REGULAR ARTICLE

blood advances

Predictors of relapse and efficacy of rituximab in immune thrombotic thrombocytopenic purpura

Lova Sun,[1,2,*] Johnathan Mack,[2-4,*] Ang Li,[5] Justine Ryu,[6] Vivek A. Upadhyay,[1,2] Lynne Uhl,[2,7] Richard M. Kaufman,[2,8] Christopher P. Stowell,[2,3] Walter S. Dzik,[2,3,9] Robert S. Makar,[2,3] and Pavan K. Bendapudi[2,3,9,10]

[1]Department of Medicine, Massachusetts General Hospital, Boston, MA; [2]Division of Hematology, Harvard Medical School, Boston, MA; [3]Blood Transfusion Service, Massachusetts General Hospital, Boston, MA; [4]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; [5]Department of Medicine, University of Washington Medical Center, Seattle, WA; [6]Division of Hematology, Boston University School of Medicine, Boston, MA; [7]Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA; [8]Department of Pathology, Brigham and Women's Hospital, Boston, MA; [9]Division of Hematology, Massachusetts General Hospital, Boston, MA; and [10]Division of Hemostasis and Thrombosis, Beth Israel Deaconess Medical Center, Boston, MA

Key Points

- RTX protects from relapse in iTTP, but this effect disappears by 3 years after administration.
- Younger age, non-O blood group, and presenting in iTTP relapse are each associated with increased risk for subsequent relapse.

Patients with immune-mediated thrombotic thrombocytopenic purpura (iTTP) often experience life-threatening relapses of the disease, and rituximab (RTX) can be used to mitigate relapse risk. However, the predictors of relapse in iTTP and the magnitude and duration of effect of RTX remain key unanswered questions. Using a multi-institutional cohort of consecutive adult patients with iTTP, we used survival analysis to compare relapse rates between patients who received RTX during the index presentation with acute iTTP and those who did not. Of 124 patients, 60 (48%) received RTX and 34 (27%) experienced relapse. Median time to relapse was 3.71 (interquartile range, 1.75-4.9) and 1.33 (interquartile range, 0.43-2.35) years for RTX-treated and untreated patients, respectively. RTX conferred protection from relapse at 1 year of follow-up ($P = .01$) but not at 5 years of follow-up. Extended Cox regression was then used to identify predictors of relapse and to estimate the protective effect of RTX. The following parameters were independently associated with increased risk for subsequent relapse: presenting in iTTP relapse (hazard ratio [HR], 2.97; 95% confidence interval [CI], 1.4-6.4), age younger than 25 years (HR, 2.94; 95% CI, 1.2-7.2), and non-O blood group (HR, 2.15; 95% CI, 1.06-4.39). RTX initially provided protection from relapse (HR, 0.16; 95% CI, 0.04-0.70), but this effect gradually diminished, returning to the baseline risk for untreated patients at approximately 2.6 years. Patients who are young, have non-O blood group, or present with relapsed iTTP are at increased risk for subsequent relapse. RTX appears to confer short-term protection from relapse.

Introduction

Thrombotic microangiopathies (TMAs) are generally thought to represent a final common pathway for a broad range of underlying disorders, including infection, malignancy, solid organ or stem cell transplantation, or drug reaction. Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a distinct subtype of TMA that results from the formation of an inhibitory autoantibody against ADAMTS13, an enzyme responsible for cleaving large von Willebrand factor multimers into smaller, less thrombogenic units.[1,2] In iTTP, severe acquired ADAMTS13 deficiency and the resultant accumulation of ultralarge von Willebrand factor multimers leads to uncontrolled platelet thrombus formation in the microvasculature.[3,4] Left untreated, iTTP can result in end-organ damage, cardiovascular collapse, and death.

The introduction of therapeutic plasma exchange (TPE), which restores ADAMTS13 activity by replacing the enzyme and removing ADAMTS13-neutralizing autoantibodies, has dramatically lowered the

Submitted 7 January 2019; accepted 1 April 2019. DOI 10.1182/bloodadvances.2019031039.

*L.S. and J.M. contributed equally to this study.

The full-text version of this article contains a data supplement.

mortality rate of iTTP from up to 90% to less than 10%.[5,6] Whereas most patients have rapid and durable recovery with timely initiation of TPE, some experience an incomplete platelet response or ongoing disease activity and require many more TPE procedures.[7] Others respond initially, but then suffer relapse with recurrent thrombocytopenia and symptoms, usually within the first 2 years but occasionally up to a decade or more after the first episode.[8,9] Relapse remains the central concern for patients who survive an episode of iTTP, yet the predictors of relapse remain unclear, particularly in the setting of increased use of rituximab (RTX) to treat this condition in recent years. Therefore, we sought to identify risk factors for relapse and characterize the effect of RTX among a large group of patients with iTTP receiving care at a consortium of large academic medical centers.

