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CORRESPONDENCE

Sir,
Aflibercept in diabetic macular edema: evaluating efficacy as a primary and secondary therapeutic option

We would like to address several challenges arising from the article by Ashraf *et al*[1] regarding the alternative roles for aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY, USA) in the management of eyes with non-naive diabetic macular edema (DME).

1. We do not agree the authors'assertion that switching to aflibercept may be a valid option for patients being treated with alternate anti-vascular endothelial growth factor (VEGF) agents. The presumed pharmacologic advantages of aflibercept over bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) or ranibizumab (Lucentis, Genentech) (for example, a higher binding affinity for VEGF-A and activity against VEGF-B, and placental-derived growth factor) were not confirmed by the poor results of the latest publications. Thus, Wood *et al*[2] reported persistent macular edema in 50% of the eyes and a loss in visual acuity (1 line) in 21.4% of the eyes after aflibercept injection. Rahimy *et al*[3] displayed incomplete resolution of the DME (significant decrease of foveal thickness to 348.7 μm, a value that was more than the cutoff for the upper level of normal foveal thickness[4]), increase in the number of eyes with epiretinal membranes from 18 to 20, and of those with vitreomacular traction from 2 to 4 after switching to aflibercept.

2. VEGF is one contributor to macular edema in patients with diabetic retinopathy. Besides, a panoply of proinflammatory and proangiogenic cytokines, chemokines, and growth factors may be associated with 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.

3. The specific anti-VEGF drugs represent the frontline therapy for the treatment of DME, but only the VEGF inhibition may not be sufficient to decrease inflammatory response. Therefore, addition of a non-specific anti-VEGF substance, that is, a corticosteroid injection, is mandatory.

Altogether, regardless of the intravitreal pharmacotherapy chosen, namely, specific (bevacizumab/ranibizumab/aflibercept) or nonspecific (corticosteroid implant) 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.[5]

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Both the authors (DC and MC) were involved in design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript.

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Sir,
Aflibercept in diabetic macular edema: evaluating efficacy as a primary and secondary therapeutic option

We thank Dan Călugăru and Mihai Călugăru for their insight into our publication; however, we disagree with several of the points they made.

There is no clear data showing the greater efficacy of switching to steroids versus aflibercept in cases of chronic DME refractory to bevacizumab/ranibizumab therapy (Table 1). In addition, steroids are known to cause complications such as elevated IOP as well as cataracts which is a limitation to their use particularly in phakic patients. The exact timing of this switch is particularly important because as suggested by the FAME study, chronic edema is estimated to begin 1.73 years post the start of edema.[1] Patients treated with steroids in the FAME study who had edema <3 years failed to show anatomic or visual gains compared with the sham group. Only patients who had edema >3 years responded significantly. If we were to consider the definition suggested, patients are expected to have received at least 19 prior injections before steroids would be a valid option. In the study by Rahimy *et al*[2] patients had a previous median of 13 injections which would fall within the predicted margin of non-chronic edema. Therefore, it is

Table 1 Summary of the major studies that looked at switching between intravitreal drugs in diabetic macular edema

