HEMOSTASIS AND THROMBOSIS

Commentary

Rituximab in the treatment of immune-mediated thrombotic thrombocytopenic purpura

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder caused by a deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). Lack of ADAMTS13, also known as von Willebrand factor (VWF) cleavage enzyme, results in the formation of microthrombi by VWF and platelets. VWF is a large glycoprotein that plays a key role in platelet adhesion on the vascular wall. Thrombi in the capillaries block blood flow and may result in ischemia in tissue and organs[1-2]. The deficiency of ADAMTS13 could be congenital (cTTP), reduced production of ADAMTS13, or reduced ADAMTS13 levels because of antibody formation (immune-mediatedTTP [iTTP])[3]. The standard treatment of iTTP is plasma exchange (PLEX) and corticosteroid, which have been shown to reduce the mortality rate from 90 to 20%[4-5].

Rituximab is a humanized monoclonal antibody against CD20 on B-lymphocytes used to treat several malignancies and autoimmune diseases. However, rituximab has also been used for treating iTTP over the last two decades[6]. There are three different indications for using rituximab in the treatment of iTTP, including 1) as an initial treatment addition to the standard treatment, 2) when refractory to standard treatment, 3) preemptive rituximab in patients with iTTP in remission with low ADAMTS13 activity **(Figure 1)**[6]. In this report, we reviewed the evidence for all three conditions.

RITUXIMAB IN FRONTLINE TREATMENT

Adding rituximab to the frontline treatment of iTTP is controversial. A randomized placebo-controlled trial designed to show the effect of adding rituximab in the initial treatment of iTTP has been terminated due to slow progress on the study (3 patients in a year [NCT00799773])[7,8]. One historical case-control study[9], one retrospective case-control study[8], and a case series[10] provided limited evidence that using rituximab as initial therapy can

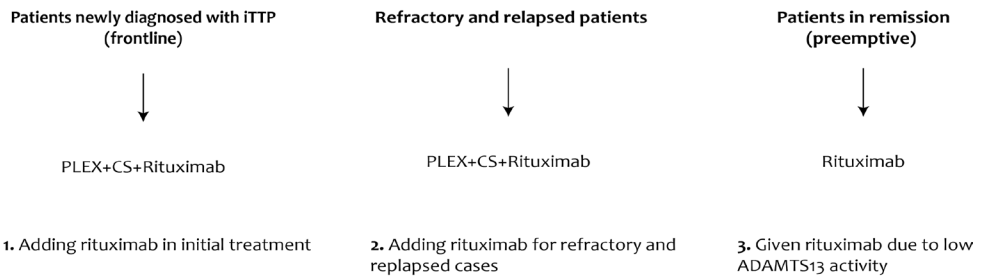

Figure 1 - There are three different indications of using rituximab in the treatment of iTTP
PLEX: plasma exchange; CS: corticosteroid.

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reduce the time to remission and relapse rate[11]. Scully *et al.*[9] reported rituximab's effects as an initial treatment for iTTP (40 patients, 34 newly diagnosed and 6 were relapsed cases) and compared it with historical controls (40 patients, 31 newly diagnosed, and 9 were relapsed cases). The remission rate was 93% in the rituximab group and 95% in the control group, but fewer patients relapsed in the rituximab group (11 *vs* 55%, respectively) during 50 months of follow-up[9]. This study provided evidence for the benefits of rituximab as initial therapy but also showed a high remission rate in patients who received the standard therapy, with nearly half of the patients not relapsing[6,9]. No serious infections and no other serious adverse events were reported in this study. A total of 26 infections were reported after rituximab infusion in a year, but infections were not reported for the historical controls. However, three patients died during the study, most likely related to iTTP, not rituximab. These results indicate that adding rituximab for the initial treatment of iTTP may be suitable for some patients; however, other patients may receive unnecessary treatment. Page *et al.*[8] reported a study that contained two groups: 21 patients with iTTP that received the standard therapy and 16 patients that had rituximab in addition to the standard therapy. In this study, all the cases presented their first episode and the follow-up time was similar for all patients[8,11]. Patients in the rituximab group had more cases of the intractable disease, underwent more PLEX (median 16 *vs* 8, p=0.01), and received a higher total dose of steroid treatment (p<0.01). However, the rituximab group also had a lower relapse rate (only 2 [13%] patients relapsed at 2.5 and 9.9 years). In contrast, 9 (43%) patients relapsed in the standard therapy group at a median of 3.1 (0.4-5.9) years[8,11]. For preventing relapse in one patient, 3.3 patients needed to be treated with rituximab, and adding rituximab as frontline therapy reduced the absolute risk of relapse by 30%[11].