Methods

Study sites and identifying patients with iTTP

This cohort study included all consecutive patients between 2004 and 2017 with TMA and suspected iTTP at 4 large academic medical centers in Boston, Massachusetts (Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Massachusetts General Hospital, and Boston Medical Center), as well as the University of Washington and Harborview Medical Centers in Seattle. Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, and Massachusetts General Hospital are part of the Harvard TMA Research Collaborative and are addressed as a single entity within this article. The project was approved by the institutional review boards at all participating institutions.

All patients who had an ADAMTS13 level checked between 8 January 2004 and 31 March 2017 were, identified. For our analysis, we included consecutive adult patients (≥18 years old) presenting with thrombocytopenia ($<150 \times 10^9$ platelets/L), schistocytosis, and 1 of the following: an ADAMTS13 activity level of 10% or less or an ADAMTS13 activity level between 10% and 20% with a positive inhibitor titer by Bethesda assay and/or detectable anti-ADAMTS13 immunoglobulin G present in the plasma. Patients were excluded if their ADAMTS13 assay was sent as an outpatient, if they had a known source of interference with the ADAMTS13 assay (eg, hyperbilirubinemia > 15 mg/dL), or if they had a secondary cause of TMA. For the purposes of this study, a patient's "index" presentation was defined as that individual's first episode of iTTP captured within our consortium, regardless of previous episodes of iTTP that may have occurred at other institutions. All index presentations were treated identically in the statistical model, regardless of whether a patient's index presentation represented de novo iTTP or a relapse.

Data collection and definition of relapse

Twenty-six laboratory and clinical parameters were recorded for each patient with iTTP. These included demographic information; ADAMTS13 activity and inhibitor level; hematology, chemistry, and other laboratory values including blood type; and presence of classic iTTP findings such as presence of fever and neurologic symptoms. The institutions included in our consortium do not systematically test remission ADAMTS13 activity levels, and this parameter was not included in our analysis. An undetectable ADAMTS13 activity level was recorded as 0%. Information on each patient's treatment course, including administration of steroids, RTX, and number of TPE procedures, was recorded. A patient was considered to have received RTX if the drug was administered during the index presentation; receipt of RTX during a subsequent relapse did not qualify. Timing of RTX administration relative to presentation was also captured. Finally, we documented outcomes data including length of hospital stay, days to platelet count recovery (defined as $>150 \times 10^9$ platelets/L for 2 consecutive days), relapse, death, or loss to follow-up. Remission was defined as stable recovery of platelet count and absence of clinical symptoms for 30 consecutive days after discontinuation of TPE. Relapse was defined as recurrence of iTTP after 30 consecutive days without TPE. A course of TPE was defined as a series of TPE procedures performed at regular intervals ranging from twice a day to every other day until the patient achieved remission.

Statistical methods

Comparisons between patient cohorts were made using χ^2 or Fisher's exact test for categorical variables, and Mann-Whitney *U* test for continuous variables. The hazard of iTTP relapse was estimated using extended Cox proportional hazards regression. Patients were included in the analysis from the date of index presentation until relapse, death, or loss to follow-up (whichever occurred first). All patients started in the no rituximab group; this status changed after the first dose of RTX was administered during the index iTTP episode. To identify covariates associated with iTTP relapse, a purposeful model selection strategy was used.[10] Covariates significant at $P < .25$ on univariate Cox regression were included in a multivariate model. Covariates selected for multivariate regression were dropped from the final model if nonsignificant at $P > .10$ and if their removal resulted in a less than 20% change in other coefficients. Covariates excluded from the initial univariate analysis were individually added to the model and included if coefficients changed by at least 20%. The proportional hazards assumption was assessed for each covariate included in the final model, and time-dependent effects were included for any covariate that violated this assumption. After identifying age to be associated with relapse risk, this covariate was dichotomized at different cutoffs using 5-year intervals (eg, <20 years, <25 years, <30 years, etc). Models with the dichotomized variable were compared using the Akaike Information Criterion. The model with the lowest Akaike Information Criterion was selected. Kaplan-Meier survival analysis was used to compare patients who did and did not receive RTX therapy. Patients contributed time to the RTX group only after RTX had been administered during the index iTTP episode. Kaplan-Meier curves were compared using the log-rank test. The hazard ratio (HR) for relapse over time adjusted by other predictors in the extended Cox model is shown separately. Data were analyzed with the use of Microsoft Excel, Medcalc version 18.6 (Ostend, Belgium), and STATA software, version 14.1 (StataCorp).

