5 years and decreased to -2.6 letters at year 7	84 months

Notes: ^aThis was not specifically a Treat-and-Extend study; however, the Treat-and-Extend approach seemed to have been favored by investigators.

Abbreviations: CNV, choroidal neovascularization; PRN, pro re nata; VA, visual acuity; BCVA, best corrected visual acuity; TREX, treat and extend; T&E, Treat and Extend; wAMD, wet age-related macular degeneration.

Neovascular AMD requires continuing intravitreal therapy over several years and perhaps indefinitely. There is also tremendous variation between patients in terms of duration of treatment response. The T&E approach is an ideal way to individualize therapy in such a heterogenous population and has gained popularity over the “one size fits all” fixed dosing approach in recent years. Additionally, the suitability of the T&E approach to a one-stop model of delivery also has advantages over the two-stop PRN model in terms of resource implications.¹⁵ As newer agents are introduced with longer duration of action and longer intervals between injections allowing longer extensions after each visit, it is even more necessary to consider the T&E regimen over the PRN or fixed dosing regimens. We hope this article will be of use for departments to include in their local training packages for new staff members and to implement and audit T&E regimen not only for currently available therapeutic agents but also for future therapeutic agents with longer duration of action.

Acknowledgments

The views and opinions of the authors are not necessarily those of Novartis or the publisher.

This supplement and the group that developed it were sponsored by Novartis Pharmaceuticals UK Ltd. All authors received honoraria, contributed to the development of the manuscript, and retained final control of the content and editorial decisions. The authors would also like to acknowledge Richard Gale, Niro Narendran, Praveen Patel, and Ramesh Sivaraj who attended earlier meetings on this topic and provided input into earlier drafts of this paper. Medical writing assistance was provided by Daniel Webber, Rock Unlimited. Novartis has checked that the content was factually accurate, balanced, and compliant with the Association of the British Pharmaceutical Industry Code of Practice.

Disclosure

The authors received honoraria from Novartis Pharmaceuticals UK Ltd for their contribution to the roundtable meetings. The authors report no other conflicts of interest in this work.

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