The ROYAL COLLEGE of OPHTHALMOLOGISTS

www.nature.com/eye

EDITORIAL

Treat & extend in neovascular age-related macular degeneration: how we got here and where do we go next?

Eye (2023) 37:581–583; https://doi.org/10.1038/s41433-022-02221-0

The development of anti-vascular endothelial growth factor (anti-VEGF) agents represented a dramatic breakthrough in the treatment of neovascular age-related macular degeneration (nAMD) and multiple phase III pivotal trials have established the efficacy of these agents. However, replicating these trial results in real world practice has been challenging and this has been documented in numerous real world studies [1–8].

The resulting efficacy gap between explanatory clinical trials and real world clinical practice provided strong impetus for a pragmatic treat & extend (T&E) paradigm. Most large T&E trails employed easy to replicate re-treatment criteria that could be successfully implemented in clinical practice [9–14]. A recent meta-analysis also demonstrated that T&E can achieve similar functional and anatomic outcomes compared to fixed or prn dosing regimens [15]. Consequently, there has been widespread adoption of T&E by clinicians globally [16].

In this issue of the EYE, Fu et al. present a large retrospective cohort study from Moorfields Eye hospital where they demonstrate that 68% of eyes could achieve at least one q12 dosing interval with aflibercept in treatment-naïve nAMD patients [17]. This study and others demonstrate that some lesions are more VEGF dependent than others.

It is imperative that clinicians continue to evolve and incorporate new knowledge to further refine and optimize this individualized approach to patient care. What are some important questions that need further evidence generation and evidence synthesis as it pertains to T&E in nAMD management?

1. *Do we always need a loading phase?* There are biological plausibility arguments to support a loading phase. Pivotal trials such as the VIEW trials with intravitreal aflibercept have demonstrated that intra-retinal fluid (IRF) reached its lowest level 1 week after the first injection, however sub-retinal fluid (SRF) could take up to 3 months to reach its trough [18–20]. Since IRF and SRF are important barometers to judge VEGF suppression in clinical practice, it seems logical to reduce fluid levels to the minimum possible level with 3 monthly loading doses. Additionally, visual acuity at month 3 appears to consistently be an important predictor of visual acuity outcomes at month 12 and month 24 [21, 22]. However, there are also valid arguments against a fixed loading dose in all nAMD cases. The CATT trial demonstrated that approximately 14% of patients in the PRN arm needed 3 or less injections in first year of treatment [23]. In addition, aggressive loading at the start does not appear to alter the underlying disease process in terms of long term anti-VEGF requirement for the patient. As such, individualizing the loading phase in future nAMD trials may provide further opportunity to optimize outcomes and reduce treatment burden.
2. *What criteria should be used to define disease activity?* Historically, treat and extend studies have defined active disease as presence of new macular hemorrhage, vison loss of > 5 ETDRS letters and/or presence of intraretinal fluid (IRF) or subretinal fluid (SRF) [11, 24–26]. However, what about other biomarkers such as new subretinal hyperreflective material (SHRM) or an enlarging serous pigment epithelial detachment? Evidence suggests that both of these are poor prognostic factors that can predict future fibrosis and exudation respectively [27–29]. Improvements in multimodal imaging and quantitative analysis of biomarkers will be important for further refining disease activity criteria.
3. *Differential impact of fluid compartments and how that might guide re-treatment intervals?* A recent systematic review on the topic demonstrated either a positive or no negative effect of SRF at baseline and during the treatment cycle on visual acuity outcomes. However, IRF was consistently associated with worse VA outcomes [30]. The FLUID study demonstrated that tolerating up to 200 microns of subretinal fluid at the fovea resulted in non-inferior visual acuity outcomes compared to aggressively treating sub-retinal fluid [31]. Optimizing T&E algorithms in terms of fluid compartments needs further validation and evidence generation.
4. *Can we further "individualize" the extension intervals for T&E?* Vast majority of T&E trials extended stable patients at 2 week intervals. Applying a homogenous extension interval for all patients seems counter-intuitive to the rational behind an individualized care pathway that is the crux of a well designed T&E algorithm. What factors might dictate if stable patients could be extended not only at two week intervals, but potentially at three or four weeks?

   One important variable might be the anti-VEGF agent itself. Data suggests that different agents have different anti-VEGF suppression time [32]. As newer agents get regulatory approval, it will be important to generate evidence to assess whether extension intervals beyond the classic 2 week interval could be employed.

