• Comment and Response •

# Comment on "Intravitreal dexamethasone implants for diabetic macular edema"

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**Dear Editor,**

We would like to address several issues with the study of Pareja-Rios *et al*[1].

The study was retrospectively conducted and 3mo of treatment with laser or anti-vascular endothelial growth factor (VEGF) agents mean a period of time too short to label a patient as nonresponder to these therapies.

There was a selection bias attributable to inclusion in the study and pooled analysis of the eyes that were naive to treatment for diabetic macular edema (DME) and eyes that had received prior treatments (anti-VEGF therapy, laser or a combination thereof). Likewise, the results were globally analyzed as a unique group consisting of pseudophakic, naive, phakic, and vitrectomized patients. Taking together, these issues make interpretation of the outcomes challenging.

We hypothesized that a whole panoply of proinflammatory and proangiogenic cytokines, chemokines, and growth factors may be associated with the multifactorial pathophysiology of the DME. They are maximally expressed in the ischemic lesions of the long-standing DME and exacerbate the deterioration primarily caused by VEGF in the initially damaged macular ganglion cell complex[2].

There were no details regarding the DME defined as retinal thickening or hard exudates at or within 1 disc diameter of the macula center and which is most commonly classified into either being clinically significant or not. Nothing was stated concerning the optical coherence tomography patterns of the DME (sponge-like swelling/cystoid macular edema/subfoveal neuroretinal detachment/mixed type) and the location of the cystoid type (ganglion cell layer/inner/outer nuclear layers) at enrollment and at the end of the study.

Initially, a comparison had to be carried out between the 3 groups of patients to establish whether or not they are comparable. Accordingly, this comparison should have been conducted only if there were no significant baseline differences between all variables of these 3 groups[3]. Of note, there were obvious baseline differences between the pseudophakic, naive, and phakic groups concerning the following findings: the mean age of patients, the mean best-corrected visual acuity (BCVA), and the mean central macular thickness (CMT). Importantly, the baseline features of the patients in the treatment-naive group completely differ from those of the patients of the other two groups, namely, they have the lowest age, the best BCVA, and the greater CMT. In addition, they are the only one who have had recent cardiovascular events.

The following relevant data are missing from the study: the age of diabetes and the duration of the DME before entry into the study after diabetes onset; the qualitative status of the retinal inner layers, the outer nuclear layer, the external limiting membrane band, the ellipsoid zone, and the interdigitation zone at enrollment and at the end of the follow-up period; the qualitative status of the retinal pigment epithelial band-Bruch membrane complex and grading of the retinal pigment epithelium (RPE) changes (pigment migration within the neurosensory retina, RPE porosity, microrips or blowouts in the RPE, focal RPE atrophy, RPE thickening, presence of reticular pseudodrusen) at the enrollment and in month 12; the prevalence of the vitreoretinal interface abnormalities, the subfoveal thickness, and the quantification of the hyperreflective retinal foci at presentation and at the end of the follow-up period; and the proportion of the eyes with sustained retina dryness at the end of the study.

In the assessment of the 12-month results of this study we considered the current assertion according to which evaluation of outcomes should be guided by the anatomic measure data with visual changes as a secondary guide[4]. Accordingly, the outcomes of this series are unsatisfactory. Specifically, despite a mean gain of 4.2 letters in BCVA, the CMT decreased to approximately 420 μm, a value much more than the cutoff of the upper level of the normal CMT. The persistence of

this high value of the CMT after treatment highlighted unresolved macular edema owing to insufficient macular deturgescence and indicated that the disease process was still active and progressive requiring further treatment with anti-angiogenic agents[5].

Nothing was stated regarding the diabetic choroidopathy, which consists in intrachoroidal vascular abnormalities and which may directly induce choroidal ischemia, leading to RPE dysfunction. The progressive thickening of the choroid layer caused by increasing the severity of the diabetic retinopathy (DR; from no DR to proliferative DR) and development of DME (being thickest in eyes with serous neuroretinal detachment type of DME) denotes progression of the diabetic choroidopathy[6].

