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RESPONSE TO LETTER

Effect of Repeated Intravitreal Injections in Glaucoma Spectrum Diseases [Response to Letter]

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Dear editor

We appreciate the authors' comment to our manuscript.[1] To date, the potentially damaging effects of repeated intravitreal anti-VEGF injections on glaucoma progression of patients with pre-existing glaucoma or ocular hypertension has been evaluated seldomly.[2–8] Previous studies on this matter have used metrics such as RNFL thickness to investigate this potential incremental damage to the optic nerve of patients with glaucoma spectrum diseases (GSD). These studies presented conflicting results and several only reported the effect of regular anti-VEGF intravitreal injections in the injected eye group, with no control for comparison.[4,6,7] Thus, their methodology to answer this relevant question was questionable, and further higher quality evidence on this topic was required. RNFL thickness, as with most metrics in the human eye, is not static and presents age-related changes throughout time. In GSD, there is an inherent RNFL thickness decrease, which can happen even when the GDS is properly managed, due to the normal age-related decay of RNFL thickness.[9] Therefore, the purpose of our study was to identify whether repeated anti-VEGF intravitreal injections led to a faster GSD progression. To that purpose, we compared the RNFL thickness variation in regularly anti-VEGF injected eyes with their fellow eyes, which presented a symmetrical GSD and a similar baseline RNFL thickness (in order to reduce selection bias as much as possible). Up to now, only four studies compared regularly injected glaucoma eyes with their fellow uninjected glaucoma eyes.[2,3,5,8] However, none included only paired eyes with symmetrical GSD or performed multivariable analysis to adjust for potential confounders.

In our study, after adjusting for potential confounders, there were no significant differences in the rate of RNFL change or absolute RNFL variation between injected and fellow uninjected eyes, with bilateral symmetric similar GSD and similar baseline RNFL thickness and intraocular pressure (IOP). These findings suggest that the transient IOP elevations that occur after repeated intravitreal injections might not be sufficient to result in an aggravated absolute RNFL thickness decrease in eyes with concurrent glaucoma spectrum diseases.[1] We do not agree that there was a lack of prior patient identification nor confirmation of definite or suspected glaucoma in the study eyes. In fact, the primary objective of our study was to compare only eyes with a symmetrical GSD and a similar baseline RNFL thickness (which we defined as an asymmetry of ≤10 μm in baseline global peripapillary SD-OCT RNFL thickness measurements). This inclusion criteria led to the exclusion of many patients which presented bilateral glaucoma but presented different types of GSD between eyes or presented a significantly lower RNFL thickness in one eye, compared to the fellow eye. Furthermore, there were no significant differences regarding the proportion of eyes under glaucoma medical treatment between injected eyes and their fellow uninjected eyes at the start of the study (55.9% vs 58.8% in the uninjected group; p=0.875) or at the end of the study (76.5% vs 76.5% in the uninjected group; p=1.000). The same applied to the number

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of glaucoma medications (p=0.833). There was a significant increase in both these parameters throughout our study, but the increase was similar in both groups and was not significantly associated with the absolute variation in RNFL thickness.

The primary conclusion of our study was that eyes with glaucomatous spectrum disorders who are submitted to repeated intravitreal anti-VEGF injections do not seem to have a significantly faster RNFL thickness decline in comparison to their fellow untreated eyes. However, in both groups, despite regular follow-up and a similar escalation in glaucoma treatment, included eyes presented a significant RNFL thinning throughout time (−1.18 ± 1.93 µm/year in injected eyes; p<0.001; −1.07 ± 0.98 µm/year in fellow uninjected eyes; p<0.001). Thus, these patients should still be regularly and closely monitored and regular optic nerve evaluations should be made to allow an early detection of glaucomatous progression and adequate early intervention. Future prospective studies with a larger sample size and a longer follow-up are warranted. Additionally, this prospective study could compare injected and fellow uninjected eyes according to their glaucoma severity, with baseline and regular visual field assessments of all included eyes.

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