In addition, some investigators suggest that patients presenting with severe iTTP might benefit from early rituximab therapy[12]. There is no predictive scoring system for the disease severity or course of disease (relapse and remission). However, disease severity in TTP was defined in previous studies by patients' characteristics, such as age (>60), clinical symptoms, signs (neurologic and/or cardiac involvement), and laboratory parameters (platelet counts $<15\times10^3/\mu L$ 2 days after PLEX initiation). These factors contribute to the severity and correlate with mortality and treatment refractoriness[13-15].

In a recent study[16], rituximab has been used in frontline therapy with PLEX and caplacizumab, a nanobody that binds the VWF A1 domain to block platelet binding. The 90 patients treated with triple therapy compared to 180 historical cases. The primary outcome was a composite of death and refractoriness within 30 days after diagnosis. The triple treatment group had fewer deaths and less refractoriness compared to the historical group (2.2 *vs* 12.2%, p=0.01). As a secondary outcome, the time to increase in ADAMTS13 activity (>20%) was 28 (IQR, 14-42) days in the triple therapy and 48 (IQR 24-83) days in the historical group. All patients in this study received rituximab as frontline therapy regardless of disease severity; however, 123 (68%) patients in the historical group received rituximab for refractoriness or exacerbation of iTTP[16]. After this study, rituximab was approved for front-line therapy in iTTP in France.

In clinical practice and all previous reports, Rituximab doses in iTTP treatment are similar to malignancy treatment (375 mg/m^2/week- 4 doses). In the ART study[17,18], patients were treated with low-dose rituximab (100 mg/week-4 doses) added to PLEX. There were 18 patients with iTTP; seven were newly diagnosed and 11 were relapsed patients in the study. Two cases experienced an exacerbation or were defined as refractory (12.5%) in 30 days. In this study, one patient had a recurrence in the first year, three patients had a relapse and the relapse-free survival rate was 72% during the two years of the follow-up period[18]. The relapse rate was 51% in a historical control group of 54 iTTP episodes in which patients did not receive rituximab after 2 years of follow-up[17]. In the ART study, the rituximab-related adverse effects were line-associated bacteremia seen in 3 and respiratory failure seen in 4 patients. However, the adverse events rate in the low-dose rituximab group did not compare patients who received regular-doses of rituximab or historical controls who did not receive rituximab[18]. Low-dose rituximab could be as effective as a regular dose and may result in fewer adverse effects, but randomized prospective studies are needed to support these findings.

ISTH guideline published in 2020, recommended rituximab in the frontline therapy for only selected cases such as patients with iTTP comorbid autoimmune

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disorders due to low levels of evidence (conditional recommendation)[19]. In summary, some reports suggest using rituximab for initial treatment in iTTP patients, but more studies are needed to show the benefits of rituximab for initial iTTP treatment.

RITUXIMAB FOR REFRACTORY TO STANDARD TREATMENT

Rituximab was first used in iTTP as a therapy for patients who became refractory to frontline treatment. In four retrospectives[8,20-22], and 2 prospective studies[23,24] patients who received rituximab had earlier and higher remission rates than patients who did not. Froissart *et al.*[23] reported 21 patients treated with rituximab who did not respond to frontline therapy. Compared to 53 historical controls, the rituximab group achieved earlier remission, underwent fewer PLEX procedures, and experienced a lower relapse rate in one year. This was likely achieved by reduced ADAMTS13 antibody production and increased ADAMTS13 activity. All patients in the rituximab group achieved remission. In contrast, the remission rate was only 78% in the control group. Patients in the rituximab group did not experience relapse, but five patients (9.4%) in the control group relapsed within the first year. However, after a year of follow-up, there was no significant difference in relapse rate between the two groups[23]. During the follow-up period, patients treated with rituximab relapsed later than those who did not receive the drug. These data further support that rituximab successfully postpones relapses in iTTP patients[6].

PREEMPTIVE RITUXIMAB TREATMENT IN PATIENTS IN REMISSION WITH LOW ADAMTS13 ACTIVITY

ADAMTS13 activity level is important for establishing a TTP diagnosis, yet the activity levels may not recover even after the patients have achieved remission[25]. In a study with 19 patients with a TTP history, ADAMTS13 activity was measured every three months, and patients were followed for at least 12 months (max 39 months). Thirteen patients achieved clinical remission but ADAMTS13 activity was below 10% during follow-up in six patients[26]. The Oklahoma group reported on 52 patients in remission with a history of iTTP whose ADAMTS13 activity was measured at least three times during follow-ups. In twenty patients, ADAMTS13 activity on one to eight occasions was lower than 10%; only six patients had relapses in the median four years of follow-ups[5]. These data suggest that ADAMTS13 activity during remission in patients with a history of iTTP fluctuates and is a controversial method to predict relapse of iTTP during remission[6,25].

