CLINICAL TRIALS AND OBSERVATIONS

Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura

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Key Points

- Patients with a history of acquired TTP and persistent severe ADAMTS13 deficiency during remission are at high risk of relapse and death.
- Preemptive infusions of rituximab in remission significantly decrease TTP relapse rate.

In acquired thrombotic thrombocytopenic purpura (TTP), the persistence of severe ADAMTS13 deficiency (<10%) during remission is associated with more relapse. Preemptive (ie, after remission) administration of rituximab in these patients to prevent relapses remains controversial. We performed a cross-sectional analysis of 12-year follow-up data to compare the relapse incidence with or without preemptive rituximab infusion. Among 48 patients who experienced at least one episode of acquired TTP followed by severe ADAMTS13 deficiency during remission, 30 received preemptive rituximab (group 1); the other 18 did not (group 2). After a median of 17 months (interquartile range [IQR], 11-29) following rituximab, the relapse incidence decreased from 0.57 episodes/year (IQR, 0.46-0.7) to 0 episodes/year (IQR, 0-0.81) ($P < .01$) in group 1. ADAMTS13 activity 3 months after the first rituximab infusion increased to 46% (IQR, 30%-68%). Nine patients required additional courses of rituximab. In 5 patients, ADAMTS13 activity failed to increase durably. Four patients experienced manageable adverse effects. In group 2, the relapse incidence was higher (0.5 relapses/year; IQR, 0.12-0.5; $P < .01$). Relapse-free survival was longer in group 1 ($P = .049$). A persistent severe ADAMTS13 deficiency during TTP remission should prompt consideration of preemptive rituximab to prevent relapses. (*Blood*. 2014;124(2):204-210)

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a specific form of thrombotic microangiopathy (TMA) characterized by the association of microangiopathic hemolytic anemia with peripheral thrombocytopenia, multiorgan failure of variable severity, and severe deficiency of the von Willebrand factor–cleaving protease ADAMTS13.[1] ADAMTS13 deficiency has been related to gene mutations in the hereditary form of the disease and to anti-ADAMTS13 autoantibodies in the autoimmune form.[2] Although immunomodulatory agents have been empirically used in TTP for many years, the direct pathogenic role of anti-ADAMTS13 antibodies was demonstrated only recently in a nonhuman primate model of acquired TTP,[3] thus providing a strong rationale for using B-cell–depleting drugs in this disease in association with daily therapeutic plasma exchange. Indeed, rituximab is increasingly proposed to patients with acute TTP who experience a suboptimal response to the standard treatment, or even as a front-line option. Specifically, rituximab hastens the episode resolution, reduces plasma requirement, and decreases the 1-year relapse rate by diminishing the production of anti-ADAMTS13 antibodies and restoring ADAMTS13 activity. However, whether rituximab reduces the long-term relapse rate remains controversial.[4-6] Despite progress in TTP

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management, decreasing the relapse frequency after remission remains a challenge. Indeed, 40% of patients may still experience a decrease of ADAMTS13 activity after remission because of the reappearance of anti-ADAMTS13 antibodies following B-cell reconstitution. In these patients, the observed relapse rate is ~38%.[7] This translates to a significant risk of mortality and morbidity related to the disease or to invasive therapeutic procedures.[8] Consequently, it is important to determine whether preemptive treatment (ie, after remission) with rituximab to deplete anti-ADAMTS13 antibodies could prevent long-term relapses. The encouraging results provided by preliminary studies[9-18] and the recommendations issued by our group led to the approval in France of rituximab for compassionate use in patients with acquired TTP and persistent severe ADAMTS13 deficiency. To ensure that all patients who received rituximab for TTP would be treated optimally and that their data would be collected in a standardized manner, our group developed recommendations for rituximab administration and for monitoring the biological response to the treatment.

Here, we report our experience on the use of rituximab in patients with persistent acquired ADAMTS13 deficiency during remission. We provide evidence that, in this context, preemptive administration of rituximab prevents relapses in most patients through rapid increase of ADAMTS13 activity.

