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CORRESPONDENCE

Efficacy of subcutaneous preemptive rituximab in immune-mediated thrombotic thrombocytopenic purpura: Experience from the first 12 cases

To the Editor:

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a potentially fatal disease in the absence of treatment, which consists of daily therapeutic plasma exchange (TPE), in association with corticosteroids and increasingly rituximab and caplacizumab, an inhibitor of von Willebrand factor-platelet interaction.[1] Thus iTTP is characterized by the occurrence of several relapses of unpredictable severity, exposing patients to death and treatment-related complications. Consequently, the prevention of relapses represents an important goal to be achieved.[1,2] In this perspective, it has been shown that a persistently undetectable activity of the von Willebrand factor-cleaving protease ADAMTS13 in patients otherwise in remission represents a reliable early predictor of full clinical relapse.[1,2] Patients with a decreased ADAMTS13 activity following an iTTP episode may also experience more frequently ischemic strokes,[3] providing further evidence for the need to improve ADAMTS13 deficiency during clinical remission. Rituximab is a chimeric monoclonal antibody targeting CD20+ B lymphocytes that has demonstrated efficacy in acute iTTP, allowing a shortening of TPE duration and delaying relapses.[1,2] Rituximab is also used as a preemptive therapy in patients in clinical remission who experience a persistent severe ADAMTS13 deficiency during follow-up.[2] Preemptive rituximab (consisting in 1 single infusion to 4-weekly IV infusions) reduces the incidence of iTTP relapse by diminishing the production of anti-ADAMTS13 antibodies and restoring ADAMTS13 activity, which parallels peripheral B cell depletion.[2,4] In France, rituximab obtained a temporary recommendation of use for patients with iTTP as a frontline treatment and as a preemptive treatment (Table S1). Rituximab is relatively non-toxic, but IV infusions typically last for 3-4 hours, making it resource intensive for the healthcare system and time consuming for patients. A subcutaneous (SC) formulation of rituximab has recently been approved as an alternative to the IV infusion in both indolent lymphomas and diffuse large B-cell lymphoma.[5] Clinical studies have shown that SC rituximab administration resulted in non-inferior levels of product in the blood and comparable clinical efficacy outcomes when compared to the IV administration, with a comparable safety profile.[5-7] The subcutaneous administration results in a highly concentrated fixed dose of rituximab, reducing treatment times and nursing workload.[5-7] Additionally, preference and satisfaction improved in patients with the SC formulation, due to time saving, less emotional distress and a more comfortable administration.[8] These results, enabling a substantial decrease in the burden of care, are particularly relevant for iTTP patients as a majority may require a preemptive treatment following the acute episode with retreatment typically every 1 to 2 years to maintain ADAMTS13 within detectable values.[2,4] The aim of our study was to address the efficacy and tolerance of SC preemptive rituximab treatment in patients in clinical remission of iTTP displaying severe ADAMTS13 deficiency during follow-up.

We included non-pregnant patients (age ≥ 18 years) with a previous iTTP episode and managed in our center.[1] All patients displayed a severe ADAMTS13 deficiency, either persisting after clinical remission or occurring after an initial partial or complete enzyme recovery. During follow-up, SC rituximab was proposed to patients instead of the IV formulation when a preemptive treatment was needed. Informed consent was obtained from all patients. This study was approved by our institutional review board in accordance with the Declaration of Helsinki.

Preemptive treatment with SC rituximab consisted of a single administration of rituximab (Mabthera; Roche, Paris, France) 1400 mg (supplemental method). After receiving SC preemptive rituximab, patients were followed-up at 1 month, and then every 3 months during at least 24 months.[2] Clinical relapse, adverse events, ADAMTS13 activity and peripheral blood CD19+ B lymphocytes count were registered at each follow-up visit.[2] During follow-up, we considered <20 IU/dL as ADAMTS13 activity threshold for the need of preemptive rituximab treatment.[2] Patients who experienced further decreases in ADAMTS13 activity during follow-up were retreated with SC rituximab. We assessed the time between two SC preemptive rituximab administrations, defined as time to next treatment before each administration. Patients were interviewed about self-experience of the SC vs IV formulation; especially, patients were offered the possibility to choose back the IV formulation. Quantitative variables are expressed as medians [25th-75th percentiles].

