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REVIEW

A systematic review to assess the 'treat-and-extend' dosing regimen for neovascular age-related macular degeneration using ranibizumab

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. Monthly or as-needed (PRN) dosing strategies of intravitreal ranibizumab have been established as efficacious treatment options for neovascular AMD. More recently, the 'treat-and-extend' dosing regimen (TREX) is being adopted in clinical practice as it represents a patient-centric and economical option, reducing treatment burden by extending injection intervals when possible. However, the efficacy of TREX using ranibizumab monotherapy remains to be defined. Therefore, we performed a systematic review to assess the current evidence for TREX using ranibizumab by searching MEDLINE, Embase and PubMed. Of the 1733 articles identified, nine TREX studies were included in our analysis ($n = 748$ eyes). Average patient age was 79.25 (range: 77.34–82.00; SD: 7.27). Baseline BCVA ranged from 48.5–68.9 ETDRS letters. BCVA improvement was 8.92 letters at 1 year (range: 6.5–11.5; SD: 7.54), as a weighted mean accounting for numbers of study eyes. The weighted mean number of injections at one year was 8.60 (range: 7.3–12.0; SD: 1.73). Previously, the landmark ANCHOR and MARINA trials reported gains of 11.3 and 7.2 letters, respectively, using monthly ranibizumab. Chin-Yee *et al* reported a gain of 3.5 ETDRS letters with 5.3 (S.D. 0.66) PRN ranibizumab injections as weighted means at 1 year in their recent systematic review. Our analysis suggests that TREX delivers visual outcomes superior to PRN and approaches similar efficacy to monthly injections. Further RCTs are needed to fully evaluate the efficacy and economy of TREX in the long-term.

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Introduction

Age-related macular degeneration (AMD) is a progressive, degenerative disease of the retina that causes central vision loss.[1] It is the leading cause of blindness in the elderly in developed nations.[2] AMD is classified as dry or neovascular (wet) based on the absence or presence of new blood vessels that have invaded the retina, respectively.[3] Neovascular AMD affects 10–15% of AMD patients.[4] In the United Kingdom (UK), over 338 000 individuals in 2013 were affected by neovascular AMD, with 50 000 cases resulting in blindness.[5]

Neovascular AMD is characterised by choroidal neovascularisation driven by vascular endothelial growth factor-A (VEGF-A), a signal protein that drives growth of morphologically fragile new vessels that tend to leak and haemorrhage, resulting in photoreceptor damage and vision impairment.[6] Agents that antagonise VEGF-A decrease the accumulated fluid at the back of the eye and cause regression of the new fragile vessels. There are two Anti-VEGF agents currently licensed in Europe and approved by the National Institute for Health and Care Excellence (NICE) for the treatment of wet AMD in the UK: ranibizumab (Lucentis, Genentech (San Francisco, CA, USA)/Novartis,

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Basel, Switzerland) and aflibercept (Eylea, Bayer, Leverkusen, Germany).[7] Ranibizumab is a recombinant, humanised, monoclonal, VEGF-specific antibody fragment. Regular monthly injections of ranibizumab are established as the gold standard treatment for neovascular AMD.[8–10] A recent UK study estimated that the National Health Service (NHS) spent over £327 million on intravitreal use of ranibizumab in the year 2015, £212 million on aflibercept and £246 000 on bevacizumab (Avastin, Roche, Basel, Switzerland), an unlicensed anti-VEGF agent also used for the treatment of neovascular AMD, totalling over £539 million.[7,11]

Until recently, the licensed dosing regimen for the treatment of neovascular AMD using ranibizumab in Europe involved fixed monthly dosing until maximum VA is achieved, followed by monitoring and treatment intervals determined by the ophthalmologist pro-*re-nata* (PRN) based on disease activity.[12] The clinical workload associated with the multiple follow-ups required with this treatment strategy is significant. Tufail *et al* demonstrated that ongoing capacity issues at AMD Clinics in the UK have prevented those departments from maintaining the regular monitoring visits, leading to delays in patients' follow-up appointments and treatments, with consequential loss of vision.[13] In addition, the VISION 2020 UK Macular Interest Group Survey revealed that necessary staffing to deliver neovascular AMD treatment is significantly below expected levels and demand far exceeds capacity.[14] Moreover, key trials for PRN ranibizumab dosing have demonstrated a wide variability in the number of injections required by patients over time, suggesting heterogeneity in disease reactivation intervals between patients and supporting the need for alternative, individualised treatment regimens.[15–17]

