## A beneficial effect of rituximab on autoimmune thrombotic thrombocytopenic purpura: Just a B-cell depletion?

*To the Editor:*

We read with great interest the article by Toyoda et al.[1] They reported an infant with Wiskott-Aldrich syndrome who developed autoimmune thrombotic thrombocytopenic purpura (TTP) with decreased ADAMTS13 activity and the existence of anti-ADAMTS13 autoantibody.[1] The patient did not respond well to repeated plasma exchange procedures, but rituximab treatment led to hematologic remission and a fast recovery of ADAMTS13 activity.[1] They speculated that rituximab administration might be effective by eradicating residual memory B cells and plasmablasts in this case.[1] However, we would like to add another possible mechanism for the beneficial effect of rituximab on autoimmune TTP: the increase in activity of regulatory T (Treg) cells. Stasi et al[2] reported that patients with idiopathic thrombocytopenic purpura who responded to rituximab treatment showed restored numbers of the peripheral blood Treg cells, identified as $CD4^+FOXP3^+$ T cells, as well as a restored regulatory function, and Sfikakis et al[3] also demonstrated that mRNA levels of Treg-cell functional marker FOXP3 increased significantly at the early phase of B-cell depletion. TGF-β, a cytokine contributing to Treg-cell induction, increased significantly in all patients after B-cell depletion with rituximab.

Sorvillo et al[4] recently reported that the formation of inhibitory autoantibodies against ADAMTS13 depends on the activation of $CD4^+$ T cells, and this process requires endocytosis and subsequent processing of ADAMTS13 into peptides that are presented on MHC class II molecules to $CD4^+$ T cells by immature dendritic cells. Endocytosis was decreased in the presence of a blocking mAb directed toward the macrophage mannose receptor and siRNA silencing of the mannose receptor.[4] Navarrete et al[5] showed that Treg cells downregulated the 2 C-type lectin-like receptors CD206 (mannose receptor) and DC-SIGN on dendritic cells and decreased the percentage of cells expressing CD206 and DC-SIGN receptors.

Therefore, we propose that the beneficial effect of rituximab on autoimmune TTP might be due to the blocking of uptake and endocytosis of ADAMTS13 in dendritic cells by downregulation of the mannose receptor induced by repopulating Treg cells, in addition to depletion of B cells.[6]

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## Reply

*To the Editor:*

We thank Shin and Eisenhut[1] for their thoughtful comments that gave us the opportunity to reconsider our findings and to further dig into regulatory T (Treg) cell function after rituximab treatment in patients with Wiskott-Aldrich syndrome (WAS). By citing reported articles, the hypothesis proposed by Shin and Eisenhut,[1] that repopulating Treg cells by rituximab treatment downregulates the mannose receptor on dendritic cells and blocks the uptake and endocytosis of ADAMTS13 by dendritic cells, is worthy of further investigation. However, Treg-cell function in patients with WAS was found to be consistently reduced,[2,3] and defective homeostasis and function of Treg cells may account for some of the observed autoimmunity seen in patients with WAS.[4] Why Treg cells are particularly affected by WAS protein deficiency is not clear, and, unfortunately, we did not collect serial data of Treg-cell function after rituximab treatment in our patient. Therefore, it is not clear whether rituximab treatment increases the activity of Treg-cell function in patients with WAS. As we mentioned in our previous report, the patient's B cells were mostly depleted by repeated rituximab.[5] At 1 month before cord blood transplantation (CBT), CD20 positive cells were only 0.13% of total lymphocytes (B-lymphocyte count, $0.42 \times 10^9$/L). Even though Treg-cell function might be increased by rituximab in patients with immune thrombocytopenia (idiopathic thrombocytopenic purpura) who responded to rituximab treatment,[1] we do believe that eradicating residual memory B cells and plasmablast by rituximab is more important to control autoimmune thrombotic thrombocytopenic purpura in patients with WAS.

The interpretation on the role of Treg cells may be somewhat different after CBT. In our case, monthly prophylactic rituximab was administered until 1 month after an unrelated CBT.[5] ADAMTS13 activity decreased to 70% posttransplantation and increased to more than 90% quickly.[5] Because cord blood–derived Treg cells possess the ability to become highly suppressive on antigen exposure[6] and rituximab treatment showed restored numbers of Treg cells as well as a restored regulatory function,[1] the numbers and activity of Treg cells after CBT might be quickly reconstituted by posttransplant rituximab administration in our patient. Highly suppressive Treg cells derived from unrelated cord blood could block the uptake and endocytosis of ADAMTS13 in dendritic cells by downregulating CD206 and