Eye (2016) 30, 1395–1400

www.nature.com/eye

Sir,
Comment on: 'Central retinal vein occlusion: modifying current treatment protocols'

In their interesting article, Ashraf *et al*[1] presented a modifying of the current treatment protocols for central retinal vein occlusion (CRVO). We want to address some issues directly related to the intravitreal therapy with anti-vascular endothelial growth factor (VEGF) agents in patients with CRVOs. The article has several shortcomings that prevent the validation of their results and that can be specifically summarized as follows:

1. Nothing was stated regarding the long-term outcomes of the intravitreal therapy with bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA, USA). Even if bevacizumab is unlicensed, it is still currently recommended in CRVO-related macular edema by a majority of retina specialists (56.7%) over ranibizumab (Lucentis, Genentech, Inc.) (22.2%) and aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) (15.1%; $P<0.0001$).[2] In 2015, we conducted a prospective clinical study[3] on the 3-year results of bevacizumab treatment in patients with acute (≤1 month after the occlusion was diagnosed) central/hemicentral retinal vein occlusions (central/hemicentral RVOs). The results of this study were the first evidence suggesting that the 3-year intravitreal bevacizumab provided sustained vision and anatomic gains in most phakic patients with acute central/hemicentral RVOs.
2. With regard to the adequate dose of ranibizumab used, Ashraf *et al*[1] have considered that patients with CRVO respond equally well to the 0.3, 0.5, and 2 mg doses of ranibizumab. Importantly, the Relate study[4] reported that visual outcomes were no better after 24 weeks of injections of 2.0 mg ranibizumab every 4 weeks compared with injections every 4 weeks of 0.5 mg ranibizumab. However, 90% of the patients in the 2.0 mg ranibizumab group had central subfield thickness of 320 μm or less compared with 52.6% of the patients in the 0.5 mg group ($P=0.03$). Considering that the presence of macular edema is mainly guided by anatomical measure data with visual changes as a secondary guide, we believe that the significant difference between the two percentages of patients emphasizes the significantly greater effectiveness of the 2.0 mg dose of ranibizumab in comparison with the 0.5 mg dose in patients with CRVO-related macular edema.
3. There were no data on the treat-and-extend (TAE) regimens with intravitreal anti-VEGF agents used in RVOs to reduce burden of treatment on patients and physicians while maintaining effectiveness in the treatment.
4. The article by Ogura *et al*,[5] which reported the 18-month results of the Galileo study, was not included in the reference list, although the content of this article was erroneously encompassed in the paper by Korobelnik *et al*,[6] which reported the 1-year results of the Galileo study.
5. We do not agree with the assertion made by Ashraf *et al*[1] that aflibercept is the only anti-VEGF agent tested in ischemic CRVO patients in randomized clinical trials. Of note, the Galileo and Copernicus trials, which were thoroughly presented by Ashraf *et al*,[1] and where aflibercept was used, included a very small percentage of ischemic occlusions, that is, 8.2% and 15.5%, respectively. On the other hand, our prospective study published in 2015[3] included 50% patients with ischemic occlusions. Based on the evidence, we concluded for the first time that bevacizumab was more effective in patients with ischemic occlusions who still required a significantly higher number of injections.
6. The benefits of switching to aflibercept have not been clinically proved. Most of the study cited by Ashraf *et al*[1] included a small number of patients, and the largest study quoted (Papakostas *et al*[7]) was retrospectively conducted with a possible existence of a bias and reported poor visual and anatomic results (a gain of approximately five letters in visual acuity; persistent macular edema in 45% of cases; and significant thinning of the retina (macular fibrosis? epiretinal membrane formation?) in 16.6% of cases).

In conclusion, central/hemicentral RVO has to be considered an ophthalmic emergency. Therefore, therapy with anti-VEGF agents has to be promptly applied as soon as possible after RVO onset. Regardless of the anti-VEGF agents used (ranibizumab/aflibercept/bevacizumab), and regardless of the treatment approaches chosen (TAE/pro re nata algorithm), the efficacy of therapy depends primarily on the precociousness of the therapy after RVO diagnosis.

Author contributions

Both 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.

Conflict of interest

The authors declare no conflict of interest.