The 'treat-and-extend' (TREX) dosing regimen is a strategy that aims to resolve macular exudation and maintain the macula in a 'dry state' with, where possible, fewer patient visits for investigation and treatment as compared to monthly dosing.[18] The regimen involves an initial loading sequence of at least three monthly injections.[19] As long as visual acuity is stable, treatment intervals are gradually increased. The maximal safe interval is not known. Some authors recommend a maximum of 10 weeks[19] while others recommend 12 weeks.[20] If there are any changes, treatment intervals are shortened by 2 weeks. TREX dosing therefore offers a practical solution to reduce treatment burden associated with multiple follow-up appointments. Furthermore, TREX may represent a more cost effective therapeutic option as compared to regular dosing. 'As-needed' or pro-*re-nata* (PRN) dosing involves initially giving regular injections, typically for a minimum of three months, followed by routine follow-up and only further injections given reactively when there is evidence of changes.[21] The TREX regimen offers a proactive, structured treatment protocol, whereas a PRN regimen does not represent a structured option; patients are treated reactively waiting for symptoms and signs of activity to appear.

The TREX dosing regimen using ranibizumab monotherapy has not yet been assessed in a systematic review. The aim of this systematic review is to assess and compare the effectiveness of the TREX-dosing regimen for intravitreal ranibizumab, with PRN and regular dosing strategies for the treatment of neovascular AMD.

Materials and methods

Search strategy

We entered the medical subject headings (MeSH) terms 'macular degeneration', 'AMD', 'ranibizumab' and 'Lucentis' into the following search platforms: the Cochrane Central Register of Controlled Trials (CENTRAL) (including the Cochrane Eyes and Vision Group (CEVG) Trials Register), Ovid MEDLINE(R) (1946 to present), Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE Classic+Embase (1947 to present) and PubMed (1948 to present).
We uploaded our search results onto EndNote X7 (Thomson Reuters, New York, NY) reference management software. No date or language restrictions were used in the electronic search for papers. Appendix 1 includes full details of keywords and MeSH terms used. We included Level IV evidence and above, i.e. case series, cohort studies, case-control studies, randomised controlled trials (RCTs) and systematic reviews, as defined by the Oxford Centre for Evidence-based Medicine.[22]

We employed a three-stage screening process first assessing titles, followed by abstracts, then full papers. Our screening questions are included in Appendix 2. Two investigators independently screened the studies delivered by the above search strategy using the screening questions, classifying the studies as 'include', 'exclude' or 'unclear'. In the event of studies assessed as 'unclear' after full text screening due to ambiguous or missing information, the study authors would be contacted for clarification. For any discrepancies arising between the two investigators, a senior author volunteered to act as the third arbitrator to make the final judgement.

Outcome measures

The primary outcome measure was the mean change in best-corrected visual acuity (BCVA) at 1 year, using Early

Treatment Diabetic Retinopathy Score (ETDRS) letters. A single-arm meta-analysis was performed by pooling the data and computing a weighted mean to account for the number of eyes per study. Secondary outcome measures included the weighted mean number of injections required and cost analyses of treatment regimes. The unit of analysis was the enrolled study eye of the participant.

Data extraction and synthesis

The following data were extracted from each study:

1. Study design
2. Study location
3. Number of eyes enrolled
4. Follow-up in months
5. Mean age in years
6. Number of injections
7. Baseline BCVA in ETDRS letters
8. BCVA at 12 months in ETDRS letters

We calculated the total number of eyes enrolled across all studies that received ranibizumab monotherapy. Where BCVA was recorded in Snellen or LogMAR, we employed the Gregori et al method to convert to ETDRS letters to facilitate comparison and to the data synthesis.[23]

Results

Search results

Figure 1 is a PRISMA flowchart summarising our screening process. Of 1733 studies identified, full data for mean BCVA improvement and mean number of injections at 1 year were obtained for nine studies comprising a total of 748 eyes. Two papers did not assess the treat-and-extend dosing protocol for neovascular AMD using ranibizumab monotherapy and were therefore excluded. Out of the 10 studies qualifying for our review, full data for number of injections and BCVA with ranibizumab monotherapy were not obtained from the study authors for one study and therefore could not be included.

Out of the nine included studies, one was a RCT while the remaining eight were observational in nature, thus providing only low-to-moderate quality of evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification.[24] Thus, the data extraction and risk of bias assessment was conducted solely for the RCT in the first instance.

Primary and secondary outcomes of RCT

This was a phase IIIb, multicenter, randomised, controlled clinical trial conducted in the United States of America.