Results

Patient population

Within our combined data set, we identified 124 patients with iTTP who presented between 8 January 2004 and 31 March 2017, including 91 within the Harvard TMA Research Collaborative, 17 from the University of Washington, and 16 from Boston Medical Center (Table 1). The median follow-up period in our cohort was 20.6 months. One hundred four patients presented with their first episode of iTTP, whereas 20 patients were enrolled in the dataset during a relapsed presentation. The median age of our patient

Table 1. Demographic, clinical, and treatment data for the patient cohort

	Entire cohort (N = 124)	RTX (N = 60)	No RTX (N = 64)
Study site, n (%)			
Harvard Consortium	91 (73)	46 (77)	45 (70)
University of Washington	17 (14)	9 (15)	8 (13)
Boston Medical Center	16 (13)	5 (8)	11 (17)
Type of presentation, n (%)			
First-time	104 (84)	50 (83)	54 (84)
Presenting in relapse	20 (16)	10 (17)	10 (16)
Sex, n (%)			
Male	38 (31)	18 (30)	20 (31)
Female	86 (69)	42 (70)	44 (69)
Age, median (IQR), y	42 (31-52)	41 (31-52)	43 (31-53)
ABO blood group, n (%)			
Group O	64 (52)	31 (52)	33 (52)
Non-group O	58 (47)	27 (45)	31 (48)
Unknown	2 (1)	2 (3)	0 (0)
Ethnicity, n (%)			
White	67 (54)	34 (57)	33 (52)
Nonwhite	52 (42)	24 (40)	28 (44)
Unknown	5 (4)	2 (3)	3 (5)
Laboratory values, median (IQR)			
ADAMTS13 activity, %*	0 (0-0)	0 (0-0)	0 (0-0)
ADAMTS13 inhibitor, BU	1.4 (0.7-2.0)	1.4 (0.8-2.0)	1.4 (0.6-2.0)
Hemoglobin, g/dL	8.9 (7.3-10.1)	8.6 (7.1-9.6)	9.4 (7.4-10.8)
Platelets, $\times 10^9$/L	16 (10-22)	15 (10-20)	17 (11-24)
Lactate dehydrogenase, U/L	1090 (742-1402)	1089 (734-1504)	1090 (782-1329)
Cr, mg/dL	1.0 (0.8-1.4)	1.0 (0.7-1.3)	1.1 (0.9-1.6)
Total bilirubin, mg/dL	2.3 (1.5-3.1)	2.4 (1.5-3.1)	2.3 (1.5-3.1)
Reticulocyte, %	4.6 (2.9-8.3)	6.2 (3.7-9.9)	3.6 (2.6-6.4)
Day 4 platelets, $\times 10^9$/L	131 (68-181)	111 (49-160)	159 (107-216)
Days to platelet normalization	5 (4-8)	6 (4-15.3)	4 (3.5-6)
Treatment			
No. (%) treated with TPE	120 (97)	60 (100)	60 (94)
Median (IQR) TPE procedures	15 (8-23)	22 (14-29)	9 (6-15)
No. (%) treated with steroids	113 (91)	58 (97)	56 (88)
No. (%) treated with second-line drug†	8 (6.5)	8 (13)	0 (0)
Median (IQR) hospital stay, d	12 (8-20)	18 (11-27)	9 (7-14)

*An undetectable ADAMTS13 activity level was recorded as 0%.
†Five patients were given cyclophosphamide, 2 were given bortezomib (1 in combination with tacrolimus), and 1 patient was given vincristine.

population was 42 years (interquartile range [IQR], 31-52 years). Patients were disproportionately female (69%) and nonwhite (42%). At presentation, individuals in our dataset were severely thrombocytopenic, with a median (IQR) platelet count of 16 (IQR, 10-22), had severe ADAMTS13 deficiency (median activity, 0%; IQR, 0%-0%), and displayed several markers of ongoing hemolysis.