Material and methods

Patients and treatment

Data on patients with various forms of TMA have been collected prospectively in the registry of the French TMA Reference Center (http://asso.orpha.net/ORPHAWEB/cgi-bin/file/Plan_Maladies_Rares.pdf; for details regarding the French TMA Reference Center, see Coppo et al[19]) for clinical, epidemiological, and research purposes starting from October 2000. For this study, we used data collected from October 2000 to January 2012. The TMA diagnostic criteria and the remission and relapse definitions were based on previous studies.[5,19] Briefly, TMA diagnosis was based on the presence of Coombs-negative microangiopathic hemolytic anemia or microangiopathic hemolysis, acute peripheral thrombocytopenia ($<150 \times 10^9$/L) and the absence of any identifiable cause of thrombocytopenia or microangiopathic hemolytic anemia, such as severe disseminated intravascular coagulopathy or malignant hypertension. Complete response was defined as full resolution of the neurologic manifestations and renal failure and recovery of normal platelet count ($>150 \times 10^9$/L) for at least 2 days. Durable remission was defined as complete response with no further thrombocytopenia, renal failure, or clinical worsening for more than 30 consecutive days from the first day of platelet count recovery (this interval included the period on maintenance plasma exchange therapy). Relapse was defined as the reappearance of neurologic manifestations, renal failure, and/or thrombocytopenia ($<100 \times 10^9$/L for at least 2 days) with no other identifiable cause after durable remission.

For this study, we focused on idiopathic TMA associated with acquired severe ADAMTS13 deficiency (activity <10%) in the acute phase (ie, idiopathic acquired TTP). Patients with detectable ADAMTS13 activity, a feature consistent with the diagnosis of hemolytic-uremic syndrome, were not included. Among patients in durable remission from a previous episode of idiopathic acquired TTP, we considered only those who had severe ADAMTS13 deficiency, either after remission or following an initial, partial, or complete enzyme activity recovery. Two groups of patients were defined: patients who received preemptive rituximab (group 1) and patients who did not because they were managed before the era of rituximab or in centers where the use of preemptive rituximab was not the standard of care (group 2). Informed consent was obtained from all patients. This study was approved by our institutional review board in accordance with the Declaration of Helsinki, and the French Data Protection Authority (Commission Nationale Informatique et Libertés, authorization No. 911539; and Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé, authorization No. 11.537, Paris, France).

Treatment of acquired TTP in the acute phase was performed according to a written protocol based on a previous study and in accordance with international guidelines.[5,20-22] This protocol was consensually acknowledged nationwide and has been implemented by all participating centers since October 2000. Briefly, therapeutic plasma exchange was carried out daily immediately after TTP diagnosis. The volume exchanged was 1.5 times the predicted plasma volume (standard intensive treatment) until remission (as defined above). The therapeutic plasma exchange sessions were then reduced over 3 weeks (maintenance treatment) and finally stopped. In the case of disease exacerbation or relapse, daily therapeutic plasma exchange sessions were resumed. Patients without signs of active infection received glucocorticoid therapy (1 mg/kg per day for 3 weeks). All patients received folic acid orally or intravenously.

Because relapses occurring after rituximab administration are reported to typically occur after at least 1 year,[4,5] both groups included only patients with long-term follow-up (ie, more than 1 year of follow-up). Preemptive rituximab treatment (Mabthera 375 mg/m^2; Roche, Paris, France) was started promptly after the detection of severe acquired ADAMTS13 deficiency. The number of rituximab infusions for each course of treatment (ie, 1 to 4 infusions per course; 1 infusion per week) was left to the physician's discretion. Premedication consisted of dexchlorpheniramine (10 mg intravenously) and acetaminophen (1 g intravenously) in all patients; patients who were not receiving glucocorticoids were also given methylprednisolone (30 mg intravenously).

Data collection

Each patient's epidemiological, clinical, and biological data were collected by a research study nurse, as previously reported,[19] by using a standardized form and were then transferred to a computerized database. The study nurse visited each center regularly to update the patients' clinical and biological data. Missing data were minimized by providing the physicians and the study nurse with a list of missing data for each patient in each center along with a request to provide such information when possible. The relapse incidence was evaluated and compared between groups. In group 1, the relapse incidence was also compared before and after rituximab administration. The frequency of ADAMTS13 activity recovery after preemptive rituximab administration and the interval between two rituximab courses to maintain detectable ADAMTS13 activity were also assessed. Biological response monitoring (before rituximab administration, at 1 month and 3 months after rituximab administration, and then every 3 months for at least 24 months) included ADAMTS13 activity, peripheral B-cell count, and standard laboratory workup. Long-term follow-up was recommended for all patients, according to a previous study.[7]

Safety assessments

Toxicity and side effects were recorded in the standardized case report form. On the basis of rituximab's long duration of action, a severe infection was defined as an infection that occurred within 12 months after rituximab administration and required hospitalization and/or intravenous antibiotics and/or resulted in death.