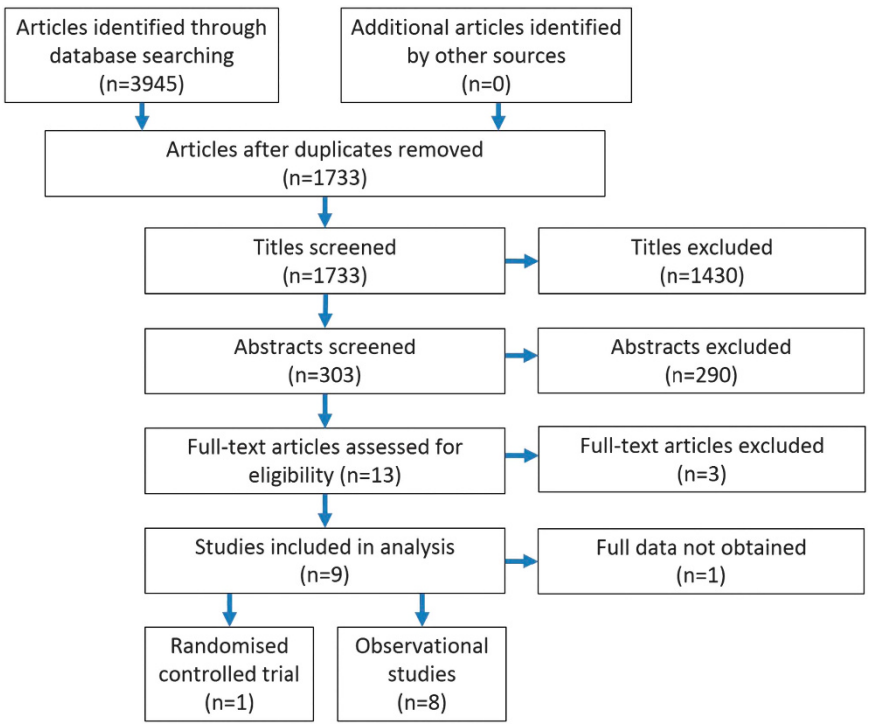

Figure 1 PRISMA flowchart summarising article screening process.

Average patient age was 77 years (range: 59–96). Mean baseline BCVA was 60 ETDRS letters. Fifty-seven eyes (95%) completed the full 12-month follow-up. Mean BCVA improved by 9.2 and 10.5 letters in the monthly and TREX cohorts, respectively ($P=0.60$). The mean number of injections given through month 12 was 13.0 and 10.1 (range: 7.0–13.0) in the monthly and TREX cohorts respectively ($P<0.0001$).

Risk of bias assessment for RCT

The Cochrane Collaboration's tool for assessing risk of bias was used.[25] Overall, this RCT was judged as low risk of bias.

The allocation sequence generation method was described in sufficient detail to demonstrate it should produce comparable groups. The method to conceal the allocation sequence was described in sufficient detail to demonstrate that intervention allocations could not have been foreseen in advance of, or during, enrolment. Thus, the risk of selection bias was low.

The nature of this RCT rendered it difficult to blind study participants and staff from knowledge of which intervention a participant received, as the intervention protocols for the monthly and TREX cohorts were different. For similar reasons, it would have been challenging to blind outcome assessors from knowledge of the allocated interventions. However, neither were stated explicitly. Therefore, the risks of performance and detection biases are unclear.

A 95% follow-up was achieved at 1 year with reasons for withdrawals stated. Intention-to-treat analysis was used. Numbers were reported per intervention arm. Therefore, the risk of attrition bias was low.

All relevant clinical outcomes were fully reported. There was no evidence of the possibility of selective outcome reporting. Therefore, the risk of reporting bias was low.

Primary and secondary outcomes including observational studies

The data from all nine studies were pooled to compute average means across the studies. Average patient age was 79.25 (range: 77.34–82.00; SD: 7.27). Baseline BCVA ranged from 48.5–68.9 ETDRS letters. BCVA improvement was 8.92 letters at 1 year (range: 6.5–11.5; SD: 7.54), as a weighted mean accounting for numbers of study eyes. The weighted mean number of injections at 1 year was 8.60 (range: 7.3–12.0; SD 1.73). This represents a 26.7% reduction in frequency of injections as compared to monthly injections. No study performed a cost analysis of the treat-and-extend protocol for their patient cohort.