Between August 2015 and July 2020, we administered SC rituximab preemptively to 12 patients (10 women/2 men) aged 44 [36-52] years. All patients were diagnosed with iTTP between 2004 and 2018 (Table S2). At presentation, seven patients had cerebral involvement. All patients had serum creatinine level < 200 μM except for patient nine, who was a 68-year-old woman with a history of chronic renal failure. All patients displayed microangiopathic hemolytic anemia (hemoglobin 8.6 [7.5-10.1] g/dL), with peripheral thrombocytopenia (18 [11-36] giga/L). All were treated with daily TPE

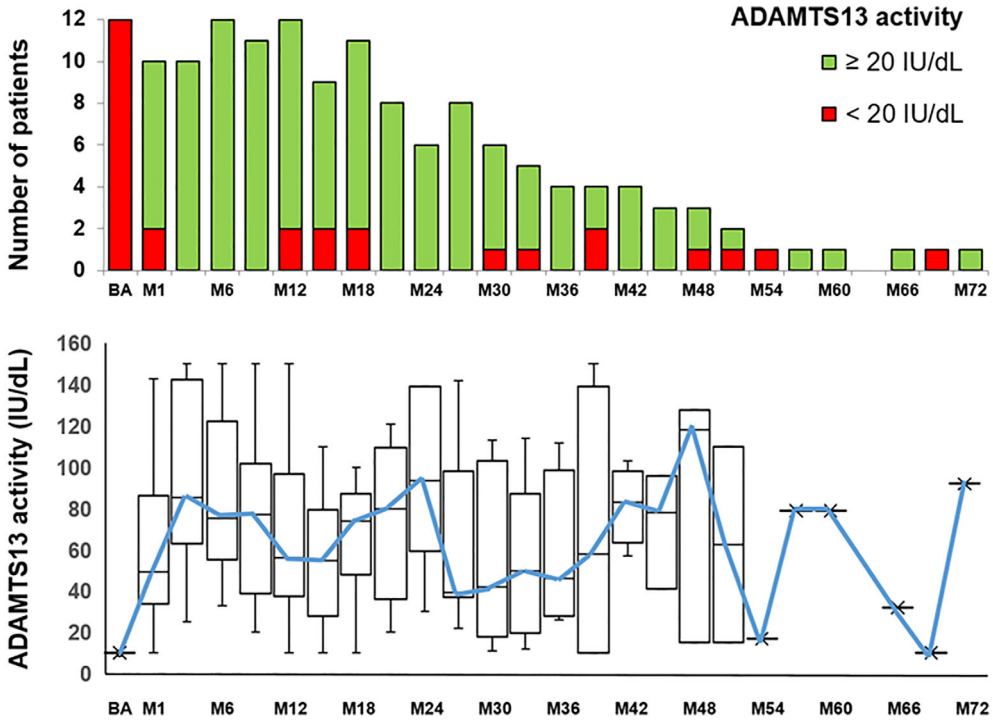

FIGURE 1 ADAMTS13 activity after subcutaneous preemptive administration. ADAMTS13 activity (IU/dL) during follow-up in patients, before (BA) and after subcutaneous preemptive rituximab administrations (M1 to M72, that is 1 to 72 months after first rituximab administration). Colored histograms represent the number of patients at each time of follow-up. Box plots represent quartiles, median, and range of ADAMTS13 activity. The blue line represents the variation of the median ADAMTS13 activity over time. After M48, only medians were reported as the number of events was small

(16 [9-18.5] exchanges) and corticosteroids; nine patients had also IV rituximab as salvage therapy. Moreover, during their follow-up, eight patients (67%) had 1-4 IV preemptive infusions of rituximab because ADAMTS13 activity was <20 IU/dL (Table S3).