Evaluation of ADAMTS13 activity and anti-ADAMTS13 antibodies

Blood collection, plasma preparation, and ADAMTS13 activity measurement were performed as previously described.[7] Severe ADAMTS13 deficiency was defined as no detectable ADAMTS13 activity (<10%), moderate ADAMTS13 deficiency as activity between 10% and 49%, and normal ADAMTS13 as activity ≥50%. Anti-ADAMTS13 antibodies were detected by enzyme-linked immunosorbent assay (Technozym R ADAMTS13 INH; Technoclone, Vienna, Austria), as recommended by the manufacturer. ADAMTS13 deficiency was considered as acquired if it was associated with anti-ADAMTS13 antibodies. The threshold for antibody positivity was ≥12 U/mL. ADAMTS13 deficiency was also considered as acquired

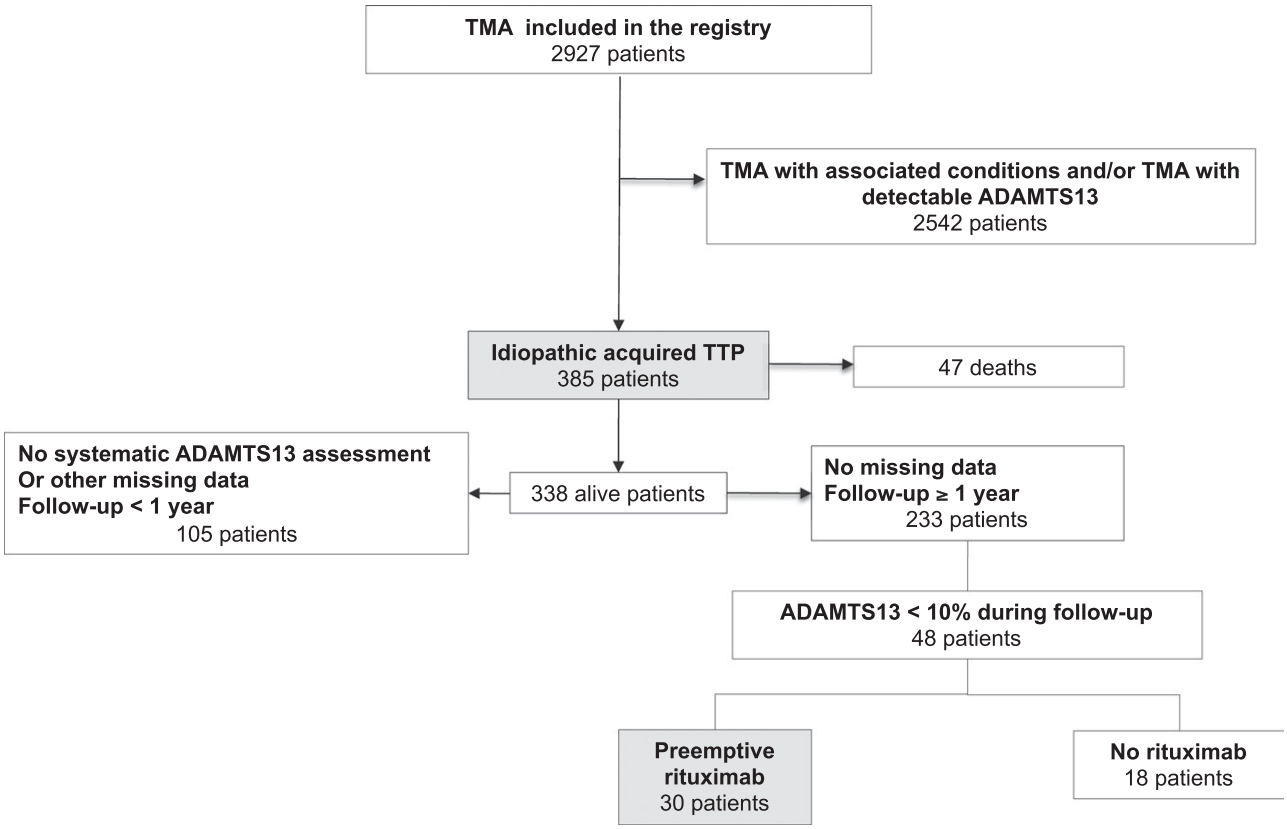

Figure 1. Study flowchart.

in patients without detectable anti-ADAMTS13 antibodies but who recovered the enzymatic activity during remission.

