

## Peer Review File

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### Reviewer A:

Comment 1. The title should be a positive statement, rather than negative. Such as: "Caplacizumab should be part of initial treatment for all patients with..."

**Reply 1. Thank you for the suggestion. We revised the title as "How should caplacizumab be used for treatment of immune thrombotic thrombocytopenic purpura?"**

Comment 2. The first sentence is confusing: "managing acquired or immune thrombotic..." This seems to suggest 2 distinct disorders.

**Reply 2. We agree with the comments. The reason acquired or immune TTP was used is because almost all acquired (idiopathic) TTP is immune-mediated. However, for clarity, we only use immune TTP instead throughout the manuscript. This helps distinguish immune TTP from secondary TTP which may be acquired, but can be resulted from variety of diseases such as cancer and medications or bone marrow transplantation.**

Comment 3. I believe that the statements about mortality, exacerbation and relapse are not correct. I believe that the current frequency of these outcomes, without caplacizumab, is much less than reported. The citations to the author's previous publications may not be the best.

**Reply 3. We agree. The mortality rate varies tremendously from region to region and country to country. In our previous cohort, the mortality rate was quite high, but in other part of country such as in Maryland, the mortality rate was relatively low. We include several other references to support this.**

Comment 4. The description of the ISTH guidelines may be accurate but it has an awkward style, probably quoting directly from the guidelines. The first sentence in paragraph 3, sounds like the jargon of the guideline, using phrases such as "conditionally recommended". It should be within quotation marks. This text should be different; it

should be clear and concise, saying what the authors believe.

**Reply 4. Thank you for pointing it out. We have revised the sentence as this: The 2020 ISTH guidelines conditionally recommend the use of caplacizumab for patients experiencing acute iTTP either in the first or in a subsequent relapsing event on top of TPE and immunosuppressives.**

Comment 5. Also in this paragraph, the authors state that caplacizumab together with TPE and immunosuppression “is considered the standard of care for iTTP today”. So why is the title a question? It seems that it has already been answered, as in citation 11. Of course, citation 11 is a review by this author. So what is the purpose of this review? What does this review add to the author’s previous review? The figure is the same as the figure in citation 11 (that should be acknowledged in the figure legend).

**Reply 5. Thank you for question. I appreciate this reviewer’s interest in reading our previous article in JTH. The reason why this review is important is that there is still a lot of resistance in prescribing caplacizumab for acute TTP. Some clinicians want to reserve the use of caplacizumab only to the severe TTP patients. The title intended to question such a reservation and want to encourage the upfront use of caplacizumab in all diagnosed TTP patients. In term of figure, we did acknowledge this as such:** This figure is adapted from Zheng *et al.* J Thromb. Haemost.

2020;18:2486–2495)<sup>13</sup>

Comment 6. The next paragraph re-states the question that is the title, but the last sentence is very awkward: “This question was raised by many practicing hematologists who do not see a iTTP patient every day.” No hematologist sees a patient with iTTP every day.

**Reply 6. Thank you pointing this out. We agree that no hematologist sees a TTP patient every day. It was an “exaggeration”, meaning “often”. Most hematologists probably see a few TTP patients in a life time. Thus, we removed this sentence.**

Comment 7. Paragraph 7, describing how to use caplacizumab and when to stop it, is not relevant to the question in the title. It primarily repeats sentences that are in the package insert.

**Reply 7. As the title has been changed to How should caplacizumab be used for treatment of iTTP? This paragraph should be kept to guide the readers when to consider stop the treatment. It may be appropriate even though it may repeat the information in the package insert. No one will read the package insert until the drug is used. This is primarily for education purpose.**

### **Reviewer B.**

Comment 1. It is a nicely written and easily readable paper that briefly reviews the role of caplacizumab in the front-line treatment of patients with iTTP.

**Reply 1. Thank you for your comments.**

Comment 2. My main comment focus on the duration of caplacizumab treatment. Though the current recommendation of the time of caplacizumab therapy is to continue it "...for 30 days after the last round of TPE..." this may be reconsidered in the next future with the increasing disposal of ADAMTS13 assays to monitor disease response to treatment.

**Reply 2. While clinical trial data demonstrate the time for stopping capla is 30 after last TPE, more and more data to suggest that capla can be safely discontinued when ADAMTS13 activity is achieving partial remission.**

Comment 3. Revisited TTP response criteria include ADAMTS13 remission and ADAMTS13 relapse defined by ADAMTS13 activity. These new definitions highlight the importance of ADAMTS13 activity as a predictor of exacerbation and relapse and will help guide therapeutic decisions, including the timing of discontinuation of TPE caplacizumab therapy.

