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LETTER

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]

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Dear editor

In a recent edition of Clinical Ophthalmology, Zarranz-Ventura and Mali presented[1] 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

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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

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