The currently available recommendations[7] that the duration of ≥3-line improvement after a dexamethasone (DEX) implant is typically 2 to 3mo, and that reinjections generally will be performed after 4 to 5mo have not been taken into account by the authors. If these assertions had been considered, the design and outcomes of the present study would have been completely different.

We believe that the specific anti-VEGF drugs [*e.g.* bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA, USA)/ranibizumab (Lucentis, Genentech, Inc.)/aflibercept (Eylea, Regeneron Pharmaceuticals, Inc. Tarrytown, NY, USA)] represent the front-line therapy for the treatment of DME but the VEGF inhibition alone may not be sufficient to decrease the inflammatory response. Therefore, the addition of a non-specific anti-VEGF substance (*e.g.* DEX implant), which inhibits the up-regulation of VEGF and suppresses the expression of the whole inflammatory factors, is mandatory[5].

Altogether, regardless of the intravitreal pharmacotherapy chosen, namely, specific or nonspecific anti-VEGF agents, the efficacy of the treatment depends primarily on the promptness of the therapy after DME diagnosis[2]. Both groups of anti-VEGF substances provide similar rates of vision improvement, but with superior anatomic outcomes and fewer injections in the corticosteroid implant-treated eyes. However, more patients receiving the corticosteroid implant lose vision mainly due to cataract[2,5].

**ACKNOWLEDGEMENTS**

**Conflicts of Interest: Călugăru D,** None; **Călugăru M,** None.

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**Author Reply to the Editor**

**Dear Editor,**

We thank the authors of the letter for their comments regarding our paper "Intravitreal dexamethasone implant for diabetic macular edema"[1]. However, we would like to make some comments back about the issues they cited.

Regarding the interval between the previous treatments and the DEX implant, we did not said that only one session of laser was applied, but it is explicitly stated that the interval between the last laser treatment and the DEX treatment was at least 6mo. Nevertheless, It is said that patients received at least 3 monthly injections of anti-VEGF (following by prorenata pattern and sometimes supplemented with macular laser) and that the last injection of anti-VEGF therapy was performed at least 3mo before starting treatment with DEX implant. This early change from anti-VEGF to DEX implant is supported by the work of Busch *et al*[2]. In their retrospective clinical study, they compared the anatomical and functional results of eyes with refractory DME after 3 monthly injections of anti-VEGF and two possible clinical actions: continuing treatment with anti-VEGF therapy, or change to DEX implant. Mean change in BCVA at 12mo was of -0.4±10.8 for the anti-VEGF group and 6.1±10.6 letters for the DEX implant group ($P$=0.004). Results were statistically significant no matter of the anti-VEGF used. At 12mo, the central subfield thickness change was of 18.3±145.9 μm in the anti-VEGF group versus -92.8±173.6 μm in the DEX implant group ($P$<0.001). We believe that the validity of our methodology is supported by the fact that in the cited study by Busch *et al*[2], eyes with DME considered refractory to anti-VEGF therapy after three

**Table 1 Data of the patients at the baseline visit**[1]

| Characteristic | Total (*n*=113) | Pseudophakic (*n*=72) | Naive (*n*=11) | Phakic (*n*=30) |
|---|---|---|---|---|
| Age (a), mean (SD) | 69 (14) | 73 (8) | 62 (13) | 65 (8) |
| BCVA (letters) | | | | |
| Mean (SD) | 43.5 (20.8) | 42.2 (20.7) | 56.5 (16) | 42.4 (21.4) |
| Range | 4-80 | 4-80 | 20-75 | 8-80 |
| CMT (μm) | | | | |
| Mean (SD) | 462.7 (145) | 460.3 (159) | 502.8 (117) | 454.3 (131) |
| Range | 194-850 | 194-850 | 380-687 | 215-828 |
| MV (μm) | | | | |
| Mean (SD) | 12.6 (2.5) | 12.7 (3) | 12.4 (1.6) | 12.5 (1.8) |
| Range | 7.8-20.2 | 7.8-20.2 | 10.7-15.5 | 9-15.7 |
| IOP (mm Hg) | | | | |
| Mean (SD) | 17 (3) | 17 (3) | 17 (3) | 17 (3) |
| Range | 9-26 | 9-24 | 15-23 | 12-26 |

There were no statistically significant differences in clinical and demographic variables between subgroups at baseline except that BCVA was higher in the naive subgroup ($P$≤0.05).

monthly injections which were switched to DEX implant, had better visual and anatomical outcomes at 12mo than those that continued treatment with anti-VEGF therapy.