Table 1 is a summary of study characteristics for all nine studies, and Table 2 is a summary of the pooled data. Although the full data for BCVA improvement and mean number of injections were obtained for all nine studies, BCVA SD were not obtained for studies 5–8, nor the patient age data for study 7. Therefore, SDs for BCVA improvement were imputed by averaging the available SDs per metric, as per the Cochrane Handbook.[25]

Table 2 Weighted means for TREX studies

	Number of injections	*Gain in ETDRS letters at one year*
Weighted mean	8.60	8.92
SD	1.73	7.54
Range	7.3–12.0	6.5–11.5

Table 1 Summary of study characteristics

Study number	*Author and year*	*Study design*	*Study location*	*n (number of eyes)*	*Follow-up (months)*
1	Abedi[32]	Prospective cohort study	Melbourne, Australia	87	24
2	Berg[20]	Multicenter, randomised, non-inferiority trial (*vs* bevacizumab)	Oslo, Norway	218	12
3	Calvo[33]	Retrospective, observational, longitudinal study (*vs* treat and observe)	Toronto, Canada	30	36
4	Chen[34]	Retrospective review	London, UK	79	31
5	Mrejen[35]	Retrospective cohort study	New York City, USA	123	72
6	Oubraham[36]	Comparative retrospective study (*vs* PRN)	Orleans, France	38	12
7	Rayess[37]	Retrospective, consecutive case series	Philadelphia, USA	91	36
8	Toalster[38]	Prospective, multicenter, nonrandomised trial	Brisbane, Australia	42	12
9	Wykoff[26]	Phase IIIb, multicenter, randomised, controlled clinical trial	Houston and West Columbia, USA	40	12

Discussion

To our knowledge, this study represents the first systematic review of the TREX-dosing regimen using ranibizumab monotherapy in the treatment of neovascular AMD. Conventional meta-analysis was not possible due to only one TREX RCT having been identified. However, both the RCT and the pooled data demonstrate that TREX can reduce the frequency of injections while improving vision. Therefore, TREX represents a viable solution in tackling the tremendous treatment burden associated with monthly ranibizumab injections.

Our pooled results demonstrate a gain of 8.92 (SD: 7.54) ETDRS letters as a weighted mean at 1 year, with 8.60 (SD: 1.73) injections as a weighted mean at 1 year, across nine TREX studies ($n=748$ eyes). Out of the nine studies, only one was an RCT comparing TREX to monthly dosing, performed by Wycoff et al.[26] This was a phase IIIb, multicentre RCT involving a relatively small cohort of 60 patients randomised 1:2 to monthly and TREX management, respectively. Fifty-seven eyes (95%) completed month 12, at which point mean BCVA improved by 9.2 and 10.5 letters in the monthly and TREX cohorts, respectively ($P=0.60$), demonstrating non-inferiority in visual outcomes. The mean number of injections administered through month 12 was 13.0 and 10.1 in the monthly and TREX cohorts, respectively. Due to the lack of RCTs, conventional meta-analysis could not be performed to ascertain whether TREX delivers comparable visual outcomes compared to monthly and PRN dosing.

Chin-Yee *et al* performed a systematic review of the TREX regimen *vs* PRN dosing for neovascular AMD, having computed their search in 2013.[27] Their systematic review demonstrated a gain of 9.17 (SD: 3.8) ETDRS letters as a weighted mean at 1 year, with 8.34 (SD: 0.66) injections as a weighted mean at one year, across eight TREX studies ($n=1073$ eyes). However, the key difference in their study method was the inclusion of patients receiving bevacizumab, presuming its efficacy to be equivalent to ranibizumab. Only four of the studies published at the time of their systematic review included ranibizumab monotherapy. Our study benefitted from a larger number of published TREX studies available. Additionally, we endeavoured to obtain results pertaining to patients receiving ranibizumab monotherapy by corresponding with study authors. Despite these differences in study methods, our study findings for TREX using ranibizumab monotherapy substantiate those of Chin-Yee *et al*. Furthermore, Chin-Yee *et al* additionally systematically reviewed studies of patients with neovascular AMD receiving ranibizumab or bevacizumab PRN, demonstrating a gain of 3.5 (SD: 4.5) ETDRS letters as a weighted mean at 1 year, with 5.3 (S.D. 0.66) injections as a weighted mean at 1 year, across 62 PRN studies (10716 eyes). They demonstrated this change in BCVA was significantly lower than that in TREX (Mann–Whitney's test; $P=0.0006$).

The landmark ANCHOR and MARINA trials assessing monthly intravitreal ranibizumab for neovascular AMD demonstrated mean gain in BCVA of 11.3 and 7.2 at 1 year, respectively.[28,29] Our systematic review demonstrates that a gain of 8.92 letters at 1 year can be achieved with TREX, but further RCTs for TREX are required for future meta-analysis to conclude that it delivers comparable outcomes to monthly dosing. Nevertheless, it is encouraging to find that our systematic review of TREX has demonstrated approximately the average of the ANCHOR and MARINA visual outcomes in real world settings.

