Peer Review File
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Reviewer Comments

Reviewer A

Comment 1: Page 3, Line 52

Is “unusually large” VWF multimer released, literally, or released/produced “usual size” VWF and just is not cleaved into various sized multimer, because of reduced activity or amount of ADAMTS13 equivalent against to newly released VWF?

Page 8, Line 171,

Page 24, Line 473,

Reply 1: Under normal conditions, the unusually large multimers of VWF are secreted and cleaved by plasma metalloproteinase ADAMTS13, resulting in smaller and less adhesive multimers. In TTP, ADAMTS13 is deficient, which does not cleave these large VWF multimers, which then acts as a bridging molecule for platelet adhesion and aggregation on activated endothelial surface or at vascular injury site.

Comment 2: Page 25, Figure 3C. Immunosupression

In addition to retuximub, belimumab, which inhibits B-lymphocytes stimulator, should be added to the novel therapeutics for iTTP because belimumab is now evident to improve prognosis in SLE patients effectively inhibiting the disease flare.

Reply 2: It is true that belimumab binds B cells and has been used in other autoimmune disorders. However, in treatment of TTP, rituximab is still the only one being recommended.

Comment 3: Page 3, Line 48

Immune thrombotic thrombocytopenic purpura (iTTP) is caused by severe deficiency of a plasma metalloenzyme ADAMTS13 (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif member 13) activity.

Reply 3: As advised, we corrected the sentence.

Comment 4: Page 3, Line 49-50

“immune complexes are cleared from circulation resulting in significantly reduced ADAMTS13 protein in some cases.” Reference is required.

Reply 4: As advised, we included the reference

Comment 5: Page 5, Line 97

“complement factor H” should be in italic, as it refer to genome name?

Reply 5: We agree. Complement factor H (*CFH*) mentioned in paragraph refer to the genome name.

Comment 6: Page 5, Line 99

ADAMTS13

Reply 6: *Adamts13* is represented the mice gene name in this paragraph. Thus, capital ADAMTS13 is not used.

Comment 7: Page 22, Line 463-467

Abbreviations used in Fig 2 require full term in the legend. For example, MP, Dis, CUB etc.
Reply 7: As advised, we have modified Fig. 2 legend.

Comment 8: Page 25, Fig 3 C. Immunosuppression
Antibodies are generally generalized by plasma cells.
Reply 8: As advised, the modified Fig. 3.

Reviewer B
Comment 1: The entire manuscript should be carefully edited for spelling/grammar (ex. abstract section – therapeutics plasma exchange should be therapeutic plasma exchange, pathophysiology section - board line should be borderline, etc. etc.).
Reply 1: As advised, we carefully edited the spelling and grammar.

Comment 2: I think it is important to include at least few sentences on epidemiology of this disease and its main complications, acute and chronic. This is important as some complications (e.g., neurocognitive) are later mentioned under therapeutics section without any preamble/explanation. Discussion of complications is also helpful as it ties in with pathophysiology and therapeutics.
Reply 2: The incidence of TTP and long-term complications following acute TTP have been added in the section of introduction.

Comment 3: Under therapeutics section, I would advise to start with a sentence about evidence-based diagnosis and treatment clinical practice guidelines from ISTH and the accompanying good practices paper. Many of your readers will have limited knowledge of this subject so adding this might be helpful – for further reading/learning. Otherwise, the summary of standard of care treatment is good. Adding a few sentences on establishing diagnosis might be helpful.
Reply 3: I have added the ISTH guidelines on the top of page 8.

Comment 4: Please include more detail on novel therapeutics. Based on the paper title, I was expecting a more fulsome discussion of this but found only a single sentence on emergent therapies in the entire paper.
Reply 4: We have included additional information about the novel therapeutic aspects of the TTP in the discussion.

Reviewer C
Comment 1: We suppose this paper a narrative review and revise the manuscript following the "Narrative Review Checklist" in our journal, we kindly suggest authors provide a Checklist as a supplementary material
Reply 1: We have revised the manuscript following the attached the structure template. The details in this manuscript are stated for each item in the checklist.

Comment 2: The description of therapies seems a little short in length and not novel enough. Authors need to enrich the treatment for iTTP, and TTP cases associated with COVID-19 could be considered.
Reply 2: We have added extensive amount of material about the novel therapeutics on pages 8 and

9.

Comment 3: The title of Fig. 3B (Inhibition of platelet-VWF interaction) is similar to the caption (Blockage of platelet-vWF interaction) in yellow block. We recommend authors to modify it, like changing as “anti-VWF nanobody”.
Reply 3: Thank for great comment, we modified the Fig. 3B figure legend.

Comment 4: P6, L11-13: An alternative hypothesis is also possible in which the binding of these antibodies to the spacer domain may result in a conformational change in the catalytic domain, thus affecting the cleavage efficiency of ADAMTS13 protease. Is there a reference missing here? Please ensure all the statement of FULL text is evidence-based.
Reply 4: we have updated the citation.