Circulating B-cell count

Circulating B-cell counts were determined after mononuclear cell labeling with anti-CD19 antibodies (B-lymphocyte marker). Cell-surface labeling was analyzed on a FACScan flow cytometer (Becton-Dickinson, San Jose, CA). Data were acquired from 10^4 cells in list mode and analyzed by using CellQuest software (Becton-Dickinson).

Statistical methods

Medians (interquartile range [IQR]) were determined for all continuous variables. Wilcoxon test was used to compare continuous variables, and the χ^2 test or Fisher's exact test were used to compare binary data. The Kaplan-Meier estimator was used to compare survival in both groups, with the corresponding 95% confidence intervals. P values $<.05$ were considered significant.

Results

The study flowchart is detailed in Figure 1. Of the 2927 patients with TMA included in the national registry, 385 had acquired idiopathic TTP and severe acquired ADAMTS13 deficiency and were treated in the acute phase according to consensual guidelines.[20-22] Forty-seven of these patients died during the acute phase of the disease. Among the 338 surviving patients in remission, 105 were not included in this study because ADAMTS13 activity was not systematically assessed during follow-up or because of other missing data, or because the follow-up was shorter than 1 year. Among the remaining 233 patients with TTP, 185 showed durable partial or complete recovery of ADAMTS13 activity after complete remission, and 38 (20%) had a relapse after a median time of 24 months (IQR, 12 to 43 months). This study focused on the remaining 48 patients (20.6%) with persistent severe ADAMTS13 deficiency (activity <10%) either at the time of remission (n = 22 patients) or after the initial partial or complete activity recovery (11 to 29 months) following remission (n = 26 patients). The median concentration of anti-ADAMTS13 antibodies was 44 U/mL (IQR, 24 to 59 U/mL). Thirty of these patients received preemptive rituximab during the follow-up (group 1) whereas 18 did not (group 2). The clinical characteristics and treatment modalities of acute TTP were comparable between groups (data not shown).

The clinical features of group 1 at the time of rituximab administration are reported in Table 1. Sixteen patients (53%) had more than 1 acute episode of TTP before preemptive rituximab administration:

Table 1. Patients' characteristics at time of rituximab administration (n = 30)

Characteristic	No.	%
Persistent undetectable ADAMTS13 activity after TTP episode	10	33
Occurrence of undetectable ADAMTS13 activity during follow-up	20	67
Age, y		
Median	38	
Range	30-44	
Female	19	63
White (North African patients included)	25	83

Results are given as medians (25^{th} to 75^{th} percentile) for quantitative variables and as number (percentage) for qualitative variables.

median of 2 acute episodes (IQR, 1 to 3 acute episodes) within a 54-month period (IQR, 33 to 63 months), corresponding to 0.57 episodes (IQR, 0.46 to 0.7 episodes) per year. Ten patients (33%) received 1 (n = 8) or 2 (n = 2) courses of rituximab in association with therapeutic plasma exchanges during the acute episode of the disease. The clinical presentation, blood cell count including reticulocytes, and hemolytic anemia workup (serum lactate dehydrogenase, haptoglobin, and indirect bilirubin) were normal at the time of rituximab administration (data not shown). The median time between the last TTP episode and the beginning of preemptive rituximab treatment was 14.5 months (IQR, 6.5 to 27.4 months). Patients received 1 (11 patients), 2 (2 patients), or 4 (17 patients) infusions of rituximab per course (1 infusion per week).

The median follow-up in group 1 after the first preemptive infusion of rituximab was 36 months (IQR, 24 to 65 months). After preemptive rituximab administration, only 3 patients (10%) had a clinical relapse at 14, 18, and 43 months. Therefore, the median relapse incidence in group 1 after preemptive infusion of rituximab decreased to 0 episodes per year (IQR, 0 to 0.81 episodes per year) compared with 0.57 episodes per year (IQR, 0.46 to 0.7 episodes per year) before preemptive treatment ($P < .001$). ADAMTS13 activity reached a median value of 35% at 1 month after rituximab administration. At 3 months, the median ADAMTS13 activity was 46% (IQR, 30% to 68%) ($P < 10^{-7}$). At this time, ADAMTS13 activity could not be detected in only 4 patients in group 1, whereas anti-ADAMTS13 antibody concentration was decreased in comparison with baseline value in 2 of these patients and it remained stable in the other 2. ADAMTS13 activity at 3 months after preemptive rituximab was apparently not affected by the interval between the onset of the acute episode and the first rituximab infusion (supplemental Figure 1, available at the *Blood* Web site; Spearman's correlation test $r_s = 0.11$; $P = .56$). The median ADAMTS13 activity further increased until month 12 after rituximab administration and then slightly decreased (Figure 2A). Accordingly, B lymphocytes were undetectable in all patients at 3 months, and then their number started to progressively increase from month 6 to reach normal values at month 18 after rituximab treatment (Figure 2B). The median number of rituximab infusions per course was comparable among patients who recovered a normal ADAMTS13 activity at 3 months after preemptive rituximab and those in whom enzyme activity was still low at this time point (3 infusions [IQR, 1 to 4 infusions] vs 4 infusions [IQR, 2 to 4 infusions], respectively; $P = .27$).