Author	*Year*	*Number of patients*	*Duration of follow-up*	*Previous treatment*	*Intervention*	*Visual acuity results*	*OCT results*	*Other*
Zhioua *et al*[8]	2015	13 eyes of 12 patients	9 months	6-monthly ranibizumab	DEX implant (mean 1.07 injections)	+5.58 letters at month 1, 4.61 letters at month 6	Decrease of 192 μm at month 1, 135 μm at month 6 ($P=0.02$) and 105 μm at month 9 ($P=0.03$)	
Totan *et al*[9]	2015	30 eyes of 30 patients	6 months	Resistant to three consecutive BVZ injections	DEX implant	+8 letters change from baseline at month 1 and+6 letters at 3 months.	Decrease of 227 μm, 203 μm, and 106 μm from baseline at months 1, 3, and 6, respectively	Rebound of macular edema between month 3 and 6. Recurrence in 25 eyes.
Lazic *et al*[10]	2014	16 eyes (15 patients)	4 months	Non responsive to three consecutive BVZ injections	DEX implant	+4 letters after 2 months ($P=0.04$)	Mean CFT decreased by 96 μm, 116 μm, and 107 μm from baseline at month 1, 2, and 3, respectively.	Significant increase in IOP at months 1, 2, and 3
Bansal *et al*[11]	2015	67 eyes of 52 patients	6 months	Mean duration of edema 45.4 ± 22.5 months	DEX implant	+9 letters from baseline at 4 months ($P=0.024$) and +10 letters at 6 months ($P=0.09$).	Mean CFT decrease from 514 μm at baseline to 316 μm at 4 months and 419.9 μm at 6 months.	Transient rise in IOP at 2 months, controlled by IOP lowering medications.
Gutierrez-Benitez *et al*[12]	2015	14 eyes of 14 patients	Mean 7.6 months	DME refractory to ranibizumab monotherapy	DEX implant	+6 letter gain from baseline at 2 months ($P=0.03$) and+4 letters from baseline at end of follow-up	Decrease in foveal thickness by –198 μm from baseline at 2 months ($P=0.01$) and –126 μm from baseline at end of follow-up	43% required re-treatment 21% had elevated IOP
Alshahrani *et al*[13]	2015	53 eyes (26 eyes with DME)		Refractory edema (no improvement of 2 or more lines in snellen VA and of the CMT on OCT that remained above 350 despite treatment for more than 6 months of any anti-VEGF (ranibizumab, BVZ or aflibercept)	DEX implant	+15 letter gains at 1 month and +20 letters at 3 months ($P<0.05$ both visits)	Decrease of 265 μm from baseline at 1 month, decrease of 183 μm from baseline at 3 months, and decrease of 123 μm from baseline at 6 months.	26% developed high IOP 1.8% developed cataract
Maturi *et al*[14]	2015	40 eyes of 30 patients.	12 months	Not specified- no specific criteria except previous BVZ treatment	Two groups: Group 1 had BVZ at baseline then DEX implant at 1, 5, and 9 months; group 2 received BVZ monthly, if needed.	Mean visual acuity change from baseline to 12 months were similar in the two groups (+5.4 letter in the combined group, +4.9 letters in the BVZ only group. ($P=0.75$)	Mean reduction in CFT was greater in the combined group –45 μm *vs* –30 μm in the BVZ only group. ($P=0.03$)	Greater number of patients had subfield thickness <250 μm. 11 *vs* 10 eyes. 6 eyes in the combined group develop high IOP

Table 1. (Continued)

Author	*Year*	*Number of patients*	*Duration of follow-up*	*Previous treatment*	*Intervention*	*Visual acuity results*	*OCT results*	*Other*
								vs 1 in the BVZ only group.
Rahimy *et al*[2]	2016	50 eyes of 37 patients	4.6 months	Previous BVZ or RBZ (at least four consecutive injections)- mean 13.7 injections.	Aflibercept (mean 4.1 injections)	Pre-switch VA 0.60 log MAR, improved to 0.55 log MAR at second visit ($P=0.12$)	Decrease of 112 microns by the second visit ($P<0.0001$). 24% had complete resolution of fluid. 56% showed improvement of edema.	No change in IOP 25 eyes (50%) had gained ≥1 line of vision, of which 11 (22%) gained ≥2 lines, and 6 (12%) gained ≥3 lines
Wood *et al*[5]	2015	14 eyes	1 month	Previous BVZ or RBZ.	Aflibercept	No significant improvement in VA	79% of eyes showed anatomic improvement. CFT decreased from 421 µm to 325 µm ($P<0.0132$) No eyes achieved dryness	23% decrease in average CST.

Abbreviations: anti-VEGF, anti- vascular endothelial growth factor; BVZ, bevacizumab; CFT, central foveal thickness; DME, diabetic macular edema; DEX, dexamethasone implant (Ozurdex); IOP, intraocular pressure; OCT, optical coherence tomography; RBZ, ranibizumab.

important to have a clear definition for chronic and refractory edema because the two are not mutually exclusive. It would be expected that steroids would not be as effective in early switching. With regards to late switching, its superiority should be assessed using a randomized control trial, with the understanding that before such a trial clear definitions have to be pre-determined.