   Another variable might be the lesion type. Should type 3 (retinal angiomatous proliferation) lesions that are exquisitely sensitive to anti-VEGF therapy be treated with the same loading phase intensity and extension intervals as the more treatment resistant type 1 choroidal neovascular membranes [33]? Is tolerating stable SRF in the context of type 1 CNVM have different implications than tolerating stable SRF in type 3 CNMV? A recent retrospective study identified presence of SRF at baseline was the most significant independent negative predictor for visual outcomes for type 3 lesions [34].
5. *How might technological advancements refine and improve the T&E paradigm?* Disruptive technologies such as home OCT monitoring have the potential to dramatically modify many aspects of traditional T&E paradigms. Day to day

Received: 19 July 2022 Revised: 10 August 2022 Accepted: 16 August 2022
Published online: 5 September 2022

remote monitoring of fluctuations in fluid status can potentially allow for increased precision in diagnosing early recurrence and allow for early identification of a patient's ideal re-treatment interval, thus further optimizing T&E paradigms. There might also be further advantage of reducing fluid fluctuations by triggering earlier treatment before significant fluid develops. Multiple post-hoc analysis including those from the CATT and IVAN trials have demonstrated a negative association between large fluid fluctuations and visual acuity [23, 35]. Similarly, advances in Artificial Intelligence may allow more accurate prediction of a patient's anti-VEGF "need" and may in-turn guide extension intervals.

6. *How to incorporate new treatments for Geographic Atrophy (GA) within the T&E paradigm for anti-VEGF treatment for nAMD?* One of the most important recent advancements recently in the field of AMD management has been a positive signal of a treatment affect for complement inhibition in reducing GA progression [36–39]. Given that GA is a common cause of progressive vision loss in nAMD patients [40], it will be imperative that any approved agent for GA can be incorporated into commonly used T&E algorithms for nAMD. This combination treatment will require innovative pragmatic trial design to assess how best to implement this in clinical practice. Which patients with nAMD undergoing anti-VEGF therapy should be candidates for combination treatment for GA atrophy? How best to combine intravitreal treatment for GA along with anti-VEGF treatment for nAMD in a T&E setting? How will this impact the treatment burden and patient compliance?

In summary, the development of pragmatic T&E paradigms for management of patients with nAMD has been a truly impactful step forward for patient care globally. However, as the art and science behind nAMD management continues to evolve, there will be an ever increasing need for robust, pragmatic randomized clinical trials that can move the field forward and further optimize treatment burden and patient outcomes.

Varun Chaudhary [1,2]✉ and Chair, Retina Evidence Trials InterNational Alliance (R.E.T.I.N.A.) Study Group*
[1]*Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada.* [2]*Department of Surgery, McMaster University, Hamilton, ON, Canada.* **A list of authors and their affiliations appears at the end of the paper.*
✉*email: vchaudh@mcmaster.ca*

