The study reports only mild epigastric burning pain in 2 subjects (2.8%) in the TMP-SMZ group.[1] The common side effects of TMP-SMZ include mild gastrointestinal symptoms and mild maculopapular rash.[2,3] Although the combination is generally well tolerated, it can be associated with several serious adverse reactions. The serious complications, which may occur immediately or months after starting therapy, include skin eruptions (Stevens-Johnson syndrome, toxic epidermal necrolysis), hematologic abnormalities (thrombocytopenia, agranulocytosis, anemia), neurotoxicity, nephrotoxicity, and potential drug interactions (warfarin, phenytoin, oral hypoglycemics, etc).[2,3] Therefore, ophthalmologists must preferably take clinician's opinion during therapy for blood counts, renal functions, and serum electrolytes. In addition, given the preponderance in young female patients, extended use as blanket coverage in women of childbearing age must be weighed against harmful effects of trimethoprim in pregnancy (category D drug).[3]

Keeping in mind the possible benefits and the rare, yet possible fatal adverse effects, the indications and regimen of treatment (type, dose, frequency, and duration) needs to be defined. The role of steroids as adjunct to antiparasitic therapy in active disease is not clear.[4] Whether steroid given during the active phase to reduce the retinal inflammation and prevent further blood-retinal barrier breakdown will affect the distribution of tissue cysts to the margin of lesion and late recurrences has not been studied. The minimum dose and frequency of antiparasitic therapy needs to be chosen based on pharmacokinetics. The duration of treatment has been variable in previous studies (6-20 months[5,6] vs 10 months in the present study), and it is unclear if shorter or longer duration will be appropriate.

Instead of recommending the prophylaxis in all cases, it may be considered only for lesions involving the macula or close to the optic disc, where reactivation may lead to profound visual loss/field defect. It would be interesting to know if drug therapy prevents recurrences adjacent to previous scars or in the normal retina or at both locations. If recurrences, remote from the pre-existing scars, had occurred at the macula in the placebo group, then the indication for treatment may be extended to even peripheral lesions.

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REFERENCES

1. Fernandes Felix JP, Cavalcanti Lira RP, Grupenmacher AT, et al. Long-term results of trimethoprim-sulfamethoxazole versus placebo to reduce the risk of recurrent Toxoplasma gondii retinochoroiditis. *Am J Ophthalmol* 2020;213:195–202.
2. Wormser GP, Keusch GT. Trimethoprim-sulfamethoxazole in the United States. *Ann Intern Med* 1979;91(3):420–429.
3. Ho JM-W, Juurlink DN. Considerations when prescribing trimethoprim–sulfamethoxazole. *CMAJ Can Med Assoc J* 2011;183(16):1851–1858.
4. Jasper S, Vedula SS, John SS, Horo S, Sepah YJ, Nguyen QD. Corticosteroids as adjuvant therapy for ocular toxoplasmosis. *Cochrane Database Syst Rev* 2017;1(1):CD007417.
5. Borkowski PK, Brydak-Godowska J, Basiak W, et al. The impact of short-term, intensive antifolate treatment (with pyrimethamine and sulfadoxine) and antibiotics followed by long-term, secondary antifolate prophylaxis on the rate of toxoplasmic retinochoroiditis recurrence. *PLoS Negl Trop Dis* 2016;10(8):e0004892.
6. Silveira C, Belfort R, Muccioli C, et al. The effect of long-term intermittent trimethoprim/sulfamethoxazole treatment on recurrences of toxoplasmic retinochoroiditis. *Am J Ophthalmol* 2002;134(1):41–46.

Reply to Comment on: Long-term Results of Trimethoprim Sulfamethoxazole Versus Placebo to Reduce the Risk of Recurrent *Toxoplasma gondii* Retinochoroiditis

FIRST, WE WOULD LIKE TO THANK KUMAWAT AND ASSOCIates for their interest and critical reading of our article entitled "Long-term results of trimethoprim sulfamethoxazole versus placebo to reduce the risk of recurrent *Toxoplasma gondii* retinochoroiditis."

