We do not agree with the authors' assertion that anti-VEGF therapy may "reset the clock" to NVG onset, extending the risk beyond the 7 months, but do not prevent the NVG occurrence. This conclusion is valid only for eyes in which initiating treatment was delayed after the diagnosis of CRVO.[3] We documented, for the first time,[4] that the prevention of NVG may be enhanced by intravitreal bevacizumab (IVB; Avastin; Genentech Inc, San Francisco, California, USA) injections administered aggressively as early as possible after the onset of occlusion. Thus, the rate of the cumulative prevalence of NVG was 4.08% in patients with acute (≤1 month after the occlusion was diagnosed) central/hemicentral retinal vein occlusions (central/hemicentral RVOs) over the course of 3 years. We believe that at a dose of 2.5 mg injected before occurrence of neovascularization and IOP elevation, IVB may offer promise for the prevention or even cure of NVG by ablation of the ischemic drive for new vessel formation in patients with acute central/hemicentral RVOs.

Altogether, the authors of this study highlighted 3 risk factors for NVG development, namely, history of systemic hypertension, worse visual acuity on presentation, and RAPD on presentation. However, the validation, extrapolation, and generalizability of these outcomes can be made only by statistical analyses including all the missing data mentioned by us in addition to the baseline characteristics already assessed in this study, serving to identify the key drivers predicting the NVG occurrence.

DAN CĂLUGĂRU
MIHAI CĂLUGĂRU
Cluj-Napoca, Romania

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Predictors of Neovascular Glaucoma in Central Retinal Vein Occlusion

REPLY

WE APPRECIATE THE INTEREST OF DRS. CĂLUGĂRU AND Călugăru in our article.[1] We wish to respond to the points raised by the respondents.

Many of the respondents' concerns are natural limitations of a retrospective study. Gonioscopy at each clinic visit and additional historical information would have been ideal. With regard to the duration of follow-up, the peak incidence of neovascular glaucoma (NVG) development occurred within the first 7 months of central retinal vein occlusion (CRVO) presentation, as per the previous work by Hayreh et al.[2] Thus, we believe that our follow-up period was sufficient to determine whether a patient would develop neovascular complications. Regarding the rate of NVG, previous CRVO natural history studies in which ischemic status was undefined demonstrated a NVG rate of 5%-21%.[3–6] Our 13% incidence of NVG was well within this range. This was stated and referenced in the first paragraph of the discussion section. Thus, we disagree with statement by Călugăru and Călugăru that our rate was "pretty high."

It is possible that there were patients in our group who could have had retinopathy that mimicked CRVO. However, we reviewed the entire medical records of 646 patients to ensure that there were no known conditions that could have mimicked or confounded a patient's diagnosis. This was noted in our exclusion criteria. Naturally, the veracity of the clinical record would limit a retrospective study. We completed subgroup analyses, specifically evaluating age younger than 50 years compared with age older than 50 years. As discussed in our paper, we did not find this to be a statistically significant factor.

The criteria that Călugăru and Călugăru cite as their own should be more accurately credited to work performed by Hayreh et al.,[2] in which they differentiated ischemic and nonischemic CRVO via an afferent pupillary defect, visual acuity, electroretinography, and kinetic visual field testing. As we acknowledged in our introduction, many providers do not have access to resources for more extensive testing, such as fluorescein angiography, electroretinography, or Goldmann visual field testing to determine CRVO risk. Thus, the study was designed to elucidate risk factors that were attainable on a routine clinic visit. Regarding their statement on optical coherence tomography (OCT) findings in CRVO, although it is possible that one could elucidate additional OCT risk factors by studying specific changes to each retinal layer, this was not the original intent of the study. One would need a large OCT-dedicated study sufficiently powered to evaluate the possible predictive role of such OCT findings. We focused on cystoid macular edema because it is commonly found in patients

with CRVO, and again, would be the most clinically useful condition to study.

Finally, with regards to Călugărus' comment using higher doses of bevacizumab, our study was not designed to determine treatment, prevention, or cure of NVG, and thus, we could not draw definitive conclusions about this topic. However, we did cite the results of the RAVE (Rubeosis Anti-VEGF) trial,[7] in which the investigators injected acute ischemic CRVO with 9 treatments of monthly anti-vascular endothelial growth factor (VEGF) therapy. In this trial, 50% of patients developed neovascularization after anti-VEGF injections were discontinued. The investigators of the RAVE trial previously responded to Călugăru regarding these differences in a published reply.[8] Although our study was not designed to answer the question of whether a series of anti-VEGF injections could prevent long-term development of NVG, we did not see a protective effect in patients who received an anti-VEGF injection on presentation compared with those who did not. We also noted, as did the RAVE trial, that those patients who suspended anti-VEGF therapy had a delayed onset of NVG compared with timelines set by previous natural history studies. Again, our study was not designed to look at prevention of NVG. However, we caution any readers who believe that anti-VEGF therapy will prevent or eliminate NVG risk to take into consideration our results as well as those of the RAVE trial.

ANDREW J. RONG
Miami, FL, USA
SWARUP S. SWAMINATHAN
Durham, NC, USA
ELIZABETH A. VANNER
RICHARD K. PARRISH II
Miami, FL, USA

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Amniotic Membrane Transplantation in Acute Severe Ocular Chemical Injury: A Randomized Clinical Trial

WE READ WITH GREAT INTEREST THE ARTICLE WRITTEN BY Elsani et al. on "Amniotic membrane transplantation in acute severe ocular chemical injury: a randomized clinical trial."[1] The investigators conducted a well-designed study to assess the role of amniotic membrane transplantation (AMT) in severe cases of acute chemical injury (Roper Hall grade 4). However, there are few concerns that we would like to highlight. The grading system used to describe severe chemical injury in this study is the Roper Hall system. It is well known that the Roper Hall grade 4 consists of patients who may markedly differ in the extent of ocular damage. To highlight, the Roper Hall grade 4 includes Dua's grade 4 (conjunctival involvement: >50%-75%; limbal involvement: 6-9 clock hours), grade 5 (conjunctival involvement: >75%-<100%; limbal involvement: 9-<12 clock hours), and grade 6 (conjunctival involvement: 100%; limbal involvement: 12 clock hours) with corresponding prognoses of good to guarded, guarded to poor, and very poor, respectively.[2] Thus, we believe, that if a subgroup analysis of the cases after subclassifying them in accordance with the Dua's grading system is done, the results may differ.

Although, Table 1 suggests that 2 groups were comparable in terms of age, sex, and type of chemical injury, were the 2 groups comparable at baseline in terms of clock hours of limbal involvement?

The investigators state that the remnants of AMT were manually removed at 3 weeks. What was the rationale behind doing the same and how many cases underwent this? Could this have affected the time to healing of epithelial defect? Also, it will be interesting to see if primary AMT affected the final outcome of ocular surface stem cell transplantation done at a later stage. Did the investigators note any difference?