Rituximab for Thrombotic Thrombocytopenic Purpura

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Thrombotic thrombocytopenic purpura is a rare systemic disease in which microvascular aggregation of platelets causes ischemia of various organs, mainly the brain and kidneys. It is manifested by thrombocytopenia, microangiopathic hemolytic anemia, fever, and neurological and renal abnormalities. TTP was initially described by Moschcowitz in 1924 [1]; however, it was not until the early 1980s that its association with large multimers of von Willebrand factor accumulating in the plasma of patients was proposed [2]. Normally these large vWF multimers are cleaved by the ADAMTS13 metalloprotease, which is markedly diminished or absent in patients with TTP. TTP may be regarded as an acquired disease or as a familial or hereditary form. Patients with acquired TTP usually have decreased enzyme activity, which may be lower than 5%; in up to 90% of them, circulating inhibitory antibodies to ADAMTS13 can be demonstrated [3,4]. The familial type of TTP has an early onset of disease and zero activity of this metalloprotease, as a result of homozygous mutations in each of the two 9q34 genes that encode ADAMTS13 [5]. Another distinction can be made between secondary or idiopathic TTP. Secondary cases are those where TTP occurred after hematopoietic stem cell transplantation or in association with pregnancy, drug-induced collagen vascular diseases, human immunodeficiency virus infection, or malignant hypertension. However, it seems that the majority of TTP cases are of the idiopathic type. The latter may be considered of an "autoimmune" nature, as anti-ADAM13 antibodies are usually detected and the condition is characterized by a more refractory course and is more likely to relapse [6].

TTP = thrombotic thrombocytopenic purpura
vWF = von Willebrand factor

The standard of care for TTP relies on corticosteroids and plasma exchange, both of which were found to decrease mortality rates from 90% to 15–10%; unfortunately, 30–60% of patients relapse [7]. Currently, only plasma exchange has been proven through randomized controlled trials to improve survival of TTP patients [8]. Its dramatic effect on the long and short-term outcome suggests that plasma exchange should be initiated as soon as possible, even if the full criteria for TTP have not been met, provided that an alternative diagnosis cannot be made [9]. The evidence regarding corticosteroid therapy relies only on case series, which demonstrated inconsistent data of corticosteroid efficacy. This may be explained by the heterogeneity of the TTP patients evaluated. Cleary, a better controlled study is needed.

For patients with a refractory course, several immunosuppressive and immune modulating agents have been tried; however, most were not effective [10]. Splenectomy may be helpful, although it seems only patients with severe ADAMTS13 deficiency will benefit from this procedure. Thus, a need for a more potent reagent to treat those patients has arisen.

In this month's edition of *IMAJ*, Stein and co-authors [11] report on four patients successfully treated with rituximab for chronic relapsing TTP despite treatment with steroids and plasma exchange. Two patients were checked and found to have low ADAMTS13 activity and high titers of anti-ADAMTS13 antibodies. One patient had persistently low ADAMTS13 activity after treatment despite a clinical remission, emphasizing the difficulty in utilizing ADAMTS13 testing as a practical test.

Rituximab, a chimeric monoclonal antibody directed against CD20 antigen, which is present on B lymphocytes, has been used for hematological (lymphoma) and other immune mediated (rheumatoid arthritis) diseases. The rationale for using rituximab in TTP is its ability to direct anti-ADAMTS13-producing B cells. However, several studies show that this treatment may be effective in TTP patients with and without ADAMTS13 inhibitory antibodies [12]. Hence, it has been proposed that in TTP patients without ADAMTS13 inhibitory antibodies, B cell depletion by rituximab may reduce excessive cytokine production, thus lowering the level of vWF multimers to a normal range [12]. For these reasons, rituximab has been used in addition to corticosteroids and plasma exchange since 2002 for refractory and chronic cases.

Due to the rare nature of this disease, only case reports and case series refer to treatment with rituximab, and most of them describe a positive response. In 2006 George et al. [13] performed a systematic review of the use of rituximab for TTP and hemolytic uremic syndrome. Twelve reports describe the treatment of 27 patients, with benefit in 25 (93%). The following year, Scully and

collaborators [14] published the largest case series to date, including 25 patients treated with rituximab for relapsing or refractory TTP. Only patients with acute idiopathic TTP, demonstrating antibodies to ADAMTS13, were included. All 25 patients achieved complete clinical and laboratory remission during a median of 11 days after beginning rituximab. In all but one patient there was no evidence of the inhibitory antibodies after treatment. A more recent review of the literature was conducted by Caramaza et al. [11] and included 118 patients with TTP-HUS from 2002 to 2009. Clinical remission was documented in up to 85% of patients treated with rituximab, of whom 64% were reported to have a refractory disease and 36% suffered from relapses. In addition, it was noted that in some patients complete remission was achieved after two to three weekly infusions of rituximab 375 mg/m^2, while in others it was achieved only after eight cycles. Treatment was generally safe and only one patient had a severe reaction manifested by severe adult respiratory distress syndrome, 6 hours post-rituximab infusion.

Following the data on rituximab's efficacy for refractory diseases, in 2009 a multi-institutional randomized phase III clinical trial, including 17 institutions across the United States (The STAR Study), was initiated. The study organizers intended to recruit 220 patients with idiopathic TTP and evaluate the combination of plasma exchange plus corticosteroids with or without early treatment of rituximab. Unfortunately this trial, sponsored by the National Heart Lung Institute and in collaboration with Genentech, has been terminated due to a low enrollment rate. Thus, the beneficial effect of early treatment with rituximab remains to be proven.

Are there any new promising treatments for severe refractory TTP and other thrombotic microangiopathies? Several agents designed to inhibit vWF have already reached phase II trials and suggest promising preclinical results. One is ARC1779, a synthetically manufactured nucleic acid macromolecule that binds to the A1 domain of the vWF and inhibits its binding to glycoprotein Ib on platelets [15,16]. ARC1779, which blocks vWF-mediated platelet function, thus inhibiting pathological thrombosis, was found effective in vivo and ex vivo (from plasma samples from TTP patients). In a recent phase IIa trial, ARC1779 was added to plasma exchange therapy in seven TTP patients and was found to be safe and tolerable [16]. However, its efficacy has not yet been determined.

In conclusion, as shown by Stein et al., rituximab is probably the best option today for severe or relapsing TTP, especially for those with an idiopathic type accompanied by anti-ADAMTS13 antibodies. Regarding treatment of early TTP, since data are still lacking the aforementioned treatment may be considered for patients presenting with a severe clinical condition or for those who suffer from intolerable side effects to plasma exchange (infection, catheter thrombosis, transfusion reaction, etc.). Other unresolved issues regarding the use of rituximab for TTP include the target population, duration of treatment, and usefulness of concomitant plasma exchange. In the future, perhaps randomized controlled studies will address these questions, while newer drugs such as vWF inhibitors may be proven effective as well.

HUS = hemolytic uremic syndrome

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