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Dear Dr. Roever,

We are pleased to re-submit for publication our review titled "**Complement-mediated microvascular injury and thrombosis in the pathogenesis of severe COVID-19: A review**". We are grateful to the editors and reviewers for providing insightful feedback on our study. We have carefully reviewed the recommendations and have revised our manuscript accordingly. Addressing each of their comments has certainly improved our manuscript. Detailed responses to the editor's and reviewer's comments are provided below:

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)
Specific Comments to Authors: Absolutely no need for me to change anything in the flow of the review. A parenthesis deleted and an acronym added. Recommend to publish.

We thank the reviewer for their comments and appreciate their suggestion for publication. We have made several changes to improve the readability of our manuscript, including review by a native English-speaking expert (Dr. Mark Goldin), who also has prior experience in the field of COVID-19 and thrombosis.

Reviewer #2:
Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: In this review manuscript (Manuscript NO: 75660), the authors discussed the role of complement in the development of thrombotic microangiopathy and summarized the current data on complement inhibitors as COVID-19 therapeutics. The topic is interesting. Some suggestions are listed as below:

1. Only a small proportion of patients develop aggressive disease but reliable clinical indicators to identify these patients early in disease progression are lacking. The time window for optimal intervention and the patient populations that could benefit from therapeutic complement inhibition have yet to be established. This point should be discussed.

We thank the reviewer for this valuable comment. We agree that the early identification of patients that may develop severe disease is of utmost importance and reliable clinical indicators are lacking. However, the combination of clinical factors with multipanel biomarkers may provide a prognostic tool and needs further investigation. We have modified the section titled **"Complement inhibition as an effective target with therapeutic implications"** as follows:

"Given the fact that only a small proportion of patients will develop aggressive disease, reliable clinical indicators to identify these patients in the early phase of disease progression are of utmost importance. The time window for optimal intervention and the patient populations that could benefit from therapeutic complement inhibition have yet to be determined. Currently available biomarkers of complement activity are too unstable and short-lived to be used predictively. Nevertheless, clinical predictors of ARDS progression combined with inflammatory biomarkers (CRP, IL-6, ferritin, and D-dimer) could potentially allow the identification of patients that could benefit from early intervention. [2,111]"

2. There are 3 distinct pathways of complement activation, the classical complement pathway, the alternative complement pathway, and the lectin pathway. In the context of thromboinflammation, the three complement pathways are capable of activating the coagulation cascade causing thrombotic microangiopathy and end-organ damage, mostly manifesting as lung, kidney, and cutaneous disease. Which pathway can be specifically targeted for severe COVID-19?

We appreciate the reviewer's feedback, and we have modified the section titled **"Complement inhibition as an effective target with therapeutic implications"** as follows:

"Theoretically, upstream targets in the complement pathway would provide the most potent anti-inflammatory results.[96] Despite the fact that the use of anti-C5a antibodies has been associated with prominent clinical improvement and decreased systemic inflammation, C5 inhibition can be partial, allowing residual terminal pathway activity in cases of excessive complement activation, as seen in severe COVID-19. In these advanced stages of COVID-19, C3 inhibition has the ability to control both ARDS and the systemic inflammation that damages the microcirculation of vital organs. Proximal complement inhibitors which target C3 or its upstream activators are appealing targets, but their benefit in mortality was not confirmed in a randomized, double-blinded, multicenter study that compared APL-9 (C3 inhibitor) to standard of care in mild to moderate COVID-19.[112] Further randomized studies comparing different complement inhibitors are necessary to identify the most appropriate therapeutic agents, as well as the benefits of upstream inhibition or pathway specific targeting."

3. How many people have been vaccinated in mentioned studies? The role of COVID-19 vaccinations in complement activation and preventing severe COVID-19 should be discussed.

We thank the reviewer for this important question. Generally, studies of complement modulation in patients with COVID-19 have not reported vaccination rates. In fact, many of the cited studies pre-date development and broad distribution of COVID-19 vaccines. The reviewer makes an important point about the potential synergy between vaccine-mediated complement activation and use of complement-targeting therapies. The theoretical implications of such a strategy, particularly the potential for enhanced C1q binding (to supplement IgG binding) of virus and prolong immune response are addressed in a new (final) paragraph of the section entitled **"Complement inhibition as an effective target with therapeutic implications**," just before the **Conclusion**.