Although it is tempting to class all anti-VEGFs together and that they are all fairly interchangeable, recent data from protocol T has demonstrated significant anatomical differences between aflibercept, ranibizumab, and bevacizumab during the first year especially for patients with baseline VA <20/40 (6/12).[3] The exact reason for this difference although speculative cannot be disregarded (CFT <250 microns in 70% of cases treated with aflibercept compared with 60% for ranibizumab and 50% for bevacizumab). It also highlights the anatomic effectiveness of aflibercept in resolving edema, especially in patients with high volumes of residual fluid.[4]

With regards to switching, the study by Rahimy *et al* showed that 25% of patients achieved dryness, whereas 56% showed improvement.[2] Wood *et al* showed that 80% of eyes showed some improvement in anatomy.[5] This anatomic improvement in a significant percentage of patients is worth exploring before switching to steroids, which has been shown in the switch studies to cause increased IOP in ~20–25% of cases with many patients requiring re-treatments (Table 1).

Finally, switching in DME has not been extensively studied; AMD has over 40 publications that have tackled switching to aflibercept compared with only 3 in DME.[5–7] This issue warrants more studies and more data before reaching a definitive conclusion regarding the efficacy and timing of switching. However, it remains a valid first option in non-responsive cases before steroid switch.

Conflict of interest

The authors declare no conflict of interest.

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Sir,

Comment on 'Comparison of subthreshold micropulse laser (577 nm) treatment and half-dose photodynamic therapy in patients with chronic central serous chorioretinopathy'

In their interesting article, Scholz *et al*[1] compare 2 treatments for chronic central serous chorioretinopathy (cCSC) on the basis of changes in central retinal thickness (CRT) and resolution of subretinal fluid (SRF) at 6 weeks after treatment. The authors conclude that significantly more patients showed a treatment response to subthreshold micropulse laser (SML) treatment and that SML leads to a greater decrease in CRT in comparison with half-dose photodynamic therapy (PDT). There was no statistically significant difference in complete SRF resolution and best-corrected visual acuity between the 2 groups after a post-treatment follow-up period of 6 weeks.

In cCSC, a complete SRF resolution may be an important anatomical outcome parameter of treatment because such a resolution reconstitutes the normal relationship between photoreceptors and retinal pigment epithelium, and persistent SRF appears to be an important risk factor for long-term vision loss.[2] In the study by Scholz *et al*, the percentage of patients who showed complete resolution of SRF on OCT in both the SML and the half-dose PDT group was remarkably low as compared with previous large retrospective studies, which describe complete resolution in 41–100% of cCSC cases.[3,4] The authors indicate that this could have been caused by a relatively long disease duration in the included patients. Indeed, the clinical definition of cCSC and treatment inclusion criteria for cCSC is variable and subject to debate, and may influence the likelihood of treatment success.[3] The relatively short follow-up period of 6 weeks to evaluate treatment success may have also influenced the rate of SRF resolution.[4] Also, abnormalities on indocyanine green angiography (ICGA) in cCSC are often more extensive than those on fluorescein angiography, indicating primary choroidal dysfunction, and may therefore favour ICGA-based treatment to increase the likelihood of complete SRF resolution.

A wide variety of treatments has been advocated for cCSC, underlining the controversy surrounding cCSC therapy.[5] On basis of the available retrospective evidence, SML and PDT appear the most promising candidate treatments.[5] As indicated by the authors, large prospective multicenter randomized controlled treatment trials are pivotal to establish the optimal treatment modality for cCSC. Treatment with both 577 nm and 810 nm SML has been used in cCSC and no clear preference can be advocated based on the available literature.

In collaboration with the authors, we are currently conducting a prospective multicenter randomized controlled treatment trial (the PLACE trial) comparing half-dose PDT with 810 nm SML in cCSC.[6] In this trial, both anatomical outcome parameters such as a complete resolution of SRF and functional outcome parameters such as visual acuity, microperimetry, and Visual Functioning Questionnaire-25 score are taken into account, within a follow-up period of up to 8 months.[6] The results of these studies may hopefully lead to an evidence-based best-practice guideline for the treatment of cCSC.