All patients had SC preemptive rituximab, when ADAMTS13 activity was <20 IU/dL during follow-up, a few months after initial TTP episode (patients seven and 11), or following a first (patients two, three, eight, nine and 10), a second (patient six), a third (patient one) or a fourth (patient four) IV preemptive infusion of rituximab. Patient five displayed a persistently undetectable ADAMTS13 activity after four IV infusions of rituximab at the acute phase of iTTP; she was thus given SC rituximab every 2 months for a period of 22 months (ie, 11 SC rituximab doses in total), which led to a durable normalization of ADAMTS13 activity. Patient 12 also had a persistently undetectable ADAMTS13 activity following the acute iTTP and subsequently received one SC rituximab injection. Of note, patient one became pregnant 8 months after her second SC preemptive rituximab administration; pregnancy was uneventful and was terminated at 37 weeks, 17 months after the SC rituximab administration, with ADAMTS13 activity levels that ranged throughout pregnancy between 21 IU/dL and normal values.

One month after first SC rituximab administration, ADAMTS13 activity was >42 IU/dL in eight patients whereas it was still undetectable in two (data were missing for two patients at this timepoint) (Table S3, Figure 1); CD19+ B lymphocytes were undetectable in all 10 patients. At 3-month follow-up, all 10 patients explored had an ADAMTS13 activity >25 IU/dL, also with undetectable CD19+ B lymphocytes. Only patients six and seven had no available data at this time; however, they had normal ADAMTS13 levels at previous and next follow-up visits, suggesting that ADAMTS13 was also detectable in these two patients (ie, in all 12 patients). From six available patients, CD19+ B lymphocytes were undetectable (<1%) at month 6 and barely detectable at month 9 (0.05% [0-1.25]). At month 12, they became detectable in all six patients (3% [1.5-5.6]), which is consistent with observations on patients treated with the IV formulation.[2]

Six patients (50%) received a single SC preemptive rituximab administration: after a median follow-up of 22.5 months (12-30 months), ADAMTS13 activity was still detectable (median, 42 IU/dL) and no further rituximab administration was needed (Table S3: patients five, eight, nine, 10, 11 and 12). Five other patients (42%) needed retreatment, consisting in one (two cases), two (two cases) or three (one case) additional administrations (Table S3: patients one, three, four, six and seven), typically every 18 months (Figure 1). Finally, one patient was lost to follow-up (patient two). Overall, median time to next treatment was 18 months [15.3-18.8] with SC rituximab, as compared to 15 [10-23] months with the IV formulation. Upon SC preemptive rituximab administration, none of the 12 patients experienced clinical iTTP relapse during follow-up.

No patient experienced immediate intolerance reaction. Patient three experienced a serum sickness of favorable outcome with corticosteroids, and an injection-site swelling. No infection was reported. When preemptive retreatment was needed, no patient chose back the IV formulation after the first SC rituximab administration.

Strategies based on B cell depletion have proved remarkably effective in the prevention of clinical relapses in iTTP, occurring soon after the acute phase of the disease, but also during long-term follow-up.[1,2,4] In this way, more than 40% of patients may require repeated preemptive rituximab administrations during long-term follow-up to maintain a detectable ADAMTS13 activity and prevent clinical relapse.[2] In addition, to circumvent unresponsiveness to standard

courses of rituximab, intensive rituximab regimens inspired from 2-year maintenance treatments performed in patients with indolent B-cell lymphoid malignancies are increasingly used in iTTP.[9] Collectively, these data support the view that a substantial number of iTTP patients require repeated administrations of rituximab, emphasizing the crucial need to avail a formulation of rituximab maximizing the alleviation of the burden of care for both health care providers and patients.

We report that the efficacy of SC rituximab in the prevention of iTTP relapses is comparable to the IV formulation. We found comparable results between the two formulations regarding the prevalence of and the time to ADAMTS13 recovery, the time to next treatment, and tolerance.[2,4] Moreover, peripheral CD19+ B lymphocytes were depleted in the first month. Importantly, patients unanimously preferred the SC formulation, and their satisfaction improved as none of them wished to choose back the IV formulation after a systematic interview. Subcutaneous rituximab, by decreasing the burden of care and improving patients' satisfaction, could represent a new standard of care in the prevention of iTTP relapses.

CONFLICT OF INTEREST

P. C. is member of the Clinical Advisory Board for Alexion, Sanofi, Takeda and Octapharma. A. V. is member of the Clinical Advisory Board for Sanofi.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.