REFERENCES

1. Arevalo JF, Lasave AF, Wu L, Acón D, Berrocal MH, Diaz-Llopis M, et al. Intravitreal bevacizumab for choroidal neovascularization in age-related macular degeneration: 5-year results of the Pan-American Collaborative Retina Study Group. Retina. 2016;36:859–67.
2. Corazza P, D'Alterio FM, Kabbani J, Alam MM, Mercuri S, Orlans HO, et al. Long-term outcomes of intravitreal anti-VEGF therapies in patients affected by neovascular age-related macular degeneration: a real-life study. BMC Ophthalmol. 2021;21:1–8.
3. Ciulla TA, Huang F, Westby K, Williams DF, Zaveri S, Patel SC. Real-world outcomes of anti–vascular endothelial growth factor therapy in neovascular age-related macular degeneration in the United States. Ophthalmol Retin. 2018;2:645–53.
4. Talks JS, Lotery AJ, Ghanchi F, Sivaprasad S, Johnston RL, Patel N, et al. First-year visual acuity outcomes of providing aflibercept according to the VIEW study protocol for age-related macular degeneration. Ophthalmology. 2016;123:337–43.
5. van Asten F, Evers-Birkenkamp KU, van Lith-Verhoeven JJ, de Jong-Hesse Y, Hoppenreijs VP, Hommersom RF, et al. A prospective, observational, open-label, multicentre study to investigate the daily treatment practice of ranibizumab in patients with neovascular age-related macular degeneration. Acta Ophthalmologica. 2015;93:126–33.
6. Rao P, Lum F, Wood K, Salman C, Burugapalli B, Hall R, et al. Real-world vision in age-related macular degeneration patients treated with single anti–VEGF drug type for 1 year in the IRIS registry. Ophthalmology. 2018;125:522–8.
7. Cohen SY, Mimoun G, Oubraham H, Zourdani A, Malbrel C, Queré S, et al. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the LUMIERE study. Retina. 2013;33:474–81.
8. Khanani AM, Skelly A, Bezlyak V, Griner R, Torres LR, Sagkriotis A. SIERRA-AMD: a retrospective, real-world evidence study of patients with neovascular age-related macular degeneration in the United States. Ophthalmol Retin. 2020;4:122–33.
9. Kertes PJ, Galic IJ, Greve M, Williams RG, Rampakakis E, Scarino A, et al. Canadian treat-and-extend analysis trial with ranibizumab in patients with neovascular age-related macular disease: one-year results of the randomized Canadian treat-and-extend analysis trial with ranibizumab study. Ophthalmology. 2019;126:841–8.
10. Berg K, Pedersen TR, Sandvik L, Bragadóttir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. Ophthalmology. 2015;122:146–52.
11. Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J, et al. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. Ophthalmology. 2018;125:57–65.
12. Wykoff CC, Croft DE, Brown DM, Wang R, Payne JF, Clark L, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. Ophthalmology. 2015;122:2514–22.
13. Ohji M, Takahashi K, Okada AA, Kobayashi M, Matsuda Y, Terano Y. Efficacy and safety of intravitreal aflibercept treat-and-extend regimens in exudative age-related macular degeneration: 52-and 96-week findings from ALTAIR. Adv Ther. 2020;37:1173–87.
14. Mitchell P, Holz FG, Hykin P, Midena E, Souied E, Allmeier H, et al. Efficacy and safety of intravitreal aflibercept using a treat-and-extend regimen for neovascular age-related macular degeneration: the ARIES study: a randomized clinical trial. Retina. 2021;41:1911.
15. Rosenberg D, Deonarain DM, Gould J, Sothivannan A, Phillips MR, Sarohia GS et al. Efficacy, safety, and treatment burden of treat-and-extend versus alternative anti-VEGF regimens for nAMD: a systematic review and meta-analysis. Eye. 2022.
16. American Society of Retina Specialists (ASRS). Annual preferences and trends survey. American Society of Retina Specialists. Chicago, Illinois, 2021.
17. Fu DJ, Keenan TD, Faes L, Lim E, Wagner SK, Moraes G, et al. Insights from survival analyses during 12 years of anti–vascular endothelial growth factor therapy for neovascular age-related macular degeneration. JAMA Ophthalmol. 2021;139:57–67.
18. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119:2537–48.
19. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, Brown DM, Chong V, Nguyen QD, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six–week results of the VIEW studies. Ophthalmology. 2014;121:193–201.
20. Yuzawa M, Fujita K, Wittrup-Jensen KU, Norenberg C, Zeitz O, Adachi K, et al. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. Ophthalmology. 2015;122:571–8.
21. Jaffe GJ, Martin DF, Toth CA, Daniel E, Maguire MG, Ying GS, et al. Macular morphology and visual acuity in the comparison of age-related macular degeneration treatments trials. Ophthalmology. 2013;120:1860–70.
22. CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364:1897–908.
23. Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119:1388–98.
24. Wykoff CC, Ou WC, Brown DM, Croft DE, Wang R, Payne JF, et al. Randomized trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: 2-year results of the TREX-AMD study. Ophthalmol Retin. 2017;1:314–21.
25. Kertes PJ, Galic IJ, Greve M, Williams G, Baker J, Lahaie M, et al. Efficacy of a treat-and-extend regimen with ranibizumab in patients with neovascular age-related macular disease: a randomized clinical trial. JAMA Ophthalmol. 2020;138:244–50.
26. Jia H, Lu B, Yuan Y, Yuan F, Li L, Song Y, et al. A randomized, controlled trial of treat-and-extend vs. pro re nata regimen for neovascular age-related macular degeneration. Front Med. 2022:1712:852519.
27. Shah VP, Shah SA, Mrejen S, Freund KB. Subretinal hyperreflective exudation associated with neovascular age-related macular degeneration. Retina. 2014;34:1281–8.

