Effect of Ruboxistaurin on the Visual Acuity Decline Associated with Long-standing Diabetic Macular Edema

We read with interest the article, "Effect of Ruboxistaurin on the Visual Acuity Decline Associated with Long-standing Diabetic Macular Edema," by Davis et al.,[1] in the January 2009 issue. Although we congratulate them for addressing a pertinent topic, we seek a few clarifications regarding the methodology and conclusions.

Baseline data for factors such as diabetes type, body mass index, hemoglobin A_{1C}, systolic and diastolic blood pressure, angiotensin-converting enzyme (ACE) inhibitor use, insulin use, serum lipid profile, and anemia are not compared between the two groups. These factors affect both the incidence of diabetic macular edema and its response to any kind of therapy.

In Figure 2, it is evident that the two arms of the study differed significantly after 18 months of therapy, but because in the prior (PKC-DRS2) study[2] only 75% of the patients completed follow-up, it is important to know how many of the patients with diabetic macular edema completed the follow-up. The authors briefly mention this issue in discussion, but the conclusions appear overdrawn and based on few data.

The authors also gave the confidence limits in Figure 2 for the drug-induced change in visual acuity, but they did not provide a confidence interval for the same statistic after regression analysis, which is likely to have overlapping results. It would have been appropriate to mention the confidence intervals of both arms and the power of the study.

We would appreciate having the authors clarify these aspects for the benefit of the readers.

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Author Response: Effect of Ruboxistaurin on the Visual Acuity Decline Associated with Long-standing Diabetic Macular Edema

We appreciate the comments and requests for clarification from Sahu and Majji on our article, "Effect of Ruboxistaurin on the Visual Acuity Decline Associated with Long-standing Diabetic Macular Edema."[1] Regarding their first question of baseline comparability between groups, the demographic factors they mention were shown to be equivalent between treatment groups in the original PKC-DRS2 study.[2] The analysis in our recent article that included eyes with a baseline visual acuity (VA) >70 letters excluded only approximately 20% of the patients, and so baseline metabolic characteristics for the roughly 80% remaining would not be expected to differ substantially from the study population as a whole. In addition, as described in the article, we performed an adjusted analysis taking into consideration baseline eye characteristics that may affect DME progression, such as visual acuity, DME severity, prior focal photocoagulation, and DR severity. The results were consistent with our unadjusted results.

Regarding their remaining concerns and questions about Figure 2, indeed, 75% of the subjects in the first PKC-DRS2 study completed the entire 36 months of follow-up, and there was no difference between treatment groups in the percentage of subjects who withdrew early. Additional valuable data were also obtained from subjects with shorter follow-up times, however, in that we were able to assess their duration of central macular involvement and to correlate it with their baseline-to-endpoint change in visual acuity, as well.

Regarding the details of the analysis and presentation of data in Figure 2, to give a visual presentation of the distribution of the data (the VA change from baseline broken down by duration of severe DME by treatment group), we used box plots. Within each box, the dot represents the mean, the dark line represents the median, and the main box shows the interquartile range (IQR, the difference between the 3rd and 1st quartiles). The two whiskers show the upper adjacent value (UAV, the largest observation that is less than or equal to the 3rd quartile plus 1.5 × IQR) and the lower adjacent value (LAV, the smallest observation that is greater than or equal to the 1st quartile minus 1.5 × IQR). No confidence interval is presented in Figure 2.

The trend analysis results mentioned in this article (relationship between duration of severe DME and VA in the results section) were based on the following analysis: Within each of five duration categories (Fig. 2), the mean and SE of the VA change from baseline of each treatment group were calculated. The duration of severe DME was calculated as either the exact time (for categories 0 month and 3 months) or the middle point of the category—for example, for category ≥6 to <18, the middle point is (6 + 18)/2 = 12. For the unadjusted analysis, a weighted linear regression analysis was performed, using the mean VA change as the response variable, the duration of severe DME as the dependent variable, and the inverse of the SE as the weight (a category containing a large number of eyes would have a smaller SE and hence a larger weight in such an analysis). This analysis was performed for each treatment group to get the estimated rate of VA change by month and its associated *P*-value. To compare the rates from two treatment groups, a likelihood-ratio test was used (a *P*-value of 0.010 was obtained). Based on that test result, we concluded that the rates of VA change were different between the two groups. With inclusion of baseline factors in this model, results related to the adjusted rate of VA change were obtained and were consistent with the unadjusted results.

Finally, given that the analyses presented in the article were post hoc and hypothesis-generating, a mention of the power of

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the study to detect a difference between treatment groups would not be appropriate.

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Linear Relation between Structure and Function

The main limitation of the study by Danesh-Meyer et al.[1] was neither discussed nor mentioned. The time axis was not taken into account. The functional change after an acute event such as anterior ischemic optic neuropathy (AION) is immediate, but there is a delay before the anatomic changes take place. In this study, most of the patients with nonarteritic anterior ischemic optic neuropathy (NAION) or arteritic anterior ischemic optic neuropathy (AAION) were tested a short period after the acute event, as described by the authors.

In a similar study by Hood et al.,[2] the patients were tested at least 5 months after the AION event, with a median of 2.95 years. The reason was to allow sufficient time to minimize the effects of optic disc swelling and to allow the retinal ganglion cell (RGC) axons to degenerate. The results of the study in Hood et al. are obviously contrary to those presented by Danesh-Meyer et al. The relationship between a structure (optical coherence tomography [OCT]–determined retinal nerve fiber layer thickness) and function (standard automated perimetry [SAP]–determined sensitivity loss) is the same in patients with AION as in those with open angle glaucoma (OAG).

It is not adequate to use visual field perimetry results as a criterion for comparison in the population examined by Danish Meyer et al.,[1] as visual acuity and visual fields improve up to ~6 months from the onset of NAION.[3]

The only conclusion that can be made from the results of Danish-Meyer et al.[1] is that a few months after the acute event of NAION/AAION the optic disc and RNFL look different than they do in OAG.

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Author Response: Linear Relation between Structure and Function

We thank Wegner and Erben for their comments and draw their attention to the Discussion in our article.[1] In that section, we addressed their concern by stating that "most of our imaging studies were performed longer than 6 weeks after presentation, with 52 (91%) of 57 NAION and 16 (80%) of 20 AAION eyes imaged with HRT and/or OCT 3 months or more after the event." We further discussed that there may have been some additional thinning of the RNFL, which continues subsequent to this time point. However, when we limited the patients included to those with data recorded greater than 3 months after the acute AION event, there were no significant changes in the results.

We also disagree that the data of Hood et al.[2] are similar to ours. They did not evaluate optic disc topography, but rather modeled the relationship of peripapillary retinal nerve fiber layer thickness to visual field mean deviation. The conclusion we drew from our work was that there was a difference in the topography of the optic disc between open angle glaucoma and the anterior ischemic optic neuropathies, not that there were differences in nerve fiber layer thickness. We believe our conclusion about differences in disc topography is strengthened by the fact that we explicitly controlled for the total amount of damage in each condition, using either visual field mean defect or average nerve fiber layer thickness. Furthermore, Hood et al. did not differentiate between AAION and NAION in their study.

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