Nine patients (30%) received 1 (5 patients), 2 (2 patients), 3 (1 patient), or 10 (1 patient) additional courses of rituximab following a new severe decrease of ADAMTS13 activity detected in at least 1 blood sample during the follow-up period. Four of these patients were among those who received rituximab in association with therapeutic plasma exchange during the acute phase of the disease.[5] Retreatment with rituximab again increased ADAMTS13 activity to detectable levels in all but 1 patient. The median time between 2 consecutive courses of rituximab was 26 months (IQR, 5 to 59 months).

In five patients (17%) who previously experienced 1 to 10 TTP episodes, ADAMTS13 activity did not increase durably after 1 (1 patient) or more (4 patients) courses of rituximab alone. In 1 of these patients, ADAMTS13 activity increased durably only after alemtuzumab treatment (Campath, Genzyme; 10 mg twice per week subcutaneously for 6 weeks). After a 30-month follow-up, ADAMTS13 activity was still within normal values, and no relapse occurred. Another patient empirically received 1 infusion of rituximab every 6 months. No further relapse was recorded with this regimen after a 6.3-year follow-up, although ADAMTS13 activity remained undetectable in all samples but 1. In the 3 remaining patients,

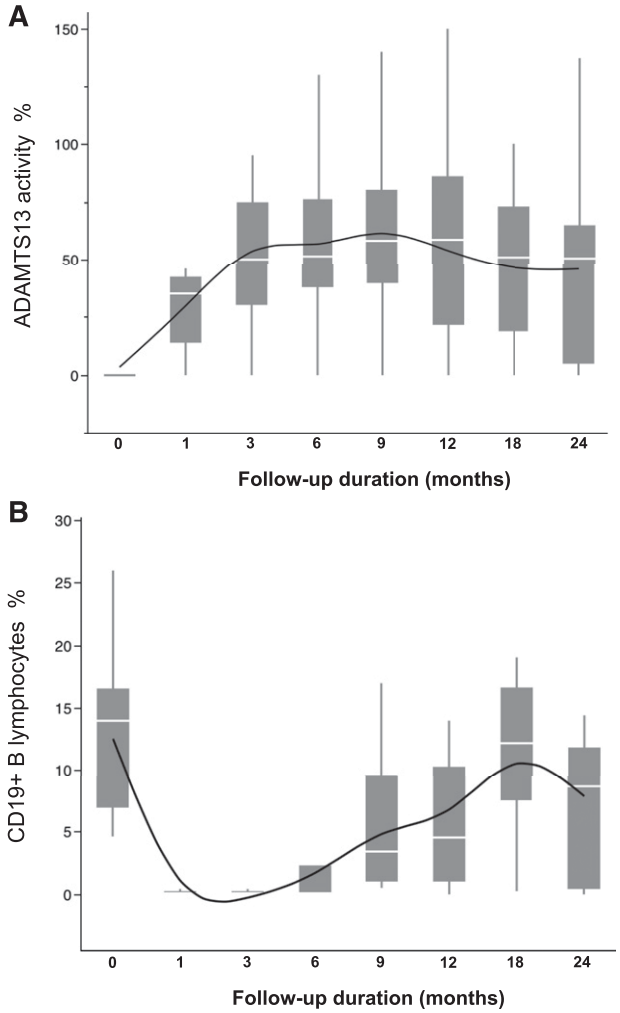

Figure 2. ADAMTS13 activity and CD19$^+$ lymphocytes during follow-up. (A) ADAMTS13 activity (%) and (B) CD19$^+$ B lymphocytes at 0, 1, 3, 6, 9, 12, 18, and 24 months after the first preemptive rituximab course. Box plots represent quartiles, median, and range of laboratory measurements. The black line represents the variation of the mean over time. Circulating B cells were counted after mononuclear cell labeling with anti-CD19 antibodies. Cell-surface labeling was analyzed on a FACScan flow cytometer (Becton-Dickinson, San Jose, CA). Data were acquired from 10^4 cells in list mode and analyzed by using CellQuest software (Becton-Dickinson). Data are the mean ± standard deviation.