Treatment course and primary outcomes

We sought to characterize outcomes for patients who received treatment of iTTP. A large majority of patients were treated with TPE (120/124, 97%) and steroids (113/124, 91%) (Table 1). Sixty patients (48%) received RTX during the index presentation, including 50 patients presenting with their first acute episode and 10 patients with a prior history of iTTP presenting in relapse. Among the 10 patients with a history of iTTP, the median number of prior acute episodes was 3 (IQR, 2-4). Four of these 10 patients had been previously treated with RTX for iTTP a median of 2024 (range, 780-3357) days before the index presentation. Among the 64 patients who did not receive RTX for treatment of the index presentation, 54 were presenting with their first acute

Table 2. Outcomes

Variable	Entire cohort (N = 124)
Number (%) who relapsed	34 (27)
Median (IQR) years to first relapse	1.96 (1.05-4.07)
Median (range) number of subsequent relapses in those who relapsed	1 (1-4)
Median (IQR) days to platelet normalization	5 (4-8)
Number (%) who died within 90 d of index presentation	6 (5.5)*

*Calculated from follow-up data available for 109/124 patients.

episode and 10 were in relapse. The median number of prior iTTP episodes among those presenting in relapse was 1 (IQR, 1-1) in the untreated group ($P = .005$ vs relapsed patients who received RTX). None of these patients had been previously treated with RTX.

In comparison with untreated patients, those receiving RTX were similar with respect to type of presentation (relapsed or first episode), sex, ethnicity, age, and presenting laboratory features (Table 1). However, treated patients were significantly more likely to have a higher reticulocyte count ($P < .01$), lower platelet count on day 4 ($P < .001$), and a greater number of TPE procedures required to achieve remission ($P < .0001$). The most commonly used dose of RTX was 375 mg/m^2 (58/60, 97%), and 50/58 (86%) patients received a total of 4 weekly doses of RTX (supplemental Table 1). Patients who received RTX did so a median of 12 (IQR, 7-24) days after the index presentation. These data are consistent with the use of RTX primarily in patients with an inadequate response to TPE and steroids. For patients receiving RTX who had not yet achieved a normal platelet count, platelet count normalization occurred a median of 8 (IQR, 5-11) days after RTX administration. No patients in our data set received maintenance or prophylactic RTX at any point during the study period. A minority of patients (8/124, 6.5%) were also treated with second-line immunosuppressive agents; all of these patients also received RTX.

Within our entire cohort, the median time to platelet count recovery was 5 (IQR, 4-8) days, with patients receiving a median of 14 (IQR, 8-23) TPE procedures. Thirty-four of 124 patients in our cohort (27%) subsequently relapsed (Table 2; supplemental Table 2), with a median time to relapse of 1.96 (IQR, 1.05-4.07) years (Figure 1). The corresponding median relapse-free survival was 6.56 years. Most relapses (53%) occurred within the first 2 years after the index presentation. Primary outcome and vital status at 90 days was known for 109 patients. By day 90, 6 of these patients (5.5%) had died and 2 had relapsed (1.8%).

Effect of RTX use on relapse

The use of RTX on initial presentation increased during the study period (supplemental Figure 1). Between 2003 and 2005, 4 (29%) of 14 patients presenting with a first episode of iTTP received RTX compared with 15 (71%) of 21 patients presenting in 2015 to 2017. Overall, we observed a 3.6% increase per year in the proportion of patients with a first presentation of iTTP who received RTX. During the same period, we observed a decline of 1.5% per year in the proportion of patients experiencing relapse at 1 year.

To further explore the possible association between RTX use and risk for relapse, we used Kaplan-Meier analysis to study this

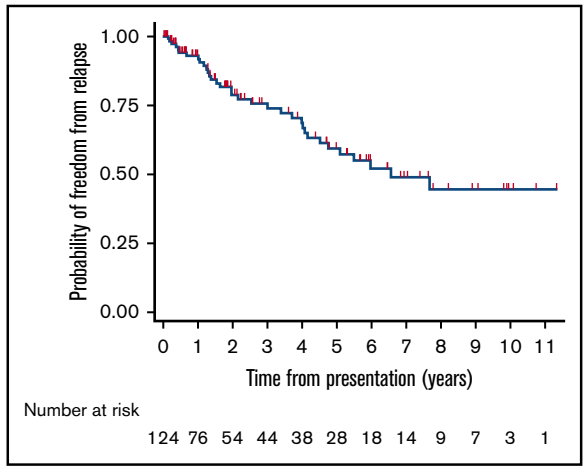

Figure 1. Kaplan-Meier curve for relapse-free survival, entire cohort. Vertical red lines indicate censored patients.

question within the entire cohort, which included patients presenting with both first-time and relapsed episodes. Patients receiving RTX appeared to be protected from relapse at 1 year ($P = .01$; Figure 2A). In contrast, cumulative risk for relapse did not differ significantly between treated and untreated patients when a longer follow-up period of 5 years was considered ($P = .45$; Figure 2B). Median time to relapse was 3.71 (IQR, 1.75-4.9) and 1.33 (IQR, 0.43-2.35) years for treated and untreated patients, respectively. Taken together, our data suggest that patients receiving RTX experience a short-term reduction in relapse risk that is not sustained over time.

