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Rituximab Therapy for Thrombotic Thrombocytopenic Purpura: A Proposed Study of the Transfusion Medicine/Hemostasis Clinical Trials Network With a Systematic Review of Rituximab Therapy for Immune-Mediated Disorders

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The rationale for immunosuppressive therapy of thrombotic thrombocytopenic purpura (TTP) was established by observations that TTP may be caused by autoantibodies to ADAMTS13. Patients with high-titer autoantibodies to ADAMTS13 may have a higher mortality, and survivors may require prolonged plasma exchange therapy in spite of adjunctive glucocorticoid treatment. More intensive immunosuppressive therapy with rituximab may provide benefit for many of these patients. The Transfusion Medicine/Hemostasis Clinical Trials Network is developing a randomized, clinical trial to test the hypothesis that addition of rituximab to standard treatment of TTP with plasma exchange and glucocorticoids will decrease initial treatment failure rates as well as subsequent relapses over the following 3 years. To provide the background data for this clinical trial, a systematic review of all published reports on rituximab treatment of immune-mediated disorders was performed. Twelve articles have reported 27 patients treated with rituximab for TTP, with benefit described in 25 (93%) of the patients. Additional reports have described rituximab treatment of 37 other immune-mediated disorders, with clinical response in most patients. These observations from small uncontrolled case series provide the background and rationale for a randomized clinical trial to establish the role of rituximab in the management of patients with TTP. J. Clin. Apheresis. 21: 49–56, 2006

Key words: rituximab; thrombotic thrombocytopenic purpura (TTP); systematic review

INTRODUCTION

The discovery that thrombotic thrombocytopenic purpura (TTP) may have an autoimmune etiology, caused by autoantibodies to a von Willebrand factor-cleaving protease (ADAMTS13), has provided an explanation for the efficacy of plasma exchange and a rationale for adjunctive immunosuppressive therapy [1]. Currently, only plasma exchange has been documented by a randomized clinical trial to improve survival of patients with TTP [2]. Observations on the efficacy of glucocorticoids have disclosed similar survival in the case series of patients who were treated with high-dose glucocorticoids [3] and without glucocorticoids [2]. However, this inconsistency could be related to heterogeneity among patients with TTP. Thus, current case series attempt to distinguish patients with idiopathic TTP, who are more likely to have an autoimmune etiology, and patients with associated conditions and potential etiologies such as stem cell transplantation, drug association, or enterohemorrhagic infection [4–6]. Among patients with idiopathic TTP, the prevalence of ADAMTS13 deficiency is 30–80%, suggesting etiologic diversity even within this subgroup [7]. Among patients with idiopathic TTP, those with high-titer autoantibodies to ADAMTS13 appear to have a more complicated clinical course and a higher risk for death [5]. It is these patients who may require not only glucocor-

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TABLE I. Participating Centers in the Transfusion Medicine/ Hemostasis Clinical Trials

Blood Center of Southeastern Wisconsin/University of Wisconsin at Madison
Case Western Reserve University
Children's Hospital Boston, Harvard University
Weill Medical College of Cornell University
Duke University
Emory University
Johns Hopkins University
Massachusetts General Hospital, Harvard University
Puget Sound Blood Center, University of Washington
Tulane University
University of lowa
University of Maryland
University of Minnesota
University of North Carolina
University of Oklahoma/University of Texas Southwestern Medical Center
University of Pennsylvania
University of Pittsburgh

ticoids but also more intensive immunosuppressive therapy in addition to plasma exchange. Initial reports have described success with rituximab in small case series.

To determine the efficacy of rituximab in addition to standard treatment of TTP with plasma exchange and glucocorticoids, the Transfusion Medicine/Hemostasis (TMH) Clinical Trials Network, comprising 17 institutions across the United States (Table I), is developing a randomized, clinical trial. This report describes the background, rationale, and preliminary outline for this study.