ADAMTS13 activity did not improve durably despite additional therapies (cyclophosphamide, alemtuzumab, cyclosporine A, mycophenolate mofetil, bortezomib,[23] and splenectomy), and additional relapses were reported.

At the end of the follow-up, the median ADAMTS13 activity in group 1 was 58.5% (IQR, 30.5% to 86.3%). ADAMTS13 activity was normal in 18 patients, moderately decreased in 8 patients, and persistently undetectable in 4 patients.

Four patients (13%) in group 1experienced adverse effects from rituximab. Mild intolerance reactions, such as transient hypotension, superficial urticaria, and sinus arrhythmia, were reported by 3 patients. All symptoms were responsive to antihistaminic therapy and corticosteroids. A benign infection (erysipelas) occurred in 1 patient. One patient who received multiple infusions of rituximab developed hypogammaglobulinemia with no infectious complication. No case of multifocal leucoencephalopathy was recorded.

In group 2 (n = 18), 8 patients were managed before the era of rituximab and the other 10 were observed in centers in which preemptive rituximab infusions were not considered the standard of

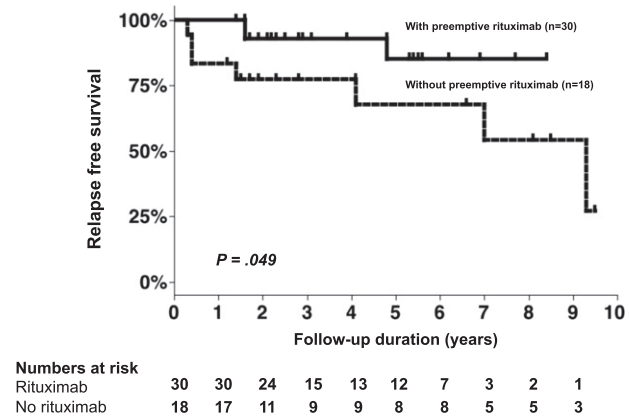

Figure 3. Kaplan-Meier survival estimates of relapse-free survival. Survival of patients with TTP who received (n = 30; group 1) or did not receive (n = 18; group 2) preemptive rituximab was compared with the Kaplan-Meier estimator.

care. In this group, the regular assessment of ADAMTS13 activity started after an acute episode, as recommended by a previous work.[7] At this time, 14 patients (78%) had a past history of TTP. Four of them showed a transient improvement of ADAMTS13 activity following the acute episode. However, ADAMTS13 activity was again not detectable at further follow-up visits. In the other 14 patients, ADAMTS13 activity was found undetectable at several follow-up visits following the acute episode, whereas anti-ADAMTS13 antibodies were repeatedly detected. Five patients (28%) received rituximab during the acute episode in association with therapeutic plasma exchange but not as preemptive treatment[5]; the use of rituximab during the acute episode in this group was comparable to that of patients in group 1 (33%; $P = .75$). During the interval from the regular assessment of ADAMTS13 activity after an acute TTP episode the last ADAMTS13 measurement (corresponding to a median follow-up of 5 years [IQR, 30 to 72 months]), 7 patients (39%) in group 2 had a relapse. Consequently, the relapse incidence in group 2 (median of 1 episode [IQR, 1 to 3 episodes] within the 5-year follow-up [IQR, 30 to 72 months]) was higher than in group 1 after preemptive treatment (0.5 episodes per year [IQR, 0.12 to 0.5 episodes per year] vs 0 episodes per year [IQR, 0 to 0.81 episodes per year], respectively; $P < .01$). Similarly, relapse-free survival from the first rituximab infusion (group 1) or from the first regular assessment of ADAMTS13 activity after an acute episode (group 2) was significantly longer in group 1 than in group 2 (log-rank test, $P = .049$) (Figure 3). Relapses in group 2 occurred within 6 months after the previous acute TTP episode (3 patients) and after the first year (4 other patients) (supplemental Figure 2 and Figure 3). Median relapse-free survival was 9.3 years in group 2 and was not reached in group 1 (Figure 3). Moreover, 2 patients in group 2 died because of a relapse during the follow-up period, whereas no fatal outcome was recorded in group 1. Overall survival was comparable between groups ($P = .13$). Figure 4 summarizes the outcome in each group.