We sought to interrogate the possibility of confounding stemming from the inclusion of patients who had experienced at least 1 previous episode of iTTP and were therefore more likely to receive RTX during the index presentation. We performed a separate Kaplan-Meier analysis restricted to patients presenting with a first episode (N = 104), and again found that RTX was associated with benefit at 1 year ($P = .017$; supplemental Figure 2A), but not at 5 years, of follow-up ($P = .66$; supplemental Figure 2B). These data suggest that heterogeneity of our patient population with respect to the number of prior episodes of disease did not drive the observed benefit from RTX.

Predictors of relapse

We sought to better characterize the possible protective effect associated with RTX, and to identify other parameters predictive of relapse. Twenty-six parameters were considered, and those associated with time to relapse in Cox univariate analysis are shown in supplemental Table 3. Because almost all patients (91%) received steroids as part of therapy, steroid use was not included as a covariate. Three predictors of subsequent relapse were identified in the final multivariate Cox proportional hazards model (Table 3): presenting with relapsed TTP (HR, 2.97; 95% confidence interval [CI], 1.4-6.4), non-O blood group (HR, 2.15; 95% CI, 1.06-4.39), and age younger than 25 years at the time of presentation (HR, 2.94; 95% CI, 1.2-7.2). In addition to these parameters, our model also revealed that treatment with RTX was associated with a significantly reduced risk for subsequent relapse at the time of administration (HR, 0.16; 95% CI, 0.04-0.70). The proportional hazards assumption was not valid for RTX, so an extended Cox