To provide the background for the use of rituximab in the management of TTP, a systematic review [8] was performed to assess all publications reporting rituximab use in immune-mediated disorders. Although rituximab has been approved by regulatory agencies in the United States and Europe only for use in refractory or relapsed low-grade B-cell non-Hodgkin lymphoma in 1997 and 1998, respectively, it has been widely used in other conditions, including extensive use in immune-mediated disorders.

METHODS

Systematic Review of Publications Describing Rituximab Treatment for Immune-Mediated Disorders.

The Medline database was searched from 1966 through March 31, 2005, with Ovid® software, for keywords "rituximab," "Rituxan," and "Mabthera." Thirteen hundred twenty-five articles were retrieved; articles were selected for preliminary review based on their title. Articles describing rituximab treatment of immune-mediated disorders other than TTP were selected if they reported results for $\geq$5 patients. Articles reporting use of rituximab for TTP or HUS or were selected if they reported results for one or more patients. Selected articles were reviewed to document the disorder, the number of patients treated, patient characteristics, regimen of rituximab, clinical outcomes, and duration of follow-up. Articles that described 4 or fewer patients with disorders other than TTP were recorded only to provide a complete list of the disorders for which rituximab treatment has been used. Articles describing the use of rituximab in the prevention or treatment of immune-mediated complications of organ or stem cell transplantation and articles on rituximab use in the treatment of drug-induced immune-mediated disorders were included. Articles describing the use of rituximab in the treatment of lymphomas, including prevention and treatment of the post-transplant lymphoproliferative disorder or autoimmune disorders associated with lymphomas, were excluded. Review articles without primary patient data were also excluded.

The TMH Clinical Trials Network

The TMH Clinical Trials Network was established in 2002, in response to a concern by the National Heart, Lung, and Blood Institute that resolution of important clinical problems related to transfusion medicine and hemostasis required a multi-institutional network. Following a national competition, 17 institutions were selected to form the TMH Clinical Trials Network (Table I). At the initial meeting of the Steering Committee for this network, the submitted protocols were organized into 7 groups based on specific groups of disorders. This report describes the effort of the group that focused on TTP. Development of a clinical trial for TTP required consideration of the rapidly evolving community standard of care for this disorder. The decision to test the efficacy of rituximab evolved during the past 3 years and was related to a growing number of reports documenting an autoimmune etiology for some patients with TTP and suggesting benefit from rituximab treatment.

RESULTS

Systematic Review of Publications Describing Rituximab Treatment for Non-Malignant Autoimmune Disorders

Table II lists the 38 immune-mediated disorders for which rituximab treatment has been reported. These comprise disorders believed to involve both humoral and cell-mediated immune mechanisms. Table III shows data from the case series having 5 or more patients in which rituximab was used for treatment of 17 different immune-mediated disorders. Only one of these studies was a randomized clinical trial [9]; all other reports were case series without controls. The one randomized clinical trial targeted patients with

TABLE II. Immune-Mediated Disorders for Which Rituximab Treatment Has Been Reported

Hematologic disorders
Thrombotic thrombocytopenic purpura (TTP)
Immune thrombocytopenic purpura (ITP)
Drug-induced thrombocytopenia
Autoimmune hemolytic anemia (warm antibody)
Idiopathic cold agglutinin hemolytic anemia
Drug-induced hemolytic anemia
Alloimmune hemolytic anemia (transfusion-related)
Evan's syndrome
Pure red cell aplasia
Autoimmune neutropenia
Acquired autoimmune factor VIII inhibitor
Alloimmune factor VIII inhibitor
Alloimmune factor IX inhibitor
Acquired autoimmune factor V inhibitor
Rheumatologic disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Antiphospholipid antibody syndrome
Wegener's granulomatosis
Dermatomyositis
Goodpasture's syndrome
Felty syndrome
Neurologic disorders
Myasthenia gravis
IgM-associated polyneuropathy
Kidney disorder
Idiopathic membranous nephropathy
Dermatologic disorders
Pemphigus vulgaris
Pemphigus foliaceus
Bullous pemphigoid
Solid organ transplantation
Prevention of humoral rejection
HLA-mismatched transplantation (kidney)
ABO-mismatched transplantation (kidney, liver)
Treatment of complications
Humoral rejection (liver, heart)
Alloimmune hemolytic anemia due to passenger donor lymphocytes
Hematopoietic stem cell transplantation (allogeneic)
Treatment of complications
Chronic graft-versus-host disease
Pure red cell aplasia due to ABO mismatch
Autoimmune hemolytic anemia
Other disorders
Type II mixed cryoglobulinemia (idiopathic)
Type II mixed cryoglobulinemia (hepatitis C)
Multicentric Castleman's disease
Type B insulin resistance (anti-insulin receptor antibody)