Assuming further RCTs support the hypothesis that TREX delivers non-inferior clinical outcomes to monthly dosing, a cost comparison between the two strategies strengthens the case for wider adoption of TREX in the UK. Using the data from the UK National Health Service (NHS) National Tariff Payment System 2016/17[30] and the British National Formulary (BNF),[31] we have estimated that the mean annual cost of treating neovascular AMD with ranibizumab using the TREX regimen is £8287.80 per patient compared to £11 545.00 annually for a patient receiving monthly intravitreal ranibizumab and monthly follow-up with OCT as per the ANCHOR and MARINA trial protocols. This equals annual saving of £3257.20, representing a cost reduction of 28.21%. These calculations assume that each TREX patient has an initial visit (£156) plus an average of 7.6 follow-up visits (£107), all including the cost of an OCT scan (£43), while patients receiving monthly doses also have monthly follow-up with OCT scans which would be highly challenging, given the tremendous associated treatment burden. Moreover, the calculation uses the BNF price of £742.00 per vial of ranibizumab, which may be confidentially negotiated to a lower price by the NHS. Nonetheless, this cost comparison demonstrates a substantial saving can be achieved by adopting the TREX regimen.

This study has a number of limitations. Crucially, we were unable to perform conventional meta-analysis with a consistent comparator across the studies. In addition to the majority of studies being rated as low-to-moderate quality of evidence based on the GRADE classification, the pooled data demonstrating a weighted mean gain of 8.92 letters using the TREX regimen cannot be interpreted as causation. The pooled data are limited by the absence of overall randomisation leading to high risk of bias. This highlights a need for future RCTs to evaluate the efficacy

of the TREX-dosing regimen *vs* PRN and monthly dosing, in order to statistically assess whether TREX delivers comparable clinical outcomes in the long term. Furthermore, this systematic review revealed the missing data relating to numbers of injections and visual outcomes in patients receiving ranibizumab monotherapy in several studies. This was because several studies only reported results for patients receiving both bevacizumab and ranibizumab. However, after contacting study authors, we obtained full data for numbers of injections and visual outcomes for patients receiving ranibizumab monotherapy and imputed the SD for BCVA improvement as this was missing for three studies. Finally, despite being unable to perform conventional meta-analysis, a strength of this systematic review was the inclusion of numerous real world outcome studies, demonstrating successful visual outcomes for TREX in real world settings.

Conflict of interest

SRR, HA and AJL have been supported by travel grants from Bayer. The remaining authors declare no conflict of interests.

Acknowledgements

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Appendix 1: Search terms

1. exp Macular degeneration/
2. AMD.tw.
3. (age-related adj3 maculopath*).tw.
4. (retina* adj3 degenerat*).tw.
5. (macula* or heredomacula*).tw.
6. (dystroph* adj3 (macula* or heredomacula*)).tw.
7. (age-related adj3 (macula* or heredomacula*)).tw.
8. (degenerat* adj3 (macula* or heredomacula*)).tw.
9. junius kuhnt.tw.
10. (atroph* adj3 (macula* or heredomacula*)).tw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. Ranibizumab.tw.
13. Lucentis.tw.
14. 12 or 13
15. 11 and 14

Search computed on 26 September 2015

Appendix 2: Screening questions

Stage 1: Title screening

Is the study Level IV evidence or above (including case series, cohort studies, case-control studies, randomised controlled trials and systematic reviews)?

Yes
No
Unclear

Is the study concerned with the use of ranibizumab in neovascular age-related macular degeneration?

Yes
No
Unclear

Stage 2: Abstract screening

Is the study concerned with variable dosing regimens for treatment of age-related macular degeneration?
Yes
No
Unclear

Stage 3: Full paper screening

Is the study concerned with variable dosing regimens featuring regular initial doses of ranibizumab followed by progressively longer treatment intervals, commonly referred to as 'treat-and-extend' dosing regimen and also known as 'inject-and-extend'?
Yes
No
Unclear

Appendix 3

Study number	*Mean number of injections*	*Mean Baseline BCVA*	*Mean BCVA at 12 months*	*Mean improvement in BCVA*
1	8.56	52.00	60.90	8.90
2	8.00	69.90	78.10	8.20
3	9.27	48.50	60.00	11.50
4	12.00	55.50	66.50	11.00
5	8.30	51.00	58.00	7.00
6	7.80	61.20	72.00	10.80
7	7.30	49.70	59.90	10.20
8	8.00	60.50	67.00	6.50
9	10.10	60.00	70.50	10.50