**Reply 3. We agree with the comments. We have added this point at the end of the paragraph and citation.**

#### **Reviewer C.**

Comment 1. Although this question is topical, the current version of this editorial does not add any novel discussion, nor does it focus on the title question – the commentary is predominated by general information about TTP which does not refer to or discuss the title question – should caplacizumab only be reserved for severe iTTP. This question is very specific and therefore the editorial content needs to be justifying in its answer to be of interest.

**Reply 1. This is a short commentary, which does not allow the expansion of this topic significantly.**

**We believe that such a commentary is timely, which helps reinforce the idea that all patients should be treated with caplacizumab upfront and not to wait for exacerbation or relapse or so called "severe" disease because all TTP patients are critically ill and require aggressive therapeutic interventions.**

Comment 2. The title of the commentary strikes interest however the content does not present any clear argument. The text is not fluent in places grammatically and may benefit from writing tools (tense and person changes throughout manuscript).

**Reply 2. With the change in title, the text is more consistent with the title how should caplacizumab be used for treatment of immune TTP. Some of the grammatic errors or awkward sentences have been revised.**

Specific comments:

Comment 3. Page 2 define ADAMTS13

**Reply 3. Thank you. It has been defined in the revised manuscript.**

Comment 4. Page 2 line 32 – rewrite ‘this comes’ grammar **Thank you, we have**

**Reply 4. revised this sentence.**

Comment 5. Page 2 line 36, 37 rewrite ‘over not use’ grammar

**Reply 5. We have revised this sentence.**

Comment 6. Page 2 line 42 – reduced what TTP complications?

**Reply 6. We have added the complications (such as death and thromboembolic events).**

Comment 7. Page 2 line 44 -? References need to include recent integrated analysis in Blood 2021, Peyvandi, et al.

**Reply 7. Yes, the new reference has been added.**

Comment 8. Page 3 – Page 2 provides background, then page 3 introduces the questions for consideration – these need to be presented more clearly and then discussed in turn.

**Reply 8. This is meant to be short commentary and we are not trying to expand it to a full review article.**

Comment 9. Page 3 line 47 – example of grammar tense, should be – ‘this question has been raised.’

**Reply 9. We have revised the sentence.**

Comment 10. Page 3 line 49 – ‘the answer is of course no’ suggest rephrase this for a better writing style, e.g based on the many benefits outlined, it would seem reasonable to offer all patients caplacizumab up front unless etc etc’ and then discuss/justify opinion

**Reply 10. We have revised this sentence for clarity.**

Comment 11. Page 3 line 52 – cost is not THE primary reason, but is a concern in some countries – the argument presented lines 54-69 is clumsy and should be completely re-written using more robust comparative cost-effective figures. There is no need for a paragraph break at line 64?

**Reply 11. We agree that cost is not an issue in many countries in Europe, but it is still the major concern in U.S. We have revised some of the sentences.**

Comment 12. Page 4 line 70 – ‘The other question is how to use caplacizumab’ – this is not another question but THE question of the editorial.

**Reply 12. Thank you. We have removed the “other” from the sentence.**

Comment 13. Page 4 line 70 ‘when to stop it’ how is this question relevant – are the authors referring to duration and therefore cost again?

**Reply 13. That is the question. The longer caplacizumab is used, the more cost to the patients and insurance. So, when to stop is a cost issue, not a safety issue.**

Comment 14. Page 4 lines 71-79 – this does not contribute to any discussion – this just outlines how the drug is administered in clinical practice – this does not add anything to answering the title/question

**Reply 14. We believe this paragraph is important for the readers as part of educational materials.**

Comment 15. Page 4 line 80 – what is the relevance of this as to whether caplacizumab should be reserved for the most severe patients?

**Reply 15. With the title change, it is important to discuss the prospective.**

Comment 16. Page 4 lines 81-86 – this is a generic conclusion about TTP therapies and is not connected in any way to the title again - the conclusion needs to provide a suggested/ supported answer to the title question for readers to take away and reflect about.

**Reply 16. Thank you for the suggestion. The conclusion statement has been provided.**

Comment 17. Page 9 Figure – the figure and legend again make no reference to the title question

of this commentary and therefore adds nothing – suggest omit or make more specific

**Reply 17. Thank you for the suggestion. However, considering the title change, we would like to include it for better understanding of the content.**