## Response to comments on: Retinal vein occlusion in COVID-19: A novel entity

Dear Editor,

We appreciate the authors for taking interest in our case report and we would like to clarify certain points raised in the letter.[1,2]

As the authors correctly point out, multiple biomarkers such as C-reactive protein, D-Dimer, interleukin-6, platelet count, cardiac troponin, lactate dehydrogenase, serum ferritin, and so on have been evaluated for their putative role in COVID-19.[3] Of these, CRP and D-Dimer have maximum utility in predicting the clinical outcomes.[4] Moreover, CRP has been noted to be the earliest biomarker to be raised in COVID-19 with its diagnostic sensitivity being higher than CT scan.[5] Hence, only CRP was performed for our patient which turned out to be normal. However, evaluating the role of other biomarkers in relation to ocular manifestation of COVID-19 is an excellent suggestion by the authors and we would greatly appreciate more studies analyzing this relationship.

Regarding the pathogenesis and role of "cytokine storm" in our case, it is imperative to note that the exact definition of the term "cytokine storm" remains undetermined till date.[6] It essentially denotes hyperactive immune response characterized by release of inflammatory cytokines, which are injurious to host cells.[6] The COVID-19 pandemic is still evolving, and we continue to learn as we go, including the mechanism and role of "cytokine storm" in its pathogenesis. Since our patient had a mild course of systemic COVID-19 with only isolated ocular involvement, it can be postulated that the proinflammatory and/or prothrombotic state was restricted to retinal vessels. In other words, the "cytokine-storm" was probably confined to retinal vessels rather than a full-blown systemic phenomenon. Nonetheless, this remains a postulation and further histopathological studies of retinal biopsy tissue and vitreous biomarker evaluation are warranted to gain better insight into the etiopathogenesis of ocular disorders related to COVID-19.

The authors raise an important issue regarding the role of antivascular endothelial growth factor (anti-VEGF) therapy and the possibility of initiating the patient on solitary systemic steroids with supplemental intravitreal therapy in case of nonresponse. Our patient was treated aggressively with oral steroids in combination with ranibizumab biosimilar for multiple reasons. At the foremost, the hallmark of COVID-19 has been its unpredictable nature with rapid systemic deterioration.[7,8] Although our patient had mild systemic disease with normal CRP levels, there was a distinct possibility of retinal vasculitis being the earliest sign of cytokine storm with a likelihood of patient worsening

systemically within a short duration. In such a scenario, it would have been difficult to follow up the patient regarding progression of ocular condition. Additionally, performing any invasive ocular procedure in a COVID hospital, including intensive care unit, would have been logistically cumbersome. So due to the unpredictable course of the disease and in the larger interest of the patient, we decided to treat the ocular disease aggressively by administering local intravitreal injection.

Regarding the choice of injection, intravitreal steroids were avoided due to the risk of cataract development (Our patient was 52 year old) and raised intraocular pressure.[9] VEGF is an important mediator of angiogenesis and vascular permeability.[10] Various inflammatory cytokines such as IL-6, interleukin-8, and tumor necrosis factor can cause upregulation of VEGF production.[10] Increased VEGF levels have been demonstrated in aqueous humor of uveitic patients with cystoid macular edema (CME) as compared to those without CME.[11] The aqueous VEGF levels have also been shown to reduce significantly with associated anatomical improvement in uveitic CME after intravitreal anti-VEGF therapy.[12] Likewise, multiple other studies too have determined and established the role of intravitreal anti-VEGF therapy in uveitic CME, including postviral CME.[10,13] The exact mechanism for anti-VEGF response in uveitic CME remains unclear, but possible antiangiogenic, antipermeability, and unexplored anti- inflammatory mechanisms have been proposed.[10] Based on the evolving role of intravitreal anti-VEGF therapy in uveitic CME, our patient was successfully treated by combining intravitreal ranibizumab biosimilar, Razumab® (Intas Pharmaceuticals, Ahmedabad, India; 0.5 mg/0.05 mL) with oral corticosteroids.

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### Conflicts of interest

There are no conflicts of interest.

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## References

1. Mahendradas P, Sethu S, Sanjay S, Kawali A, Shetty R. Comments on: Retinal vein occlusion in COVID-19: A novel entity. Indian J Ophthalmol 2021;69:194-5.
2. Sheth JU, Narayanan R, Goyal J, Goyal V. Retinal vein occlusion in COVID-19: A novel entity. Indian J Ophthalmol 2020;68:2291-3.
3. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19-A systematic review. Life Sci 2020;254:117788.
4. Pan F, Yang L, Li Y, Liang B, Li L, Ye T, *et al*. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): A case-control study. Int J Med Sci 2020;17:1281-92.
5. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, *et al*. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol 2020;92:856-62.
6. Sinha P, Matthay MA, Calfee CS. Is a "Cytokine Storm" relevant to COVID-19? JAMA Intern Med 2020;180:1152-4.
7. Criado PR, Criado RFJ, Pincelli TP, Yoshimoto TA, Naufal GGA, Abdalla BMZ. Chronic spontaneous urticaria exacerbation in a patient with COVID-19: Rapid and excellent response to omalizumab. Int J Dermatol 2020. doi: 10.1111/ijd.15134.
8. Goh KJ, Choong MC, Cheong EH, Kalimuddin S, Duu Wen S, Phua GC, *et al*. Rapid progression to acute respiratory distress syndrome: Review of current understanding of critical illness from COVID-19 infection. Ann Acad Med Singap 2020;49:108-18.
9. Sarao V, Veritti D, Boscia F, Lanzetta P. Intravitreal steroids for the treatment of retinal diseases. ScientificWorldJournal 2014;2014:989501.
10. Kozak I, Shoughy SS, Stone DU. Intravitreal antiangiogenic therapy of uveitic macular edema: A review. J Ocul Pharmacol Ther 2017;33:235-9.
11. Fine HF, Baffi J, Reed GF, Csaky KG, Nussenblatt RB. Aqueous humor and plasma vascular endothelial growth factor in uveitis-associated cystoid macular edema. Am J Ophthalmol 2001;132:794-6.
12. Jeon S, Lee WK, Jung Y. Changes in the intraocular cytokine levels after intravitreal bevacizumab in uveitic macular edema. Ocul Immunol Inflamm 2012;20:360-4.
13. Chawla R, Sundar DM, Gupta P, Mittal K. Intravitreal bevacizumab for postviral fever retinitis: A novel approach for early resolution of macular oedema. BMJ Case Rep 2018;2018:bcr2017222410. doi: 10.1136/bcr-2017-222410.



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