However, Schieppatti *et al.*[27] showed low activity of ADAMTS13 (<20%) during remission is related to relapse of iTTP. In the last decade, ADAMTS13 activity measurement became widely available and a predictive marker for relapse of iTTP[28-31]. Therefore, the international working group categorized relapse of iTTP as clinical relapse and ADAMTS13 relapse[28]. The clinical relapse is defined by low platelet count ($150\times10^6/\mu L$) with low ADAMTS13 activity (<10%); the ADAMTS13 relapse is defined as decreased ADAMTS13 activity (<20%) in patients who achieved higher ADAMTS13 activity during remission (complete [>60%] or partial [>20 and <60%])[28].

Preemptive rituximab therapy in patients in remission has been investigated in 4 studies[31-34]. In the first study[31], ADAMTS13 activity was measured 21 times in samples from 15 patients in remission. Out of 15, it was measured once in 11 patients and more than once in 4 patients. The activity levels were lower than 5% in 13 measurements, ranged between 6-14% in four, and were normal in the remaining four measurements. However, the patients were on long-term immunosuppressive therapy and experiencing a tolerance problem (cyclosporine and/or tacrolimus). Preemptive rituximab treatment was given to 15 patients during their remission period; two received the drug twice and two patients had three courses. After 3 months of rituximab, ADAMTS13 activity was normalized in 16 of 17 iTTP episodes, and long-term immunosuppressive therapy was discontinued in the four patients after rituximab therapy. In this study, all patients were followed up for a median of 23 months (range 1-89), and one patient relapsed at 70 months. The four patients whose ADAMTS13 activity dropped under 5% in 6 measurements without any symptoms and they received additional rituximab therapy during a median 13-month follow-up (range 10-26 months)[31].

In the second study[32], 48 patients were followed-up and had low ADAMTS13 activity during their remission. Thirty patients received preemptive rituximab compared to 18 who did not receive any additional intervention (historical controls). Rituximab reduced the relapse rate from 0.57 per year within the median follow-up month,

54 (33-63 months), to zero per year after a median of 36 months of follow-up (range 24-65) (p<0.01). The relapse rate in the non-rituximab group was 0.50 per year within the median 60 months (30-72 months). After rituximab therapy, ADAMTS13 activity increased to a median of 35% at one month and 46% at three months (range 30-68), respectively. In this study, the control group had a longer follow-up time than the rituximab group (median 60 *vs* 36 months, respectively). Moreover, due to low ADAMTS13 activity during remission, nine patients in the rituximab group received additional rituximab infusion, and five out of the nine patients received additional treatments (cyclophosphamide, alemtuzumab, cyclosporine A-CsA, mycophenolate mofetil-MMF, bortezomib, and splenectomy)[6,32]. In both studies, patients did not experience serious adverse events[31,32]. These reports suggest that preemptive rituximab therapy in patients with iTTP in the remission period with low ADAMTS13 activity may reduce relapse of iTTP within a short follow-up time[6,25]. However, limitations in these studies are 1) shorter follow-up time in the rituximab group compared to the control group, 2) the requirement of additional treatments due to lower ADAMTS13 activity in the rituximab group may obfuscate effects of preemptive rituximab therapy in the patients during remission[6,25].

In the third study[33], 76 episodes (female; n=60) from 45 patients (female; n=34) with iTTP in the remission period were retrospectively analyzed. The median platelet count was $268\times10^6/\mu L$, but platelet counts were lower than $150\times10^6/\mu L$ in 3 episodes from 2 patients; these patients did not have any symptoms and did not receive PLEX and these episodes were defined as a subacute iTTP in the study. The median ADAMTS13 activity was 5% (<5-17%). During these episodes, the patients received different doses of rituximab including the standard dos (375 mg/m^2, 4 weeks; 24 episodes), the low dose (200 mg, 4 weeks; 19 episodes), the intermediate dose (500 mg, 4 weeks; 17 episodes), and the other doses (100-1,000 mg, 1 to 5 doses; 16 episodes). The decisions for rituximab doses were not made based on patient-related or laboratory parameters in the study. After the preemptive rituximab therapy in a total of 76 episodes, 70 of them achieved remission (92.1%). In 60 (78.9%) episodes had complete remission (ADAMTS13 activity >60%) at a median of one month (0-5 months) and 10 episodes had partial remission (ADAMTS13 activity 30-59%) at a median of <1 month (0-3 months). In 6 episodes, 2 of the ADAMTS13 activities increased up to 23%, in 3 episodes no responses on ADAMTS13 activity were noted, and one was lost during follow-up. These 3 (3.9%) nonresponder patients had clinical relapses; they all received preemptive low-dose and relapsed at 9, 10, and 32 months. The relapse rate was lower compared to historical cases from the United Kingdom TTP registry (3.9 *vs* 17.3%). In addition to clinical relapses, ADAMTS13 activity dropped ≤15% in 35 episodes. A total of 38 (50%) episodes from 20 out of 45 patients received additional rituximab treatment after the preemptive dose at a median of 17.5 months (9-112) in the study. Additional rituximab treatment was required significantly more often (p=0.039) in the low-dose group (0.38 episode/year) compared to the standard dose (0.17 episode/year). However, a median treatment-free survival time was similar in the low- and standard-dose group (25 *vs* 29 months). In this study[32], the most common adverse events were infusion-related. Overall, the patients tolerated rituximab well and there was no increased risk for infections. One patient developed serum sickness after infusion (intermediate dose) and one had severe allergic reactions (standard dose) during infusions. Both of these patients developed anti-rituximab antibodies[33]. Compared to the first two studies that retrospectively evaluated preemptive rituximab therapy, this study had a higher number of episodes, a larger patient group, and only one patient was treated with additional immunosuppressive treatment (MMF) during remission. However, rituximab doses are not uniform and decisions on the doses were not given based on patient-related factors or laboratory parameters in the study.

