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EDITORIAL

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The need for a pragmatic, individualized treat-and-extend (T&E) treatment paradigm for centre-involving diabetic macular oedema

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Eye (2023) 37:2431–2433; https://doi.org/10.1038/s41433-023-02455-6

There is robust evidence to support anti-VEGF treatment as first line for management of patients with centre-involving diabetic macular oedema (CI-DMO) and vision loss [1]. However, after treatment initiation, what treatment paradigm is ideal to optimize outcomes and reduce monitoring and treatment burden?

Fixed dosing regimens have demonstrated robust vision gains in pivotal trials, however, due to the high treatment and monitoring burden, this paradigm cannot be effectively implemented in routine clinical practice [1]. In this issue of EYE, Sivaprasad et al. provide important insights into how clinicians are employing aflibercept in clinical practice as part of the DRAKO study. Their findings once again reinforce that fixed dosing is not used routinely in clinical practice. Even during the loading phase, only one-third of patients received five loading doses.

In contrast to fixed dosing, a pro re nata (PRN) approach where treatment decisions are based on disease activity can reduce treatment burden. However, as demonstrated by Sivaprasad et al., there is still a need for frequent monitoring visits and although the treatment burden decreases in year 2, there was still a significant monitoring burden. In DRCR Protocol I for example, a median number of 38 and 40 visits were required in the ranibizumab + prompt laser and ranibizumab + deferred laser respectively over a 5 year period. Real world data demonstrates suboptimal frequency of monitoring and inferior visual outcomes [2–4]. Moreover, extension studies from pivotal trials have demonstrated on going need for treatment in ~75% of patients with significant heterogeneity in treatment burden [5, 6]. There is also evidence of disease instability and worsening with a PRN approach in extension studies with 20–40% of patients experiencing worsening of diabetic retinopathy severity score [7]. In addition, worsening of functional vision has been demonstrated with a PRN approach in the Protocol T extension study where patients had initially gained a mean of 7.4 letters from baseline to year 2, however, then lost a mean of 4.7 letters from year 2 to year 5 [8].

In contrast to fixed dosing or PRN approach, treat-and-extend (T&E) aims to individualize both the monitoring and treatment burden based on markers of disease activity at a patient level.

A recent meta-analysis compared T&E versus alternate dosing paradigms (fixed/prn) with anti-VEGF agents for CI-DMO and demonstrated similar visual acuity improvement and anatomic outcomes for central subfield thickness in both groups at year 1 and year 2 [9]. However, the certainty of this evidence as assessed using the GRADE approach ranged from very low to moderate [9].

Given these areas of evidence gap, how do we move the field forward? What are key questions that future T&E trials need to address?

(1) Pragmatic, easy to apply T&E paradigm: every trial to date has employed a different re-treatment algorithm. Moreover, the clinical applicability is further limited by the fact that it remains unclear which of these algorithms can be effectively employed in clinical practice. Most studies to date did not have a mechanism in place to assess whether clinicians were indeed making decisions consistent with the prescribed T&E algorithm. Future trials need to not only develop pragmatic T&E algorithms, but also demonstrate high internal validity by assessing whether treating physicians were able to consistently replicate the algorithm accurately.

(2) Individualizing the loading phase: most T&E trials have employed a fixed loading phase. Trex-DME for instance employed 4 monthly loading doses in the T&E arm [10]. However, there is well established heterogeneity in treatment response among patients with CI-DMO. To further individualize treatment and monitoring burden, future trials should assess if a pragmatic T&E paradigm can be commenced as soon as "disease stability" is established without the need for a fixed loading phase in every case. The impact of early extensions impact long term visual and anatomic outcomes needs further assessment.

(3) What is an ideal extension interval? Many trials in CI-DMO management have extended patients in 2 week intervals similar to the neovascular AMD trials. However, as more durable agents get regulatory approval, can we employ longer extension intervals as part of a pragmatic T&E algorithm? Yosemite and Rhine trials for example demonstrated non-inferior visual acuity results with faricimab extension intervals of 4 weeks in the personalized treatment interval (PTI) arm compared to fixed dosing aflibercept [11]. Can similar results be replicated outside of phase 3 explanatory trials? Pragmatic T&E trials are needed to further validate this in real world practice. In addition, the maximal extension interval in T&E trials do date has been capped to 16 weeks. Could we further individualize treatment by extending stable patients safely beyond 16 weeks?

(4) Impact of a pragmatic T&E paradigm on key biomarkers: retinal non-perfusion (RNP) is a hallmark of progressive diabetic retinopathy (DR). It is present in a substantial portion of patients even without clinical evidence of DR [12] and increases in area as DR severity worsens [13]. There is evidence that fixed dosing with anti-VEGF for CI-DMO may fundamentally impact underlying disease pathophysiology of progressive RNP. RISE/RIDE have demonstrated a significant reduction in RNP development at 2 years with monthly ranibizumab compared to sham [14]. Similarly, VISTA trial demonstrated benefit of fixed dosing aflibercept

Received: 23 December 2022 Revised: 10 January 2023 Accepted: 13 February 2023
Published online: 27 February 2023

compared to control subjects [15]. Future trials should assess the impact of a pragmatic T&E compared to gold standard fixed dosing on this fundamental biomarker in DR. Improvements in DR severity scale (DRSS) score levels is another important biomarker that should be assessed to establish the relatively efficacy of a pragmatic T&E algorithm.

(5) How to establish non-inferiority of a pragmatic T&E paradigm: individualizing treatment burden based on patient need is a fundamental concept that is the crux for a T&E regime. However, it is vital that this reduction in treatment does not negatively impact visual acuity outcomes. As such, a robust pragmatic T&E trial must test for non-inferiority on visual acuity as primary outcome in the long term (at least 2 years or longer). Moreover, clinicians should ensure that the "constancy" assumption of a non-inferiority trial design is met. For a non-inferiority trial design to be valid, it is critical that the control arm provides standard of care treatment that is expected to achieve optimal results in clinical practice. In the context of anti-VEGF treatments for CI-DMO, there is no consensus around a "gold standard" PRN or T&E regime. As such, it is important that fixed dosing (established gold standard in pivotal trials) be used as a comparator to ensure non-inferiority on visual acuity outcome is achieved.

In summary, although there is a growing body of evidence supporting a personalized T&E algorithm for CI-DMO management, there are important areas of evidence gap that still remain. Key amongst them is the need for a pragmatic, easy to replicate T&E algorithm that can provide similar long term outcomes to gold standard fixed dosing regime while reducing treatment and monitoring burden. Some of these key areas of evidence gap will be explored in an upcoming multinational, multicentre randomized controlled clinical trial called INSITE-DME [NCT05610319].

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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

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