Discussion

Relapsing TTP is a debilitating and life-threatening condition that occurs in up to 40% of patients with a history of idiopathic acquired TTP.[7] We report here that preemptive administration of rituximab after remission in patients with persistent severe acquired ADAMTS13 deficiency significantly reduces the incidence of TTP relapse by diminishing the production of anti-ADAMTS13 antibodies and restoring ADAMTS13 activity, which occurs in parallel with B-cell depletion.[4,5] Conversely, patients who did not receive rituximab had significantly more relapses, and a few fatal outcomes were recorded. Because the follow-up was longer in patients without preemptive rituximab treatment (40% of these patients were managed before the era of rituximab), we provided relapse rates for patients of both groups per time unit to limit the consequences of this possible bias in the analysis. A major strength of our study is the management of all patients according to consensual French national guidelines. Indeed, all patients received the standard treatment (therapeutic plasma exchange and steroids) in the acute phase, and throughout the entire follow-up period, biological monitoring was homogeneous. Therefore, only the use of rituximab differed throughout the duration of the study, with a progressive increase in the use of rituximab for the acute phase of

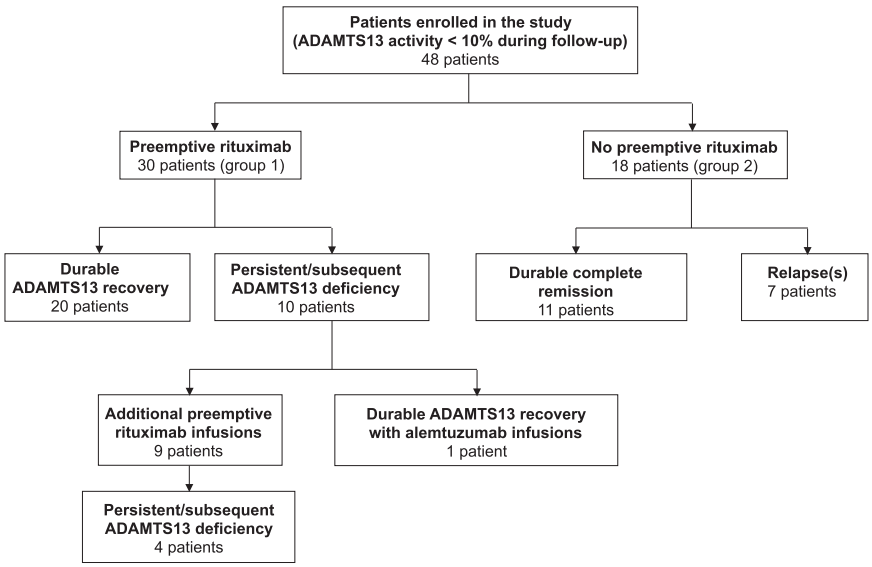

Figure 4. Outcome in patients with TTP according to treatment. Patients of group 1 (n = 30) received preemptive rituximab; patients of group 2 (n = 18) did not.

the disease from 2005 forward[5] and also during clinical remission as preemptive therapy (this study).

Our empirical monitoring schedule, based on the systematic assessment of ADAMTS13 activity and antibodies every 3 months, allowed us to efficiently anticipate TTP recurrence by performing a course of rituximab before overt relapse. However, ADAMTS13 recovery after preemptive rituximab administration was not sustained in up to 30% of patients,[14] and 1 or multiple additional severe drops of ADAMTS13 activity were observed in such patients, typically 18 to 24 months after rituximab administration, as a consequence of peripheral B-cell reconstitution.[24] Interestingly, these patients responded to further rituximab therapy.[14] Consequently, our results are consistent with the view that ADAMTS13 activity needs to be regularly assessed, even after rituximab administration, for early identification of patients at risk of relapse. Moreover, in this study, ADAMTS13 activity was assessed for at least 2 years after remission on the basis of empirical recommendations; beyond this time, the schedule of ADAMTS13 measurement was left to the investigator's discretion. In our experience, patients who recover a detectable and durable ADAMTS13 activity may also experience late relapses. These may occur in up to 40% of patients and more than 3 years after TTP remission, while regular ADAMTS13 assessment is usually suspended (data not shown). This finding suggests that ADAMTS13 measurement should be continued regularly for many years, even in patients with persistent normal ADAMTS13 activity to identify late-onset severe ADAMTS13 deficiency.