References

1 Ashraf M, Souka SSR, Singh RP. Central retinal vein occlusion: modifying current treatment protocols. *Eye* 2016; **30**: 505–514.
2 Wang MD, Jeng-Miller KW, Fend HL, Prenner JL, Fine HF, Shah SP. Retina specialists treating cystoid macular oedema secondary to retinal vein occlusion recommend different

treatments for patients than they could choose for themselves. *Br J Ophthalmol*; e-pub ahead of print 30 December 2016; doi: doi:10.1136/bjopthalmol-2015-307849.
3 Călugăru D, Călugăru M. Intravitreal bevacizumab in acute central/hemicentral retinal vein occlusions: three-year results of a prospective clinical study. *J Ocul Pharmacol Ther* 2015; **31**(2): 78–86.
4 Campochiaro PA, Hafiz G, Mir TA, Scott AW, Solomon S, Zimmer-Galler I *et al.* Scatter photocoagulation does not reduce macular edema or treatment burden in patients with retinal vein occlusion. The Relate trial. *Ophthalmology* 2015; **122**(7): 1426–1437.
5 Ogura Y, Roider J, Korobelnik JF, Holtz FG, SImader C, Schmidt-Erfurth U *et al.* Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion. 18-month results of the phase 3 Galileo study. *Am J Ophthalmol* 2014; **158**(5): 1032–1038.
6 Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U *et al.* Intravitreal Aflibercept Injection for macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. *Ophthalmology* 2014; **121**(1): 202–208.
7 Papakostas TD, Lim L, van Zyl T, Miller JB, Modjtahedi BS, Andreoli CM *et al.* Intravitreal aflibercept for macular oedema secondary to central retinal vein occlusion in patients with prior treatment with bevacizumab or ranibizumab. *Eye (Lond)* 2016; **30**(1): 79–84.

D Călugăru and M Călugăru

Department of Ophthalmology, University of Medicine, Cluj-Napoca, Romania
E-mail: mihai.calugaru@mail.dntcj.ro

Eye (2016) **30,** 1395–1396; doi:10.1038/eye.2016.83; published online 22 April 2016

Sir,
Response to: 'Comment on Central retinal vein occlusion: modifying current treatment protocols'

We would like to thank Călugăru and Călugăru[1] for their comments on our paper, Central retinal vein occlusion: modifying current treatment protocols.

Although bevacizumab is widely used in common practice, there are no large-scale randomized control trials that have studied bevacizumab. Even the quoted paper[1] had a relatively small cohort of 57 patients. It is difficult to extrapolate recommendations especially with regard to long-term outcomes until larger studies have been conducted.

Although the 2 mg ranibizumab dose in the Relate study[2] did show a better anatomical response compared with the other doses, this was not mirrored in visual outcomes. In addition, with the absence of a commercially available 2.0 mg dose and in the context of a visual acuity guided strategy, it would be difficult to advocate quadrupling the dose of ranibizumab.

There have been no large studies that have looked into treat and extend for treating CRVO. However, we did not advocate this particular strategy. We proposed gradually extending the follow-up periods based on the data from HORIZON, which showed that in the second year patients followed up every 3 months post vision.[3] Hence with regard to certain patients following them closely would allow identification of early recurrences. Furthermore, we believe that the mandatory treatments during extension cycles typically reserved for age-related macular degeneration (AMD) is unnecessary in CRVO. In AMD, each recurrence is associated with a drop in final visual acuity as evidenced by a difference in final visual outcomes between monthly and PRN dosing regimens.[4] In diabetic macular edema and in CRVO, the pathology is quite different and as evidenced by the SHORE study, there is no difference between the patients treated using a PRN regimen and maximum monthly dose regimen.[5] Hence with regard to the treatment, PRN would seem to be the 'better' dosing option, and the standard Treat and extend would overtreat a significant number of patients.

The data from Călugăru and Călugăru[1] regarding the use of bevacizumab in cases of ischemic CRVO included 21 patients with ischemic CRVO/HRVO. These data are important, however, was not included because of the relatively small number. It would be interesting to study the effects of bevacizumab in ischemic CRVO on a larger scale.

Switching to aflibercept,[6] although still a relatively novel approach to treating resistant CRVO, has been gaining significant traction in real-world practice. It is a more appealing option than using steroids and there are mounting data that it might be a good option.[7,8] However, this has yet to be confirmed with larger studies conducted in a prospective manner.

Finally, we appreciate the in-depth analysis and the debate with regard to treating CRVO, and we acknowledge that this is a serious disease that requires aggressive and timely intervention to preserve vision.

Conflict of interest

The authors declare no conflict of interest.

References

1 Călugăru D, Călugăru M. Intravitreal bevacizumab in acute central/hemicentral retinal vein occlusions: three-year results of a prospective clinical study. *J Ocul Pharmacol Ther* 2015; **31**: 78–86.
2 Campochiaro PA, Hafiz G, Mir TA, Scott AW, Solomon S, Zimmer-Galler I *et al.* Scatter photocoagulation does not reduce macular edema or treatment burden in patients with retinal vein occlusion: the RELATE trial. *Ophthalmology* 2015; **122**: 1426–1437.
3 Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG *et al.* Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology* 2012; **119**: 802–809.
4 CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011; **364**: 1897–1908.
5 Campochiaro PA, Wykoff CC, Singer M, Johnson R, Marcus D, Yau L *et al.* Monthly versus as-needed ranibizumab injections in patients with retinal vein occlusion: the SHORE study. *Ophthalmology* 2014; **121**: 2432–2442.