rheumatoid arthritis and documented improvement of signs and symptoms in the rituximab-treated patients over a 24-week follow-up. Benefit was also suggested in the other case series. In most reports, the regimen used was that initially described for use in low-grade, non–Hodgkin lymphoma, 375 mg/m^2/week for 4 weeks.

Table IV summarizes the published experience with rituximab in patients with TTP. Twelve reports describe the treatment of 27 patients, with individual reports describing 1–5 patients. All of these were case series without controls. All describe apparent benefit in most patients. However, benefit is difficult to document since multiple agents in addition to plasma exchange were used in most patients. In one report [10], two patients who had had multiple recurrences of TTP were treated with rituximab without plasma exchange and achieved remission. The longest follow-up in any of these reports was 23 months [11].

TMH Protocol (Table V)

TTP Registry. It was considered critical to enroll all consecutive patients with a clinical diagnosis of TTP in a registry, in order to characterize the spectrum of patients from which the eligible patients are subsequently enrolled into the randomized clinical trial. Since this registry is to involve only routine clinical observations and samples for ADAMTS13 and inhibitor measurements, it is anticipated that all patients will consent. Inclusion criteria will be more stringent for the randomized clinical trial itself, excluding patients who are critically ill and unable to provide consent, and who are believed to have other disorders with clinical features resembling TTP, such as malignant hypertension [12]. Also patients who are at risk for adverse reactions to rituximab, such as patients who have antibodies to HBsAg [13], will be excluded. Pregnant patients will also be excluded because of the unknown risk of rituximab during pregnancy.

Rituximab as adjunctive treatment for TTP, a randomized double-blind, placebo-controlled clinical trial. When the decision was made to focus the clinical trial for TTP on the efficacy of rituximab, several other key decisions had to be made.

First, patient selection was considered. It was determined that the focus should be on patients thought to have idiopathic TTP. Therefore, it was decided to exclude patients in whom TTP occurred after hematopoietic stem cell transplantation, women who are pregnant, patients in whom a drug-induced etiology seems likely, and patients with other coexisting disorders that may cause signs and symptoms similar to TTP, such as systemic lupus erythematosus or other collagen vascular diseases, HIV infection, or malignant hypertension [6]. The objective was that many of the remaining patients would have severe ADAMTS13 deficiency caused by an autoantibody. However, it was decided that ADAMTS13 activity measurements would not be a criterion for patient randomization, a decision deemed appropriate given the time required for ADAMTS13 measurement and also potential assay variability. Rather, it was considered that an important outcome of the trial would

TABLE III. Articles That Describe Rituximab Treatment of Immune-Mediated Disorders and Include Data on ≥ 5 Patients*