Contrary to what is said in the letter, we did not include any vitrectomized patient in the study. In fact, it is stated in the results section that we excluded 2 vitrectomized eyes from the study precisely for that reason. It is true that results were globally analyzed as a unique group consisting of pseudophakic, naive and phakic. However, it is also true that the results were also analyzed for each of the sub-group individually, as can be seen in each and every one of the tables and figures within the article. In addition, rigorous statistical analyses were carried out comparing the subgroups with each other, whose results are showed both in the results and in the discussion.

In the letter, it is said that "a comparison had to be carried out between the 3 groups of patients to establish whether or not they are comparable". Such a comparison can be found in Table 1[1] of our work. As indicated in the text, there were no statistically significant differences in the clinical or demographic variables between the sub-groups at baseline except that the BCVA was higher in the naive subgroup. This is an interesting aspect of our paper that we have not commented on in the original work and it makes us wonder if it is possible that there was a ceiling effect that would explain the lower BCVA gain in this sub-group[3].

In the letter it is also stated that the outcomes of our series are unsatisfactory and the results in CMT are much higher than the cut-off of the upper level of the normal CMT. As can be seen in Figure 4[1] of our work, CMT reached normal values in naive group and values were very close to normality in the rest of subgroups at 1mo. It is worthy to note that CMT was statistically lower ($P$<0.05) for the whole sample and for all the subgroups with respect to baseline values at 1mo and 3mo.

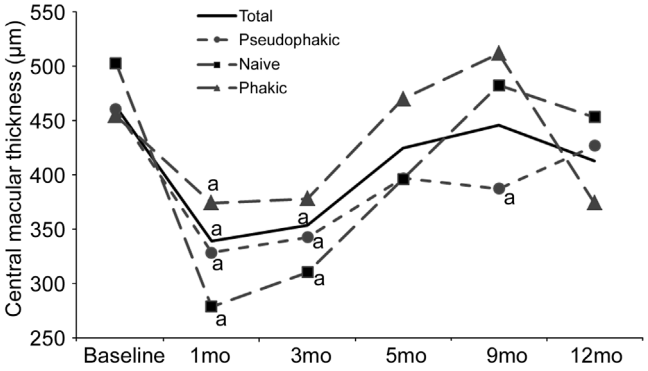


**Figure 4 Mean CMT for each subgroup at baseline, months 1, 3, 5, 9 and 12**[1] [a]$P$≤0.05.

We agree that the persistence of fluid may indicate disease activity, but it is not a ground truth that it should be treated with combined therapy of anti-VEGF and DEX implant. Another option would be to deal with more frequent intervals DEX implant (every 3-4mo)[4-6].

In the letter, it is asked for a huge variety of data to be missing. Although it is true that a large number of data can benefit the results of a study, an excessive number can increase its complexity, its economic cost and its readability. In fact, it is not usual for this type of studies to collect as much data as the authors of the letter suggest, even when the study is designed prospectively as for example in the work of Călugăru *et al*[7] exploring the effects of intravitreal bevacizumab in retinal vein occlusions.

Authors of the letter suggest that we should have followed the recommendations of Kuppermann *et al*[8] regarding the reinjections rate of DEX implant. In one hand, as reflected in the article, at the time DEX implant was not yet accepted by the European Medicines Agency and therefore, there were no official recommendations for its use in DME. On the other hand, the recommended article refers to macular edema due to venous occlusion not to DME.

By last, authors of the letter seem to support a combined therapy, however there is not yet enough scientific evidence to support one therapy in front of the other.

Alicia Pareja-Ríos[1], Sergio Bonaque-González[2], Paloma Ruiz-de la Fuente-Rodriguez[1], Pedro Romero-Aroca[3], Maribel López-Gálvez[4]

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