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RESEARCH ARTICLE

REAL-WORLD OUTCOMES OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY IN DIABETIC MACULAR EDEMA IN THE UNITED STATES

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ABSTRACT

The authors are commenting on the article entitled "Real-world of anti-vascular endothelial growth factor therapy in diabetic macular edema in the United States" published by Ciulla et al. in Ophthalmology Retina; http:/dx.doi.org /10.1016/j.oret.2018.06.004. Published online July 28, 2018.The conclusion resulting from this article is that regardless of the intravitreal pharmacotherapy chosen, namely, specific (bevacizumab, ranibizumab or aflibercept) or nonspecific (corticosteroid implant) anti-vascular endothelial growth factor agents, the efficacy of the treatment depends primarily on the promptness of the therapy after diabetic macular edema diagnosis. The validation, extrapolation, and generalizability of the authors' conclusion can be made only by statistical analyses including all the missing baseline potential predictive factors mentioned by us in addition to the baseline characteristics already evaluated in the study, which serve as potential prognosticators influencing functional and anatomic improvements.

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INTRODUCTION

We would like to address several issues with the study of Ciulla *et al*. (2018).

1. Their retrospective study had several relevant limitations, namely, the utilization of the non standardized visual acuity (VA) assessment from the sites, the possibility of prior treatment for diabetic macular edema (DME) in a practice that does not report to the database, and the classification of DME patient eyes based on initial anti-vascular endothelial growth factor (VEGF) agent, without accounting for switching between agents. Taking into account these findings it is not surprising that no differences among therapeutic agents were noted, thereby limiting the ability to evaluate the relationships between visual outcomes and anti-VEGF therapy.
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. Moreover, the criteria used to define the clinically significant DME, if it was present in some patients, were not indicated.

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3. The following relevant data are missing in the study: the age of diabetes, the duration of DME before entry into the study after diabetes onset, and the degree of control of diabetes; the existence or otherwise of the diabetic retinopathy; the classification (center-involved/non-center-involved/ clinically significant) and the optical coherence tomography patterns of the DME (sponge-like swelling/ cystoids changes/ subfoveal/ neuroretinal detachment/ mixed type); the systemic comorbidities associated (hypertension/chronic renal insufficiency); and the prevalence of the vitreoretinal interface abnormalities (vitreomacular adhesion/ traction/ epiretinal membranes).

4. In the assessment of the final results of this study we considered the current assertion that evaluation of outcomes has to be guided by anatomical measure data with visual changes as a secondary guide (Freund *et al.* 2015). Although the mean 12-month improvements in VA were 5.5, 5.5, and 4.0 Early Treatment Diabetic Retinopathy Study (ETDRS) letters after treatment with aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY), bevacizumab (Avastin, Genentech, Roche Group, South San Francisco, CA), and ranibizumab (Lucentis, Genentech, Roche Group), respectively, the effectiveness of the treatments in this series cannot be assessed owing to lack of OCT data of retinal morphology. Moreover, nothing was stated about the existence of otherwise of a washout period, which is essential between different periods of

treatments administered (anti-VEGF agents/focal laser/panretinal photocoagulation/ corticosteroid injections [triamcinolone with or without preservative and dexamethasone implant] [Ozurdex, Allergan, Irvine, CA]) in terms of aliased effects. Thus, the impact of significant carryover effects may be confounded with direct treatment effects because these effects could not be estimated separately; carryover effects may bias the interpretation of data analysis.

5. An interesting statement was made by the authors, namely, the largest VA gains were observed in eyes that started treatment with the worst vision. We documented for the first time, (Călugăru *et al*. 2015), the impact of initial VA on bevacizumab treatment outcomes in patients with macular edema secondary to acute central/hemicentral retinal vein occlusions. Although VA improvements at month 36 were significant in patients with both the nonischemic and ischemic occlusions, the magnitudes of response to treatment were totally different, namely, an increase in VA of 17.5 ETDRS letters (from 48.6 to 65.75 ETDRS letters) in case of nonischemic forms and of 26.81 ETDRS letters (from 7.6 to 34.41 ETDRS letters) in patients with ischemic occlusions. The proportions of VA increases (from baseline values) were 36% in patients with better initial VA and 352.7% in patients having a poor initial VA, respectively. The assumption according to which patients with poor initial VA may benefit most from anti-VEGF suppression and vice versa, seems to be a somewhat paradoxical and counter-intuitive finding because patients with poor initial VA usually have advanced lesions with ischemia and atrophy that could limit recovery. And yet, this assertion is logical because patients with low initial VA have a larger range of the interval in which VA can be improved compared to patients with a better initial VA having a more narrow interval and small possibilities for improving. This is the treatment "ceiling effect" thereby limiting improvement in VA.

6. We believe that the specific anti-VEGF agents (e.g., aflibercept/bevacizumab/ ranibizumab/) represent the front-line therapy for the treatment of DME, but the VEGF inhibition alone may not be sufficient to suppress the whole panoply of proinflammatory and proangiogenic cytokines, chemokines, and growth factors associated with the multifactorial pathophysiology of 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. Therefore, the addition of a non-specific anti-VEGF substance (e.g., a corticosteroid implant), which inhibits the up-regulation of VEGF and suppresses the expression of the whole inflammatory factors, is mandatory (Călugăru *et al*. 2018). Regardless of the intravitreal pharmacotherapy chosen, namely specific of nonspecific anti-VEGF agents, the efficacy of the treatment depends primarily on the promptness of the therapy after DME onset. 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 (Călugăru *et al.* 2018a).

Altogether, the validation, extrapolation, and generalizability of the authors' conclusion can be made only by statistical analyses including all the missing baseline potential predictive factors mentioned by us in addition to the baseline characteristics already evaluated in the study, which serve as potential prognosticators influencing functional and anatomic improvements.

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