28. Casalino G, Scialdone A, Bandello F, Chakravarthy U. Hyperreflective material as a biomarker in neovascular age-related macular degeneration. Expert Rev Ophthalmol. 2020;15:83–91.
29. Karampelas M, Malamos P, Petrou P, Georgalas I, Papaconstantinou D, Brouzas D. Retinal pigment epithelial detachment in age-related macular degeneration. Ophthalmol Ther. 2020;9:739–56.
30. Chaudhary V, Matonti F, Zarranz-Ventura J, Stewart MW. Impact of fluid compartments on functional outcomes for patients with neovascular age-related macular degeneration: a systematic literature review. Retina. 2022;42:589.
31. Guymer RH, Markey CM, McAllister IL, Gillies MC, Hunyor AP, Arnold JJ, et al. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. Ophthalmology. 2019;126:723–34.
32. Fauser S, Muether PS. Clinical correlation to differences in ranibizumab and aflibercept vascular endothelial growth factor suppression times. Br J Ophthalmol. 2016;100:1494–8.
33. Levine ES, Custo Greig E, Mendonça LS, Gulati S, Despotovic IN, Alibhai AY, et al. The long-term effects of anti-vascular endothelial growth factor therapy on the optical coherence tomography angiographic appearance of neovascularization in age-related macular degeneration. Int J Retin Vitreous. 2020;6:1–5.
34. Sacconi R, Forte P, Tombolini B, Grosso D, Fantaguzzi F, Pina A, et al. OCT predictors of 3-year visual outcome for type 3 macular neovascularization. Ophthalmol Retina. 2022;6:586–94.
35. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet. 2013;382:1258–67.
36. Heesterbeek TJ, Lechanteur YT, Lorés-Motta L, Schick T, Daha MR, Altay L, et al. Complement activation levels are related to disease stage in AMD. Investigative Ophthalmol Vis Sci. 2020;61:18.
37. Desai D, Dugel PU. Complement cascade inhibition in geographic atrophy: a review. Eye. 2022;36:294–302.
38. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. Retina. 2017;37:819.
39. Jaffe GJ, Westby K, Csaky KG, Monés J, Pearlman JA, Patel SS, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial. Ophthalmology. 2021;128:576–86.
40. Grunwald JE, Pistilli M, Ying GS, Maguire MG, Daniel E, Martin DF. Growth of geographic atrophy in the comparison of age-related macular degeneration treatments trials. Ophthalmology. 2015;122:809–16.

AUTHOR CONTRIBUTIONS

VC was responsible for conception of idea, writing, and critical review of manuscript.

COMPETING INTERESTS

VC: Advisory board member: Alcon, Roche, Bayer, Novartis; Grants: Bayer, Novartis – unrelated to this study.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Varun Chaudhary.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

CHAIR, RETINA EVIDENCE TRIALS INTERNATIONAL ALLIANCE (R.E.T.I.N.A.) STUDY GROUP

Varun Chaudhary[1,2]✉, Mohit Bhandari[1,2], Charles C. Wykoff[3,4], Sobha Sivaprasad[5], Lehana Thabane[1], Peter Kaiser[6], David Sarraf[7], Sophie J. Bakri[8], Sunir J. Garg[9], Rishi P. Singh[10,11], Frank G. Holz[12], Tien Y. Wong[13,14] and Robyn H. Guymer[15,16]

[3]Retina Consultants of Texas (Retina Consultants of America), Houston, TX, USA. [4]Blanton Eye Institute, Houston Methodist Hospital, Houston, TX, USA. [5]NIHR Moorfields Biomedical Research Centre, Moorfields Eye Hospital, London, UK. [6]Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA. [7]Retinal Disorders and Ophthalmic Genetics, Stein Eye Institute, University of California, Los Angeles, CA, USA. [8]Department of Ophthalmology, Mayo Clinic, Rochester, MN, USA. [9]The Retina Service at Wills Eye Hospital, Philadelphia, PA, USA. [10]Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA. [11]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA. [12]Department of Ophthalmology, University of Bonn, Bonn, Germany. [13]Singapore Eye Research Institute, Singapore, Singapore. [14]Singapore National Eye Centre, Duke-NUD Medical School, Singapore, Singapore. [15]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, VIC, Australia. [16]Department of Surgery, (Ophthalmology), The University of Melbourne, Melbourne, VIC, Australia.