The optimal schedule of ADAMTS13 measurement and preemptive rituximab administration still remains to be accurately defined. In this study, the number of rituximab infusions per course was left to the clinicians' discretion, and patients usually received 4 infusions per course during the first 2 years of the study, whereas progressively relapsing patients received only 1 rituximab infusion per course, with apparently a comparable efficiency concerning the frequency of further severe ADAMTS13 deficiencies and the interval of time before the new reduction of ADAMTS13 activity. However, further studies with a larger number of patients are required to confirm this view. Additionally, the administration of rituximab based on the anti-ADAMTS13 antibody concentration or the residual B-lymphocyte number may be an alternative option that deserves further investigation. Conversely, the natural history of ADAMTS13 activity in patients with acquired TTP still remains poorly understood. Indeed, we cannot totally exclude the possibility that in patients with an identified severe acquired idiopathic ADAMTS13 deficiency, ADAMTS13 may subsequently increase spontaneously. Consequently, whether the detection of a severe acquired ADAMTS13 deficiency during follow-up should systematically lead to a preemptive infusion of rituximab (as performed in this study), or whether additional measurements are required before intervention remains to be determined.

Further studies are urgently needed to accurately evaluate the cost-effectiveness of the systematic assessment of ADAMTS13 activity during the long-term follow-up of patients with acquired TTP. Here we show that only a minority of patients required multiple courses of rituximab and that in most individuals, ADAMTS13 activity remained within normal values after 1 or 2 preemptive courses of rituximab. Although we did not perform a systematic cost-effectiveness analysis, we believe that systematic preemptive infusion of rituximab is less cumbersome and less expensive than the complete management of a TTP relapse, which includes, on average, the cost of 16 therapeutic plasma exchange sessions,[19,25] several days of hospitalization in an intensive care unit, and possible associated therapy-related complications.[8]

Importantly, no significant side effects were observed in group 1, which included patients with a long follow-up who received multiple courses of rituximab, providing further evidence that the use of rituximab in acquired idiopathic TTP is safe. This observation argues for a more systematic use of rituximab in acquired TTP as adjuvant[4] and preemptive therapy. However, in a small number of patients, repeated rituximab courses may be required to maintain a detectable ADAMTS13 activity, thus putting people who are young at risk of infectious complications.[26,27] Consequently, the long-term risk-benefit balance of this procedure needs to be accurately evaluated in a larger number of patients. For instance, between October 2000 and January 2012, 198 patients with a diagnosis of acquired TTP who were treated with rituximab, either in the acute phase or as a preemptive therapy, were recruited in our registry. A total of 35 side effects possibly related to rituximab were reported in 25 patients (13%), including 31 cases of intolerance to rituximab and 4 cases of infection, all with favorable outcome, which provides further evidence for the view that rituximab may be considered as a safe therapy in a disease as serious as acquired TTP. In this context, forthcoming studies should also address the advantages and limits of alternative therapeutic options, such as splenectomy.[28,29]

In conclusion, we report here that rituximab efficiently prevents TTP relapses with acceptable side effects. Our results also support the view that ADAMTS13 should be systematically monitored during long-term follow-up in patients with idiopathic acquired TTP. On the basis of our experience, we suggest that the persistence of severe acquired ADAMTS13 deficiency in patients who clinically recovered from a TTP episode or the subsequent occurrence of a severe ADAMTS13 deficiency during the follow-up should prompt consideration of preemptive rituximab to prevent relapses.

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Authorship

Contribution: M.H. performed the cross-sectional analysis for the French Registry for Thrombotic Microangiopathies, carried out most of the phenotypical analysis, and performed the statistical analysis; P.C. and L.G. designed the study, interpreted the results, wrote the manuscript, and critically reviewed the manuscript; A.V. performed ADAMTS13 analysis and critically reviewed the manuscript; and J.G., L.G., F.P., C.P., P.P., G.B., A.W., Y.B., P.V., A.S., D.B., J.-P.C., M.H., J.-P.V., and P.C. enrolled patients, collected clinical and laboratory information, and critically reviewed the manuscript.

A complete list of the members of the Reference Center for Thrombotic Microangiopathies appears in the online data supplement.

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