4. Potential side effects of complement inhibitors should be discussed.

We have added information and relevant references on common side effects of several complement inhibitor therapies throughout the section entitled "**Complement inhibition as an effective target with therapeutic implications,"** notably the following passages on pages 13-14:

"Common side effects for Conestat alfa and Berinert include nausea and vomiting alongside with other gastrointestinal symptoms and coinfections."

"Common side effects [of narsoplimab] include nausea, vomiting, diarrhea, hypokalemia, neutropenia and fever."

"The increased risk of opportunistic infections, most notoriously with encapsulated organisms (*Neisseria*, *Haemophilus*, or *Streptococcus* species) in unvaccinated individuals and those with asplenia or functional asplenia, through the inhibition of terminal complement proteins has historically limited complement inhibitor use."

5. Dynamic changes of complement levels in the conditions of severe and non-severe COVID-19 should be shown.

We have added information and relevant references based on the reviewer's comment to highlight the dynamic changes of complement levels in COVID-19, as follows:

"...while case series demonstrated that lower serum C3 on hospital admission or its progressive decline during hospitalization were associated with up to a 4-fold higher risk of disease progression.[29,30]"

“Dynamic changes of complement levels have been reported in patients with COVID-19. Alosaimi et al. reported higher C3a, C5a, and factor P (properdin) levels in severe COVID-19 that were also higher in critical COVID-19 non-survivors. Further, the levels were increased during the early stage and gradually decreased during hospital course.[34] Continuous sampling in hemodialysis patients with severe COVID-19 identified that C5a levels were elevated prior to clinical deterioration. C3a levels remained elevated during the severe phase, whereas C5a levels started decreasing on day 7.[35] Interestingly, erythrocytes have been proposed as a diagnostic marker of disease progression based on the expression of complement receptors and complement binding. COVID-19 patients admitted to the ICU had an increased percentage of RBCs coated with C3b/iC3b/C3dg and C4d during the first 72 hours of admission and the percentage increased further by day 7 in the study by Lam et al.[36]”

6. Some similar reviews have already been published.

We thank the reviewer for their thoughtful comment. We have attempted to make our review as comprehensive and current as possible. The rapid dissemination of data in the era of COVID-19 mandates an ongoing review of the available data to facilitate evidence-based decision making. From our perspective, the presence of similar reviews published months ago should not preclude the publication of updated reviews.

(1) Science editor:

In this review, the authors discussed the role of complement in the development of thrombotic microangiopathy and summarized the current data on complement inhibitors as COVID-19 therapeutics. However, there are a few minor issues that should be addressed before publication:

1. As some similar reviews have already been published, the authors should Authors should properly articulate their innovations.

We thank the Editor for their thoughtful comment. We have attempted to make our review as comprehensive and current as possible. The rapid dissemination of data in the era of COVID-19 mandates an ongoing review of the available data to facilitate evidence-based decision making. From our perspective, the presence of similar reviews published months ago should not preclude the publication of updated reviews.

2.The discussion has certain limitations. The authors may add some content based on the reviewers' comments to make the discussion more complete and informative.

We appreciate the Editor's feedback, and we agree that additional content is needed. To this end, we have modified the discussion part of our manuscript according to the reviewers' comments (as described above). We hope that our edits will enhance the quality, as well as the readability of our manuscript.

3. Please provide documents following the requirements in the journal's Guidelines for manuscript type and related ethics:

（1）Conflict-of-Interest Disclosure Form；（2）Copyright License Agreement.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

We have provided the (1) Conflict-of-Interest Disclosure Form; (2) Copyright License Agreement, signed by all authors, with the revised manuscript.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Experimental Medicine, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: https://www.referencecitationanalysis.com/. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or

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We appreciate the Editor’s feedback. We have revised the discussion part of our manuscript according to the reviewers’ comments (as described above). We hope that our edits will enhance the quality, as well as the readability of our manuscript.