choroidal thickness (subfoveal, 1000 μm nasal and temporal to the fovea).

In addition, the authors raised a concern about systemic data not presented in our study. Our study was conducted in a real-world, clinical setting. As stated in the methods section (treatment protocol), all patients had blood testing including kalemia and creatininemia at baseline and during the follow-up. However, we did not routinely evaluate endogenous cortisol (neither the type A personality nor *Helicobacter pylori* infection).

Finally, although the study is limited by its retrospective design, it offers clinically relevant insights and potential predictive factors for treatment response. Obviously, further prospective studies are needed to confirm these factors.

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Predictive Factors of Response to Mineralocorticoid Receptor Antagonist in Nonresolving Central Serous Chorioretinopathy

EDITOR:

WE WOULD LIKE TO ADDRESS SEVERAL ISSUES WITH THE study of Bousquet and associates.[1]

The study had a retrospective design and a short follow-up duration, with a fairly high proportion of eyes lost (34.37%) until the end of the follow-up period. Moreover, the measurements of the subfoveal choroidal thickness and the optical coherence tomography angiography (OCTA) images were not available in 27.11% and 23.72% of patients, respectively.

Two causes might explain the pretty high percentage of nonresponder patients (33.89%), namely, the corticosteroid intake and the choroidal neovascularization (CNV) detected by OCTA.

There was a significant difference regarding the previous or ongoing corticosteroid intake between patients in the nonresponder and responder groups (61.1% and 38.3%, respectively). Systemic corticosteroids have been associated with occurrences, prolongation, exacerbation, and recurrences of central serous chorioretinopathy (CSC) resulting in the paradoxical pro-edematous effects of glucocorticoids in CSC. Importantly, inappropriate or excessive activation of the mineralocorticoid receptor pathway involved in the development of CSC in ocular cells by the glucocorticoids can favor or even trigger the accumulation of subretinal fluid in CSC patients instead of acting on its absorption, as observed in macular edema of other origins. The molecular mechanisms include expression of the calcium-dependent potassium channel (KCa2.3) in the endothelium of choroidal vessels, inducing subsequent vasodilation with choroidal thickening.[2,3]

Nothing was stated referring to the types of CNV encountered in this series, namely, the type 1 located under the retinal pigment epithelium (RPE), the type 2 located in the subretinal space, or the type 3 intraretinal, attesting the existence of the neovascular CSC. The difference concerning the percentages of the neovascular CSC between patients in the responder and nonresponder groups (5.9% and 25%, respectively) was obvious but insignificant. Of note, the OCTA images for the detection of the neovascular CSC were not available in 23% and 25% of patients in the responder and nonresponder groups, respectively. The CNV might be considered as a factor of poor response to treatment with the mineralocorticoid receptor antagonists by preventing them from reaching and binding to the structurally similar mineralocorticoid and glucocorticoid receptors.

The qualitative status of the RPE band–Bruch membrane complex (which is primarily involved in the nonresolving CSC and has a contribution in the CSC pathogenesis), and grading of the RPE changes (serous pigment epithelial detachment, pigment migration within the neurosensory retina, RPE porosity, microrips or blowouts in the RPE, focal RPE atrophy, RPE hypertrophy, and diffuse or scattered leakage points through the RPE on fluorescein angiography), were not documented in the study groups.

There were no data in patients of the 2 study groups on the multimodal imaging of the overlying photoreceptor cell layer, which may suffer progressive and irreversible damages in cases of the chronic CSC because of the persistence of the subretinal fluid caused by pronounced dysfunctional RPE outer blood–retinal barrier. These alterations include outer nuclear layer thinning, external limiting membrane band disruption, discontinuity of the ellipsoid zone, elongation of the photoreceptor outer segments, interdigitation zone loss,

intraretinal cystic changes, and subretinal hyperreflective deposits.[4]

There were no comparative data referring to the baseline renal function, the level of endogenous and exogenous corticosteroids, the personality type of the patients, and the testing of patients with regard to *Helicobacter pylori* infection in patients of the study groups.

The authors of this study found that a thick baseline choroid (>515 μm) was the only predictive factor associated with treatment response in the multivariate analysis. Importantly, using the enhanced depth imaging OCT model the choroidal thickness measurements can be limited in cases of severe subretinal detachment, where the underlying chorioscleral interface may become obscured, resulting in a selection bias toward eyes with less severe disease. Moreover, eyes with a thinner choroid at baseline may not undergo additional thinning owing to a "floor effect."[5]

Altogether, the validation, extrapolation, and generalizability of the authors' conclusions 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 assessed in this study, which serve as potential prognosticators influencing functional and anatomic improvements.

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Serum Angiotensin-Converting Enzyme Has a High Negative Predictive Value in the Investigation for Systemic Sarcoidosis

EDITOR:

NIEDERER AND ASSOCIATES[1] CONCLUDED THAT ADDITIONAL screening tests for sarcoidosis-associated uveitis are not necessary in patients with normal serum angiotensin-converting enzyme (ACE), though the authors subsequently add that further testing in patients with ACE within the normal limits might be of value only when clinical suspicion is high. We would like to discuss some aspects regarding the interpretation of their results, specifically the high negative predictive value (NPV) of serum ACE, by comparison to our previous work on the same subject.

Firstly, the pretest probability (often the prevalence of the specific disease) is important in the interpretation of predictive values. Sarcoidosis has a prevalence ranging from 10% to 15% in the uveitis population (see also Supplementary Table 1).[2] The lower NPVs in previous studies can be due to testing in a population with higher sarcoidosis prevalence (eg, pretest probability) (see Supplementary Table 2). Secondly, the cut-off value that is chosen for the test may change the NPV. In Niederer's study, the cut-off was lower compared to ours, creating a higher sensitivity (while the prevalence of sarcoidosis in the population remains stable), raising the NPV (Supplementary Tables 1 and 2). Another important aspect is the influence of race on ACE levels. Previous research has shown that in the sarcoidosis-associated uveitis population, mean ACE values are higher for African Americans compared to whites.[3] In a uveitis population with higher proportion of black patients the sensitivity will be higher, increasing the NPV.

In conclusion, the prevalence of sarcoidosis in the population, the cut-off value for ACE, and the proportion of black patients in the specific population influence the diagnostic value of ACE. In populations with a higher prevalence of sarcoidosis and lower proportion of black patients and in centers using a higher cut-off, the NPV will be lower. In these settings, further screening tests in patients with normal results of ACE remain useful.

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