Letter to the Editor Regarding the “Effectiveness of 190 µg Fluocinolone Acetonide and 700 µg Dexamethasone Intravitreal Implants in Diabetic Macular Edema Using the Area-Under-the-Curve Method: The Constant Analysis” Article [Letter]

This article was published in the following Dove Press journal:
Clinical Ophthalmology

Kasserine Taylor¹
Michael W Stewart²

¹Department of Ophthalmology, Mayo
Clinic Florida, Jacksonville, FL, USA;

²Cornell University, Ithaca, NY, USA

Dear editor

In a recent edition of *Clinical Ophthalmology*, Zarranz-Ventura and Mali presented¹ an area-under-the-curve (AUC) analysis that directly compared the best corrected visual acuity (BCVA) improvements in the pivotal diabetic macular edema (DME) trials (FAME and MEAD) for the fluocinolone acetonide implant (Iluvien) and the dexamethasone implant (Ozurdex). They concluded that patients in FAME had superior BCVA improvement over the course of 36 months. We contend that this analysis and the resultant conclusions are flawed because of methodologic deficiencies in the MEAD trial.

Two major design problems in MEAD resulted in what appear to be inferior BCVA improvements – six-month dosing of the implant and delayed removal of cataracts. The developers of the dexamethasone implant hoped to demonstrate that it was effective for six months after each injection because this would decrease the treatment burden associated with monthly injections of drugs that inhibit vascular endothelial growth factor. Both pre-clinical pharmacokinetic studies^{2,3} and post-approval observations show that the implant's duration of action is only three to four months.⁴ Not surprisingly, the six-month dosing in MEAD consistently produced local BCVA peaks three months after the previous injections, after which the BCVA fell until the next injections (six months). This created a sawtooth BCVA pattern that is characteristic of inadequate dosing. The localized minimums in BCVA decrease the AUC, thereby producing differences between the two drugs that may be largely due to underdosing. By locking physicians and patients into a q6month regimen without regard for recurrent DME, patients were badly undertreated throughout the trial.⁵

Cataracts are expected to develop in trials that evaluate the efficacy of intraocular corticosteroids, and how quickly they are removed will affect the AUC. Best corrected visual acuity in both FAME and MEAD peaked at +6 letters at 6 months, after which it trended down in both trials. In FAME the minimum BCVA was +2 letters at 18 months, after which it returned to +6 letters by 27 months; in MEAD

Correspondence: Michael W Stewart
Department of Ophthalmology, Mayo
Clinic Florida, 4500 San Pablo Road,
Jacksonville, FL 32250, USA
Tel +1 904-953-2232
Fax +1 904-953-7040
Email stewart.michael@mayo.edu

the minimum BCVA was 0 letters at 24 months, and it returned to only +2 letters by 36 months. The shape and depth of the BCVA curve in MEAD were determined by the development of cataracts and how quickly they were removed. With this, two conclusions can be made regarding cataract development: 1) investigators in MEAD were slower to perform cataract surgery and 2) even by the conclusion of the MEAD trial, all of the corticosteroid-induced cataracts had not yet been removed. Supporting these conclusions is the fact that pseudophakic eyes in both trials had rapid BCVA improvements of +6 letters that were maintained for the duration of the trials.

In clinical practice, physicians inject the dexamethasone implant every three to four months to prevent localized BCVA losses and they remove cataracts in a timely manner to minimize the depth and duration of the cataract-induced trough.

Though we agree that the AUC analysis by Zarranz-Ventura and Mali is mathematically correct, it fails to account for the design deficiencies in MEAD and the compensatory strategy that is usually employed by clinicians.

Disclosure

Dr Michael W Stewart reports personal fees from Alkahest and Bayer and grants from Allergan, during the conduct of this communication. The authors report no other potential conflicts of interest for this communication.

References

1. Zarranz-Ventura J, Mali JO. Effectiveness of 190 µg fluocinolone acetonide and 700 µg dexamethasone intravitreal implants in diabetic macular edema using the area-under-the-curve method: the constant analysis. *Clin Ophthalmol*. 2020;14:1697–1704. doi:10.2147/OPTH.S253370
2. Bellocq D, Akesbi J, Matonti F, et al. The pattern of recurrence in diabetic macular edema treated by dexamethasone implant: the PREDIAMEX study. *Ophthalmol Retina*. 2018;2(6):567–573. doi:10.1016/j.oret.2017.10.016
3. Hatz K, Ebnetter A, Tuerksever C, Prunte C, Zinkernagel M. Repeated dexamethasone intravitreal implant for the treatment of diabetic macular oedema unresponsive to anti-VEGF therapy: outcome and predictive sd-oct features. *J int d'ophthalmologie*. 2018;239(4):205–214. doi:10.1159/000485852
4. Stewart MW. *Diabetic Retinopathy: Current Pharmacologic Treatment and Emerging Strategies*. Singapore: ADIS; 2017.
5. Boyer DS, Yoon YH, Belfort R, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904–1914. doi:10.1016/j.ophtha.2014.04.024

Dove Medical Press encourages responsible, free and frank academic debate. The content of the Clinical Ophthalmology 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the Clinical Ophthalmology editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

Clinical Ophthalmology

Dovepress

Publish your work in this journal

Clinical Ophthalmology is an international, peer-reviewed journal covering all subspecialties within ophthalmology. Key topics include: Optometry; Visual science; Pharmacology and drug therapy in eye diseases; Basic Sciences; Primary and Secondary eye care; Patient Safety and Quality of Care Improvements. This journal is indexed on PubMed

Central and CAS, and is the official journal of The Society of Clinical Ophthalmology (SCO). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/clinical-ophthalmology-journal>