Regarding the indication for prophylaxis of recurrent disease, we agree that prophylaxis should be considered only for lesions involving the macula or close to the optic disc, where reactivation may lead to profound visual loss/field defect. In our study, the recurrences were adjacent to previous scars, and recurrences from the peripheral pre-existing scars had not occurred at the macula.

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CONFLICT OF INTEREST DISCLOSURES: SEE THE ORIGINAL article for any disclosures of the authors.

Comment on: Corneal Epithelial Thickness Measured Using AS-OCT as a Diagnostic Parameter for Limbal Stem Cell Deficiency

EDITOR:

WE READ WITH INTEREST THE ARTICLE BY LIANG AND ASSOciates that evaluated the diagnostic performance of the corneal epithelium thickness (CET) measured using an anterior segment optical coherence tomography (AS-OCT) and in vivo confocal microscopy (IVCM) in patients with limbal stem cell deficiency (LCSD).[1] The measurements obtained were the average of 3 independent scans performed by 2 independent, masked observers. The authors reported the interobserver variation of these measurements by calculating the interobserver differences only. Furthermore, they analyzed the CET data using a 3-point measurement on the AS-OCT (OCT-CET3) only, but not the 1-point measurement (OCT-CET1) because of the greater correlation with IVCM-CET in the former than the latter CET. We have reservations regarding these statistical approaches.

Multiple measurements were manually obtained by 2 observers from the AS-OCT and IVCM. The reliability of these measurements should be assessed by both the interrater reliability and intrarater reliability using the intraclass correlation coefficient (ICC). The repeatability coefficient (RC), defined as $1.96 \times \sqrt{(2 \times \text{within-subject variance})}$, is the 95% confidence limit of the difference of measurements between examinations. RC is another reliability index that should be considered because it lends itself to easy clinical interpretation, since it is quantified in the same unit as the measurement device. Without the ICC and/or RC reliability evaluations, it is difficult to interpret the results presented by the authors in a clinically meaningful context.

Although the authors found a higher correlation between IVCM-CET with OCT-CET3 than OCT-CET1, a higher correlation does not imply there is a better agreement between these 2 methods. This concept has been discussed in detail by Bland and Altman in their article, one of the most highly cited papers in medical research, highlighting that the correct approach is to calculate the limits of agreement and not correlation.[2] Without considering the limits of agreement, systemic bias, and scaling bias between these 3 measurements, the OCT-CET1 data should not have been disregarded entirely in their analysis, as it might have been a useful diagnostic and staging biomarker.

Lastly, without calculating the area under the receiver operator characteristic curve (AUC) for OCT-CET1 or IVCM-CET and comparing these AUCs with OCT-CET3 using a statistical test (ie, DeLong's test[3]), it is premature to state that OCT-CET3 has the highest diagnostic value for LSCD in the present study. It would be of interest if the authors could provide the analyses described above so that the results can be better put into a clinical perspective to address the question the authors set out to answer.

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REFERENCES

1.. Liang Q, Le Q, Cordova DW, Tseng CH, Deng SX. Corneal epithelial thickness measured using AS-OCT as a diagnostic parameter for limbal stem cell deficiency [published online ahead of print]. *Am J Ophthalmol* 2020;216:132–139. pii: S0002-9394(20)30173-2.
2. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1(8476):307–310.
3. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44(3):837–845.

Reply to Comment on: Corneal Epithelial Thickness Measured Using AS-OCT as a Diagnostic Parameter for Limbal Stem Cell Deficiency

REPLY

WE SINCERELY THANK DR. WAN AND COLLEAGUE FOR THEIR interest in our recent article, entitled "Corneal Epithelial Thickness Measured Using AS-OCT as a Diagnostic Parameter for Limbal Stem Cell Deficiency",[1] and for giving us the opportunity to further elaborate on our study. We previously showed that central corneal epithelial thickness (CET) obtained using in vivo confocal microscopy (IVCM-CET) decreased substantially in eyes with limbal stem cell deficiency (LSCD).[2,3] In addition, the degree of epithelial thinning in the central cornea reflected the global function of limbal stem cells. The purpose of our recent study was to develop the methodology of CET measurement using anterior segment optical coherence tomography (OCT) as a diagnostic test for LSCD. Our decision to