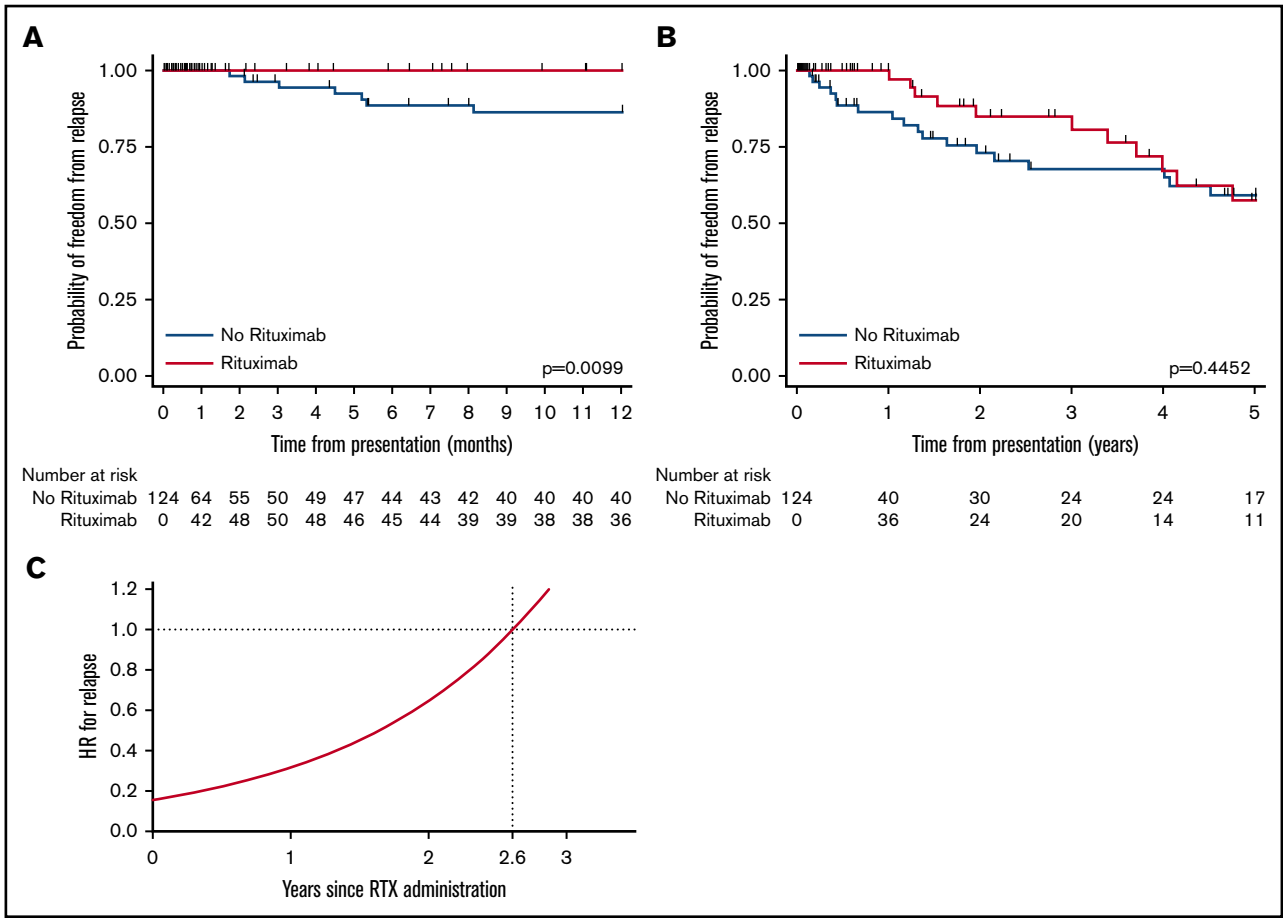

Figure 2. Relapse-free survival of patients according to treatment with RTX. (A) Unadjusted Kaplan-Meier analysis for relapse-free survival at 1 year, stratified by administration of RTX. Patients begin contributing time to the RTX group starting on the day of RTX administration. The curves were compared using the log-rank test. (B) Unadjusted Kaplan-Meier analysis for relapse-free survival at 5 years, stratified by administration of RTX. Patients begin contributing time to the RTX group starting on the day of RTX administration. The curves were compared using the log-rank test. (C) Graphical representation of increasing hazard ratio of relapse rate over time for patients receiving RTX, derived from the Cox proportional hazards model.

regression including an interaction between RTX administration and time was included in the final model (HR for time interaction, 1.002 per day after RTX; 95% CI, 1.0007-1.003). Thus, the protective effect of RTX gradually diminished with time, with the hazard of relapse increasing by 6.2% per month after RTX administration (Figure 2C).

Discussion

Increasingly, RTX is being used in the upfront, adjuvant, and maintenance settings for the management of iTTP, a trend that is reflected in our data set. Despite widespread recognition of the benefits of RTX in autoimmune disease, data for RTX in iTTP are lacking with regard to the magnitude of effect, duration of action, and appropriate target patient population. As a result, there remains no consensus standard of care for the treatment of iTTP patients with RTX, particularly in the upfront and maintenance settings.

An improved understanding of the determinants of relapse risk could assist clinicians in deciding whether to employ disease-modifying agents like RTX in the upfront setting. While previous work has suggested that the presence of an inhibitor to ADAMTS13 at presentation[11,12] and persistent ADAMTS13 deficiency in remission[13-16] are risk factors for relapse, these findings were not confirmed by other investigators.[9,12,17] Unfortunately, these earlier studies were limited by small sample size, the use of analytical approaches that did not account for duration of follow-up, consideration of a small number of covariates, and/or the inclusion of patients with TMA without severe ADAMTS13 deficiency, factors that may explain their differing conclusions.

In contrast, we have assembled a large data set composed exclusively of iTTP patients and used time-dependent Cox

Table 3. Cox multivariate model for predictors of subsequent relapse (N = 124)

Parameter	HR (95% CI)
Presenting in iTTP relapse	2.97 (1.4-6.4)
Non-O blood group	2.15 (1.06-4.39)
Age <25 y	2.94 (1.2-7.2)
RTX*	0.16 (0.04-0.70)

*Effect varies with time; reported HR is for day of administration. The effect of RTX was time-varying with an HR of 1.002 (95% CI, 1.0007-1.003) per day after administration.

proportional hazards modeling to evaluate 26 different covariates for their ability to independently predict relapse. Because we have access to complete patient-level data for all cases enrolled in our registry, we were able to include in our model a much more comprehensive set of covariates than previously attempted, including a broad range of clinical, laboratory, and demographic parameters, as well as the presence of concomitant autoimmune disease and the use of RTX and secondary immune suppressive agents. Using this approach, we have identified predictors of subsequent relapse that can be used in combination with remission ADAMTS13 activity levels to optimally guide the use of disease-modifying agents such as RTX.

The 3 covariates we identified are plausible, given the known pathophysiology of iTTP, and may provide the basis for further biological investigations. It has been previously theorized that individuals with group O blood are at lower risk for iTTP because their von Willebrand factor is more easily cleaved by ADAMTS13.[18-20] However, to date, no studies have been able to demonstrate a clear association between blood group and the development of iTTP. Our data suggest that although group O patients may not be protected from a first episode of iTTP, they are at lower risk for recurrence. Likewise, after adjusting for follow-up time, presentation with iTTP at a younger age was predictive of recurrent disease. This feature, as well as a history of previous episodes before the index presentation, may represent a more severe autoimmune phenotype that is predisposed to further relapse. Notably, markers of disease severity at presentation such as lactate dehydrogenase and platelet count did not predict relapse, suggesting that acuity is independent of relapse risk.

