

COMMENTARY

Anti-CD20 therapeutic options in immune-mediated thrombotic thrombocytopenic purpura

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Email: robert.maitta@case.edu**Summary**

Immunosuppression with rituximab in immune-mediated thrombotic thrombocytopenic purpura helps decrease production of autoantibody mediating ADAMTS13 clearance from circulation. Failure to respond to rituximab in a satisfactory way or made difficult by adverse events to the medication does not represent a reason to stop considering anti-CD20 therapies to control antibody production. Therefore, both of atumumab and obinutuzumab with specificity to CD20, represent potentially valuable therapeutic tools in patients who are not candidates for rituximab.

Commentary on: Doyle et al. The use of obinutuzumab and ofatumumab in the treatment of immune thrombotic thrombocytopenic purpura. *Br J Haematol.* 2022;198:391-396.¹

KEYWORDS

anti-CD20 therapeutic options, immune-mediated, thrombotic thrombocytopenic purpura

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a diagnostic emergency that demands prompt therapy initiation to prevent severe known complications associated with the disease.² Deficiency of the metalloprotease ADAMTS13 with generation of autoantibodies to this enzyme characterize iTTP, resulting in the formation of diffuse microthrombi that can affect all organ systems. Thus, therapy to treat this disease requires not only active removal of these autoantibodies from circulation [through therapeutic plasma exchange (TPE)] but use of immunosuppression to reduce the amount of autoantibody produced.³ Recently, caplacizumab, the first TTP-specific therapy, was approved. It is given in conjunction with TPE to treat iTTP and is supported by current expert guidelines,³ and may represent the best approach to achieve prompt platelet recovery and reduce length of hospitalizations.

In terms of preventing formation of anti-ADAMTS13 autoantibody, off-label use of the anti-CD20 monoclonal antibody rituximab in iTTP for over a decade has resulted in

non-specific significant decreases in the amount of such autoantibodies, leading to sustained platelet count improvement, an increase in ADAMTS13 activity, and longer time periods between disease relapses.⁴ Importantly, when there is concern about this monoclonal's usage, rituximab can still suppress antibody production even at lower doses, with similar responses to the standard dose.⁵ This argues that anti-CD20 is an essential therapeutic tool in the setting of iTTP but its use can be limited since some patients may fail to respond appropriately to rituximab or have adverse events due to exposure to this medication. As a result, it would be tempting to think that other types of immunosuppressant agents could be equivalent to rituximab in iTTP, having similar efficacy in such settings. However, patients at times could respond in unexpected ways to these agents.⁶ Therefore, use of anti-CD20 or other B-cell-specific alternatives to treat iTTP patients represents the most direct way to reduce antibody production.

However, it needs to be stressed that like any other therapeutic some patients have adverse events while receiving

rituximab and this could influence decision-making and discourage clinicians from using it during an iTTP presentation. Rituximab is a humanized chimaeric anti-CD20 monoclonal antibody that can result in limited reactions, like those seen at time of infusion, to more diffuse ones such as allergic that may be as significant as anaphylaxis, and even acute or delayed rituximab-induced serum sickness.⁷ The latter can be seen in up to 10% of patients receiving rituximab due to the presence of anti-rituximab immunoglobulins.⁸ Therefore, development of these anti-rituximab antibodies or interaction with IgE stores due to rituximab activation of the immune response explains possible hesitation for its utilization in patients, but these reactions are not unique to those afflicted with iTTP.

That is why the report by Doyle *et al.* showing the use of other anti-CD20 monoclonal options in iTTP is an exciting study.¹ In this report it is shown that ofatumumab and obinutuzumab, both monoclonals with specificity to epitopes different from rituximab on CD20, can be effectively utilized in iTTP patients either not responding as expected or reacting adversely to rituximab. This report describes how these monoclonals were used as monotherapy pre-emptively if there was evidence of ADAMTS13 activity decrease or clinical suspicion of relapse, by either starting at lower test doses and then increasing them as tolerance to the medication was established or starting at a therapeutically appropriate larger dose while taking under consideration clinical need. These monoclonals were given to 15 patients during 28 separate treatment regimens that resulted in restoration of platelet counts and achieving remission in 26/28 (93%) of these episodes with an overall increase in peak ADAMTS13 activity after 120 days post therapy initiation. Even though all patients had received rituximab during their first presentation, obtaining complete or partial response at the time, when they relapsed (ADAMTS13 activity <20 IU/dL or due to clinical concerns of relapse) patients were initiated on either ofatumumab or obinutuzumab. Clinical criteria for use of these two monoclonals were due to the development of those reactions previously reported with rituximab use or secondary to short response duration with its usage requiring additional treatment. Importantly, 8/15 patients did not experience relapses while the other seven patients had median relapse-free periods of 17.4 months. Speaking of safety, infections triggered by these two monoclonals were noted in two patients while two others suffered either reactions limited to the skin or allergic in nature characterized by pruritus and pharyngeal discomfort, with no cases of serum sickness. Accordingly, it can be ascertained that these two medications did not have a safety profile that was worse to that observed with rituximab use. Looking at the long time needed for obtaining a normal or peak ADAMTS13 activity, these medications being well tolerated suggests that higher doses or increased frequency of dosing for an extended period of time could theoretically result in a shorter time period till achieving improvement in ADAMTS13 activity.

To conclude, determination of the type of long-term immunosuppression can represent one of the challenges in patients with iTTP. Even though caplacizumab is being used in iTTP this does not address the suppression of antibody production needed in those patients making anti-ADAMTS13. Based on the results described in this report, when difficulties are encountered while using rituximab in iTTP patients, either ofatumumab or obinutuzumab represent effective alternative anti-CD20 therapies that appear to suppress antibody production similarly to rituximab. In light of these findings, immunosuppression limited to B cells producing antibody may reduce unintended effects over other parts of the immune response. Thus, deficient or limited responses, or ones hampered by adverse events to rituximab, are no longer an impediment to achieve suppression of antibody production through the use of either one of these two anti-CD20 agents. Considering that this is the largest study to date describing positive outcomes using these two monoclonals in iTTP patients, it does increase the therapeutic repertoire available to treat patients not only presenting with relapses but also those presenting with their first event.

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