In the fourth study[34], 92 patients (female; n=67) with a history of iTTP and had low ADAMTS13 activity (<10%) during the remission period were prospectively included the study. Before receiving preemptive rituximab, 37 patients had more than 1 TTP episodes (median; 3 episodes, 54 months). Overall 79 patients received a standard dose (375 mg/m^2) and 13 received high doses (500 mg/m^2) of rituximab with different numbers of infusions (range 1-9). After preemptive rituximab, 13 (14%) patients' ADAMTS13 activity did not increase and 3 of them developed clinical relapse despite the additional preemptive rituximab

and one had a fatal clinical relapse after additional immunosuppressive treatment (CsA). The ADAMTS13 activity in 79 (86%) patients recovered; while 34 (37%) patients' ADAMTS 13 activity recovered and did not drop during follow-up (median 31.5 months; IQR, 18-65). The remaining 45 (49%) patients developed severe ADAMTS13 deficiency and 6 (7%) had a clinical relapse during follow-up. Thirty-eight out of 45 patients received additional preemptive rituximab doses; 4 had a clinical relapse, and 3 had low ADAMTS13 activity after the additional doses. After preemptive treatment, the median incidence of relapse decreased significantly from 0.33 (IQR, 0.23-0.66) to 0 (IQR, 0-1.32) episodes per year (p<0.001). A total of 14 patients (15%) experienced a clinical relapse at a median of 37.8 months follow-up. Compared to 23 historical patients who did not receive preemptive rituximab, the clinical relapse rate (74 *vs* 15%) and median incidence of relapse per year (0.26 *vs* 0) decreased significantly (p<0.001). However, follow-up time was longer in the control group at a median of 7 years (IQR, 5-11). In this study[33], the most common adverse events were infusion-related, and the patients tolerated rituximab well. Severe infections were not seen. Four patients developed serum sickness after infusion[34].

The presented studies are case studies; 3 retrospective and one prospective with historical controls. In these 4 studies, preemptive rituximab treatment reduces the rate of clinical relapse and delays the time of the relapse compared to historical controls. All these studies compared their results with historical controls because designing a randomized controlled trial on this topic may be difficult and/or unethical. Patients with persistently low ADAMTS13 activity (<20%) are ideal candidates for preemptive rituximab treatment[35]. The ISTH guideline published in 2020, recommended rituximab for preemptive therapy in selected cases due to low levels of evidence (conditional recommendation)[19].

The preemptive rituximab treatment during remission in iTTP may need to be investigated in larger patient groups with more extended follow-up periods in future studies.

RITUXIMAB TREATMENT IN PREGNANT ITTP PATIENTS

Rituximab has been used in the treatment of iTTP for refractory cases during pregnancy[36-39]. Most of the reported patients responded well and recovered after rituximab treatment[36-38] and one maternal death was recorded[39]. In these cases, pregnancy outcomes resulted in preterm deliveries[37,38,40] and therapeutic abortion[36]. In addition, cytomegalovirus hepatitis was reported in one of the neonates[40]. Rituximab should be avoided during pregnancy for all indications to avoid short and long-term adverse effects and safety issues[41]. However, rituximab may be used in selective refractory cases with caution and monitoring of the adverse effects on both the maternal and fetal side. The non-pregnant patients who received rituximab for acute or preemptive treatment should be avoided pregnancy for at least 6-12 months[41,42].

CONCLUSION

In summary, rituximab is an effective therapy in iTTP, particularly in patients with refractory disease and relapses. In addition, it has been shown that rituximab reduces relapse rates when added to the frontline treatment and is used as preemptive treatment during the remission period. However, more studies are needed to assess the efficacy of rituximab as a frontline therapy and for the preemptive treatment of iTTP.

Keywords: *TTP, Rituximab, frontline, refractor, relapse, preemptive.*

The Authors declare no conflict of interest.

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