The precise time frame in which retreatment with RTX should be considered remains undefined. Using an extended Cox regression model, we have quantified for the first time the gradual loss of protection from RTX. We found that treated patients experienced an immediate reduction in relapse risk, but slowly returned to the baseline risk for untreated patients after approximately 2.6 years. Our results are consistent with the experience of using RTX in other hematologic diseases such as autoimmune hemolytic anemias,[21] in which the protective effect of RTX gradually fades and retreatment on relapse is an accepted practice.

A number of other groups have investigated the efficacy of RTX in smaller cohorts,[8,15,22-25] with conflicting results. Scully and colleagues[15] enrolled 40 patients from a mixed population with first-episode and relapsed iTTP who were given RTX within 3 days of diagnosis, and compared outcomes against 40 matched historical controls. They reported a significant increase in the median time to relapse for patients given RTX and identified low remission ADAMTS13 activity as a predictor of recurrence. Limitations of this study include its less sophisticated statistical approach, small cohort size, and the use of historical controls. More recently, Page and colleagues[22] and Falter and colleagues[25] compared outcomes among consecutive patients with a first episode of acute iTTP. An important strength of these studies, each of which examined approximately 40 patients, is the use of a homogenous patient population, thereby avoiding potential bias associated with the inclusion of relapsed patients who may be at intrinsically higher risk for further relapses. In the Page study, RTX administration was associated with a significantly reduced risk for relapse that endured over nearly a decade of follow-up, whereas the Falter study showed an enduring but statistically nonsignificant trend toward protection with RTX. In contrast, Froissart and colleagues[24] prospectively enrolled 22 patients who were refractory to treatment with TPE and compared outcomes against 53 historical controls. RTX was associated with a significantly higher proportion of patients achieving platelet count recovery within 35 days, but not with a durable protection from relapse. Here, we sought to provide a more definitive and quantitative look at the effect of RTX on relapse by using a large cohort of patients with contemporaneous controls and an analytical approach appropriate for assessing relapse risk, a time-dependent parameter.

An important limitation of our study is its retrospective design. In particular, it remains possible that RTX-treated and untreated patients have different disease biology that could influence the perceived effect of RTX therapy. Second, our model did not include remission ADAMTS13 activity levels as a covariate because this parameter was rarely obtained by clinicians within our consortium. Of note, Jestin and colleagues[26] recently reported an innovative study on the use of remission ADAMTS13 activity levels to guide preemptive RTX use in another large cohort. Although our work seeks to answer a separate question, their results showed that RTX use in patients with severe ADAMTS13 deficiency during remission protects from relapse and are consistent with the findings we report here. Third, since our data set included an assortment of RTX dosing schemes, we are not able to evaluate the efficacy of any particular regimen. Fourth, the true incidence of relapse may differ from that reported here because of subjects who were lost to follow-up.

In summary, RTX administration is associated with reduction in risk for relapse in iTTP, but this effect fades over time. Patients may benefit from retreatment or maintenance therapy with RTX. Furthermore, we report 3 clinical parameters predictive of relapse that, if validated in other cohorts, may help identify patients who should be followed more closely or in whom more aggressive disease-modifying therapy could be employed.

Acknowledgments

This work was generously supported by the Luick Family Fund of the Massachusetts General Hospital. P.K.B. was supported by a career development grant from the National Institutes of Health, National Heart, Lung, and Blood Institute (1K08 HL136840-01), and A.L. was supported by a National Heart, Lung, and Blood Institute training grant (T32 HL007093).

Authorship

Contribution: L.S., J.M., L.U., R.M.K., C.P.S., W.S.D., R.S.M., and P.K.B. conceived of and designed the study; L.S., A.L., J.R., and V.U. conducted chart review and collected data; L.S., J.M., R.S.M., and P.K.B. analyzed the data; and L.S., J.M., R.S.M., and P.K.B. wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: J.M., 0000-0002-8304-1953; A.L., 0000-0002-8455-2309.

Correspondence: Pavan K. Bendapudi, Division of Hematology, Massachusetts General Hospital, Yawkey 7B, 55 Fruit St, Boston, MA 02114; e-mail: pbendapudi@partners.org; and Robert S. Makar, Blood Transfusion Service, Massachusetts General Hospital, GRJ-148, 55 Fruit St, Boston, MA 02114; e-mail: rmakar@partners.org.

