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

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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

demonstrate that the progression of DRIL, ERM, and EZ damage accelerates, particularly in the late phase when the number of injections is significantly reduced. However, the decrease in the number of injections over time cannot be solely explained by a "burn-out" phase. It is known that the need for anti-endothelial growth factor treatment can similarly decrease over time in diabetic macular edema. Furthermore, real-world studies utilizing the DEX implant have reported a reduction in scheduled injection frequency over the years. For example, the AUSSIEDEX study reported an average annual number of injections of approximately 2.5.[4] In this respect, our total number of injections over an average follow-up period of approximately 49 months is generally consistent with real-world data reported in the literature.

In our study, no specific correlation analysis was performed to evaluate the relationship of DRIL, EZ-external limiting membrane (ELM) damage, and ERM progression to injection frequency, follow-up intervals, or duration of treatment-free periods. Due to the retrospective real-world design, it is not always possible to definitively distinguish whether the treatment-free follow-up periods reflect disease stabilization, reduced need for treatment, or variability in follow-up/treatment.

Nevertheless, as discussed in our study, we believe that the recurrent edema episodes and associated retinal thickness fluctuations that can occur under PRN treatment regimens may contribute to cumulative retinal stress over time. Therefore, we think the relationship between injection frequency, treatment-free periods, and structural OCT progression should be evaluated through prospective and standardized follow-up protocols.

To better assess the potential impact of ERM on long-term retinal structural outcomes, we performed an additional subgroup analysis between eyes with and without ERM at the final follow-up visit. In the final follow-up evaluation, the DRIL rate was found to be 47.1% in eyes without ERM and 64.8% in eyes with ERM, and the difference between the two groups was not statistically significant (p=0.191). Similarly, at final follow-up, the EZ-ELM defect rate was 41.2% in eyes without ERM and 51.9% in eyes with ERM, and this difference did not reach statistical significance (p=0.443). Evaluated overall, it was observed that both DRIL and EZ-ELM defect rates increased over time, independent of the presence of ERM. This suggests that a statistically significant long-term impact on DRIL progression or the deterioration of EZ-ELM integrity could not be demonstrated in our study cohort.

Drawing attention to the methodological point regarding the inclusion of bilateral eyes in the analysis is also highly valuable. The inclusion of both eyes was preferred to reflect real-world clinical practice and to ensure the optimal evaluation of the available data in this long-term cohort. While inter-eye correlation is a known phenomenon in such studies, similar approaches have also been used in comparable real-world studies in the literature.[5,6,7] Considering the retrospective nature and sample size of our study, an additional statistical correction method was not applied.

We thank the author for their comment regarding the non-reporting of the inter-observer agreement analysis (kappa/intraclass correlation coefficient), despite the OCT findings being evaluated by two independent researchers. The main aim of our study was to evaluate long-term changes, and reproducibility analysis was not among the primary objectives. Nevertheless, consistency was targeted by ensuring the evaluations were conducted by experienced researchers in accordance with predefined criteria.

In our study, 40 (97%) of the 41 initially phakic eyes underwent phacoemulsification surgery during the follow-up period. This rate demonstrates that cataract development in patients scheduled for long-term DEX implant monotherapy is a clinically expected and important process that requires management. Similarly, the IRGREL-DEX study reported that 15 of 16 initially phakic eyes in the treatment-naïve diabetic macular edema group underwent cataract surgery during 24-month follow-up.[8]

The main reason for not including a pseudophakic subgroup or sensitivity analysis in our study was that almost all initially phakic eyes underwent cataract surgery during the follow-up period, making the cohort predominantly pseudophakic at the final follow-up. Therefore, performing a meaningful and balanced subgroup comparison based on lens status would be statistically limited. However, the impact of lens status was considered and discussed in the interpretation of the significant increase in visual acuity in our study. We are of the opinion that cataract surgery is an expected and manageable outcome of DEX implant therapy in long-term follow-up. Therefore, lens status may be an important confounding factor in the evaluation of visual outcomes.

We once again thank the author for their constructive contributions and believe that this valuable discussion will contribute to diabetic macular edema treatment approaches.

Declarations

Authorship Contributions

Design: F.K., Data Collection or Processing: Ö.A., T.U., A.M.Ö., Analysis or Interpretation: A.Ç., H.Ö., M.N.E., Literature Search: G.K., Writing: G.K.

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