Letter to the Editor Re: Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naïve Patients with Diabetic Macular Edema

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Dear Editor,

I read the article titled "Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naïve Patients with Diabetic Macular Edema" published in your journal with great interest.[1] I congratulate the authors for making a significant contribution to the literature by presenting the long-term outcomes of dexamethasone (DEX) implant monotherapy in the treatment of diabetic macular edema (DME) in a large cohort of treatment-naïve patients with a follow-up period of up to 80 months. The longitudinal follow-up over six years is highly enlightening, especially considering the "treatment fatigue" that the anti-vascular endothelial growth factor (VEGF) injection burden creates for both the patient and the healthcare system.[2]

As the authors note, despite the significant improvement in best-corrected visual acuity (BCVA) and the reductions in hyperreflective foci (HRF), pearl necklace sign, and intra-cystic hyperreflective material, the progressive increase observed in optical coherence tomography (OCT) markers such as disorganization of the retinal inner layers (DRIL), epiretinal membrane (ERM), and ellipsoid zone (EZ) damage presents a "functional-anatomical paradox" that must be addressed.[3] The authors attributed this phenomenon to natural disease progression and recurrent edema episodes caused by the pro re nata (PRN) treatment regimen, suggesting that a "treat-and-extend" regimen could mitigate this structural damage. This hypothesis could lead to a treat-and-extend protocol utilizing DEX alone or in combination with anti-VEGF therapy. DEX monotherapy is successful in reducing macular thickness. However, the "retinal stress" created by chronic inflammation or the edema-resolution cycles inherent in PRN regimens can cause permanent structural damage.[4] Did the rate of the structural defects demonstrated in the study accelerate after the third year, when the scheduled injection frequency was reduced to as low as 0.5 per year? If so, could this indicate that the retinal tissue had entered a "burn-out" phase rather than disease remission? A notable point is the dramatic reduction in the frequency of administered injections from the fourth year of the study onward. While this is encouraging for clinicians, in real-world data, the fine line between "treatment discontinuation" and "loss to follow-up" is not always clear. Administering 6.83 injections over a mean follow-up of 49 months indicates a remarkably low treatment burden for a chronic pathology like DME.

According to the study's findings, EZ-external limiting membrane (ELM) damage and HRF were among the independent factors influencing the final BCVA. This highlights the complex relationship between anatomical progression and functional outcomes. At this juncture, I would like to ask the authors the following question: Was there a correlation between the development of these structural defects detected on OCT and the frequency of injections, the intervals between follow-up visits, or the duration of treatment-free observation periods? The study included patients with ERM causing superficial traction, yet none underwent ERM surgery. Were there any differences

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in long-term outcomes between eyes with and without ERM, particularly in terms of DRIL and EZ-ELM integrity?

Meanwhile, a few methodological clarifications could further strengthen the interpretation of the findings: (1) It was stated that bilateral eyes were included in the analysis; clarifying whether a statistical approach was used for inter-eye correlation (two eyes from the same patient) would enhance the robustness of the results. (2) As two independent researchers evaluated the OCT findings, reporting inter-observer agreement (kappa/intraclass correlation coefficient) would be beneficial for reproducibility, especially for parameters such as DRIL and EZ-ELM integrity. (3) Finally, compared with the MEAD study, the cataract surgery rate in this cohort was remarkably high (97%), indicating that cataract development in patients scheduled for DEX implant monotherapy should be considered an inevitable "stage" of the treatment rather than a "side effect."[5] Was pseudophakic subgroup analysis or sensitivity analysis considered to mitigate the impact of lens status when interpreting visual gains over time?

The data shared by the authors will raise the need to re-evaluate the anti-VEGF-prioritized treatment paradigm in DME management for selected treatment-naïve cases.

Declarations

Conflict of Interest: No conflict of interest was declared by the author.

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Reply

We thank the author for their interest and valuable feedback regarding our study published in your journal. We believe that these constructive comments make important contributions to addressing the findings of our study from a broader perspective.

Regarding the author's first point, we thank them for highlighting this important issue. Indeed, despite the significant improvement in best-corrected visual acuity and the reduction in inflammatory optical coherence tomography (OCT) biomarkers, such as hyperreflective foci, pearl necklace sign, and intra-cystic hyperreflective material, the progression observed in the disorganization of the retinal inner layers (DRIL), epiretinal membrane (ERM), and ellipsoid zone (EZ) damage is a noteworthy finding. We consider this situation to be largely associated with the chronic progressive nature of the disease and the retinal stress caused by recurrent edema-resolution cycles that can occur during a pro re nata (PRN) treatment regimen.

This interpretation is also consistent with studies evaluating retinal thickness fluctuations in diabetic macular edema.[1,2] Previous studies have shown that greater fluctuations in retinal thickness are associated with poorer functional and structural outcomes, and that recurrent edema reactivations can exacerbate neuroretinal damage. Therefore, not only the anatomical thinning of the macula but also the provision of a more stable retinal microenvironment may be important. We also believe that the chronic nature of the disease and the edema-resolution cycles that can occur during PRN treatment regimens may contribute to progressive structural damage by creating cumulative retinal stress. In this context, proactive treatment approaches that can provide more continuous inflammation suppression and anatomical stability may theoretically offer advantages. The PRODEX study also highlighted the potential importance of dexamethasone (DEX) implants in providing more stable anatomical control.[3]

The structural changes reported in our study did not accelerate after the third year. The results are based on assessments made throughout the entire follow-up period. Therefore, there is no temporal analysis that can directly