References

1. Moake JL, Chow TW. Thrombotic thrombocytopenic purpura: understanding a disease no longer rare. *Am J Med Sci*. 1998;316(2):105-119.
2. Tsai HM. Deficiency of ADAMTS13 and thrombotic thrombocytopenic purpura. *Blood*. 2002;100(10):3839-3842.
3. Tsai HM. Current concepts in thrombotic thrombocytopenic purpura. *Annu Rev Med*. 2006;57(1):419-436.
4. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. *Blood*. 2008;112(1):11-18.
5. Rock GA, Shumak KH, Buskard NA, et al; Canadian Apheresis Study Group. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *N Engl J Med*. 1991;325(6):393-397.
6. Bendapudi PK, Li A, Hamdan A, et al. Impact of severe ADAMTS13 deficiency on clinical presentation and outcomes in patients with thrombotic microangiopathies: the experience of the Harvard TMA Research Collaborative. *Br J Haematol*. 2015;171(5):836-844.
7. Coppo P, Froissart A; French Reference Center for Thrombotic Microangiopathies. Treatment of thrombotic thrombocytopenic purpura beyond therapeutic plasma exchange. *Hematology (Am Soc Hematol Educ Program)*. 2015;2015(1):637-643.
8. Bhagirath VC, Kelton JG, Moore J, Arnold DM. Rituximab maintenance for relapsed refractory thrombotic thrombocytopenic purpura. *Transfusion*. 2012; 52(12):2517-2523.
9. Kremer Hovinga JA, Vesely SK, Terrell DR, Lämmle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood*. 2010;115(8):1500-1511, quiz 1662.
10. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;3(1):17.
11. Zheng XL, Kaufman RM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. *Blood*. 2004;103(11):4043-4049.
12. Vesely SK, George JN, Lämmle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood*. 2003;102(1):60-68.
13. Jin M, Casper TC, Cataland SR, et al. Relationship between ADAMTS13 activity in clinical remission and the risk of TTP relapse. *Br J Haematol*. 2008; 141(5):651-658.
14. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Clinical importance of ADAMTS13 activity during remission in patients with acquired thrombotic thrombocytopenic purpura. *Blood*. 2016;128(17):2175-2178.
15. Scully M, McDonald V, Cavenagh J, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood*. 2011;118(7):1746-1753.
16. Peyvandi F, Lavoretano S, Palla R, et al. ADAMTS13 and anti-ADAMTS13 antibodies as markers for recurrence of acquired thrombotic thrombocytopenic purpura during remission. *Haematologica*. 2008;93(2):232-239.
17. Goyal J, Adamski J, Lima JL, Marques MB. Relapses of thrombotic thrombocytopenic purpura after treatment with rituximab. *J Clin Apher*. 2013;28(6): 390-394.
18. Zuberi L, Yerasuri D, Kuriakose P. Effect of blood group on idiopathic thrombotic thrombocytopenic purpura. *J Clin Apher*. 2009;24(4):131-133.
19. Terrell DR, Motto DG, Kremer Hovinga JA, Lämmle B, George JN, Vesely SK. Blood group O and black race are independent risk factors for thrombotic thrombocytopenic purpura associated with severe ADAMTS13 deficiency. *Transfusion*. 2011;51(10):2237-2243.
20. Staropoli JF, Stowell CP, Tuncer HH, Marques MB. An inquiry into the relationship between ABO blood group and thrombotic thrombocytopenic purpura. *Vox Sang*. 2009;96(4):344-348.
21. Maung SW, Leahy M, O'Leary HM, et al. A multi-centre retrospective study of rituximab use in the treatment of relapsed or resistant warm autoimmune haemolytic anaemia. *Br J Haematol*. 2013;163(1):118-122.
22. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Rituximab reduces risk for relapse in patients with thrombotic thrombocytopenic purpura. *Blood*. 2016;127(24):3092-3094.
23. Lim W, Vesely SK, George JN. The role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura. *Blood*. 2015; 125(10):1526-1531.
24. Froissart A, Buffet M, Veyradier A, et al; Experience of the French Thrombotic Microangiopathies Reference Center. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. *Crit Care Med*. 2012;40(1): 104-111.
25. Falter T, Herold S, Weyer-Elberich V, et al. Relapse rate in survivors of acute autoimmune thrombotic thrombocytopenic purpura treated with or without rituximab. *Thromb Haemost*. 2018;118(10):1743-1751.
26. Jestin M, Benhamou Y, Schelpe AS, et al; French Thrombotic Microangiopathies Reference Center. Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. *Blood*. 2018;132(20):2143-2153.