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Targeting B cells in Severe Thrombotic Thrombocytopenic Purpura-A road to cure?

Vasileios C. Kyttaris, MD
Division of Rheumatology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

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Thrombotic thrombocytopenic purpura (TTP) is a rare disease characterized by microangiopathic hemolytic anemia and thrombocytopenia (reviewed in [1]). The underlying mechanism is the failure of the protease ADAMTS 13 (a disintegrin and metalloproteinase with thrombospondin motif-13) to cleave ultra large von-Willebrand factor (ULVMF) multimers. These ULVMF multimers provoke platelet aggregation and disseminated thrombosis. The most common cause for acquired TTP is an antibody (most often IgG) against ADAMTS 13 that causes complete (>90–95%) loss of ADAMTS 13 activity in the blood.

If left untreated, TTP may lead to severe organ dysfunction or even death due to widespread thrombosis. Plasma exchange has emerged as the preferred treatment for TTP as it is effective in filtering the pathogenic antibodies while providing active ADAMTS 13 protease. The current treatment regimens consisting of plasma exchange and corticosteroids have effectively decreased mortality from 90% to less than 20%[2, 3]. Still, a significant number of patients are refractory to treatment or relapse after the first episode of TTP. These patients are treated with intensification of the plasma exchange regimen, increased doses of corticosteroids and second-line cytotoxic agents such as vincristine or cyclophosphamide.

Rituximab is a monoclonal chimeric antibody against CD20, a molecule that is expressed on all mature B cells, but not long lived plasma cells. The FDA approved rituximab initially for the treatment of Non-Hodgkin Lymphoma. More recently it was approved for the treatment of autoimmune diseases such as rheumatoid arthritis [4] and ANCA-associated vasculitis [5], and was found useful in the treatment of chronic immune thrombocytopenia [6].

Rituximab causes a rapid (within 2–4 weeks) and profound decrease in circulating B cells through multiple mechanisms (antibody-mediated cell cytotoxicity, complement activation and apoptosis). The decrease in B cells lasts for several months following the typical four weekly infusions of rituximab. The antibody forming plasma cells are not affected by rituximab, hence the overall immunoglobulin levels remain within normal limits [7]. There is some evidence that B cell depletion may lead to modest decrease in autoantibody levels [4, 7] but that cannot fully explain the therapeutic effect of rituximab. It has been suggested

Correspondence: 330 Brookline Ave, CLS-936, Boston MA 02215, vkyttari@bidmc.harvard.edu, tel: 617-735-4162, fax: 617-735-4170.

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that elimination of B cells effectively deprives the immune system from important auto-antigen presenting and inflammatory cytokine producing cells, thus abrogating the autoimmune response.

Given the profile and mode of action of rituximab and its effectiveness in autoimmune diseases, it emerged as an attractive candidate for the treatment of TTP. Several preliminary trials and case series reported that rituximab was well tolerated and effective in patients with TTP including the ones with recurrent or refractory disease [8, 9]. A phase II trial of rituximab as first line treatment suggested that when added onto the standard of care, rituximab decreases the rate of relapse from 57% in historical controls to only 10%[10]. Subsequently, a randomized phase III clinical trial comparing rituximab to placebo was initiated but terminated early due to slow subject accrual (clinicaltrials.gov; NCT00799773).

In this issue of the journal, Froissart et al [11] asked whether rituximab is effective in the treatment of refractory/relapsing TTP. Patients with low ADAMTS 13 activity (<10%) who had suboptimal response to standard treatment in the acute phase of TTP or relapsed after the initial episode were treated with rituximab. Rituximab, in contrast to common practice and in order to circumvent the problem with daily plasma exchange, was given in 3 doses within the span of a week with the 4th dose given two weeks later. The patients were recruited prospectively; but instead of an active comparator group, historical controls treated with a variety of regimens including cytotoxic medications (cyclophosphamide, vincristine) were used.

The biologic effect of rituximab was profound as expected with the B cell population become undetectable in the blood within a few days of infusion. More importantly anti-ADAMTS 13 antibodies virtually disappeared and ADAMTS 13 activity normalized within 3 months after initiation of treatment. The clinical results were equally encouraging: only one out of 22 patients did not respond to rituximab. Rituximab-treated patients achieved remission quickly, within the first month after initiation of treatment, with no patient relapsing within the first year as opposed to 9.4% relapses in the control group. Of note, the differences between rituximab and control treatment were not as apparent after 12 months as B cell population recovered.

The importance of this study lies within the fact that rituximab proved very efficacious, even more so than cytotoxic treatments, in inducing a quick remission that lasted for over a year in all patients. This is similar to previously published experience. Moreover, rituximab-treated patients did not require the use of cytotoxic drugs or splenectomy, thus avoiding potentially serious side effects associated with these treatment modalities.

The main caveat in this study is the lack of blinding, randomization and use of a control treated group. One has to be careful in drawing definite conclusions as it was exemplified in trials of rituximab in systemic lupus erythematosus: despite showing effectiveness in preliminary reports, rituximab was similar to placebo in rigorous randomized trials [12]. It has to be noted though that such a trial (the ultimate proof of the usefulness of rituximab in relapsing/refractory TTP) although desirable, is difficult to conduct given the rarity of the condition and the lack of a universally accepted salvage therapy protocol. On another note, the small number of enrolled patients prevents us from estimating rituximab-associated toxicity including opportunistic infections.

In conclusion, the study by Froissart et al despite its limitations, adds significantly to the mounting evidence that rituximab is effective as salvage therapy in refractory/relapsing TTP that is characterized by the presence of anti-ADAMTS 13 antibodies and low ADAMTS 13 activity.

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