Author	Year	Reference	Country	Disease	Regiments	Patients	Responded	Follow-up (months)	Median age (range)
Levine and Pestronk	1999	[17]	USA	IgM-associated polyneuropathy	375 mg/m^2/wk ×4	5	5	3–6	51 (44–68)
Pestronk et al.	2003	[18]	USA	IgM-associated polyneuropathy	375 mg/m^2/wk ×4	21	18	12–24	NA
Renaud et al.	2003	[19]	Switzerland/ Germany	IgM-associated polyneuropathy	375 mg/m^2/wk ×4	9	6	12	69 (48–77)
Saleh et al.	2000	[20]	USA	ITP	50–375 mg/m^2/wk ×4	12	3	3	54 (21–77)
Giagounidis et al.	2002	[21]	Germany	ITP	375 mg/m^2/wk ×4	12	9	6–15	44 (28–71)
Narang et al.	2003	[22]	USA	ITP	375 mg/m^2/wk ×4–8	6	5	12–40	53 (30–70)
Zaja et al.	2003	[23]	Italy	ITP	375 mg/m^2/wk ×4	20	13	2–16	57 (16–76)
Shanafelt et al.	2003	[24]	USA	ITP	375 mg/m^2/wk ×1–4	12	6	1–11	53 (22–79)
Cooper et al.[b]	2004	[25]	USA/Italy	ITP	375 mg/m^2/wk ×4	57	31	4–42	66 (21–79)
Quatier et al.	2001	[26]	France/Belgium	AIHA	375 mg/m^2/wk ×4–12	6	6	15–22	1 (1–3)
Zecca et al.	2003	[27]	Italy	AIHA	375 mg/m^2/wk ×2–4	15	13	7–28	2 (0.3–14)
Shanafelt et al.	2003	[24]	USA	AIHA	375 mg/m^2/wk ×3–8	5	2	4–13	39 (21–79)
Stasi et al.	2004	[28]	Italy	Factor VIII inhibitor	375 mg/m^2/wk ×4	10	10	12–41	62 (27–78)
Leandro et al.	2002	[29]	UK	RA	200–500 mg/m^2/ wk-2wk ×1–4	22	17	6–36	58 (33–81)
De Vita et al.	2002	[30]	Italy	RA	375 mg/m^2/wk ×4	5	4	5–12	65 (51–73)
Kneitz et al.	2004	[31]	Germany	RA	375 mg/m^2/wk ×4	5	4	10	62 (40–67)
Moore et al.	2004	[32]	Australia	RA	1000 mg/2wk ×2	10	9	12	47 (25–61)
Edwards et al.[c]	2004	[9]	11 countries	RA	1000 mg/2wk ×2	121	47	11.2	54 (mean)
Leandro et al.	2002	[33]	UK	SLE	300–350 mg/m^2-2wk ×2	6	5	6–18	36 (17–40)
Looney et al.	2004	[34]	USA	SLE	100 mg/m^2 ×1 375 mg/m^2 ×1 375 mg/m^2/wk ×4	16	10	12	39 (22–47)
Levine	2005	[35]	USA	Dermatomyositis	100 and 375 mg/m^2/wk ×4	6	6	6–12	48 (21-64)
Keogh et al.	2005	[36]	USA	ANCA-associated vasculitis (10 Wegener's granulomatosis, 1 microscopic polyangiitis	375 mg/m^2/wk ×4	11	11	14	31 (14–71)
Sfikakis et al.	2005	[37]	Greece	Proliferative lupus nephritis	375 mg/m^2/wk ×4	10	8	12	28 (19–38)
Ruggenenti et al.[d]	2003	[38]	Italy	Idiopathic membranous nephropathy	375 mg/m^2/wk ×4	8	8	12	57 (24–75)
Gloor et al.	2003	[39]	USA	HLA-mismatch kidney transplantation (preconditioning)	375 mg/m^2 ×1	14	12	1–20	40 (mean, 21–61)
Sonnenday et al.	2004	[40]	USA	ABO-incompatible kidney transplantation (preconditioning)	375 mg/m^2 ×1	6	6	4–14	58 (32–73)
Becker et al.	2004	[41]	USA	Kidney transplant humoral rejection (treatment)	375–500 mg/m^2 ×1	27	24	20	47 (18–72)
Ratanatharathorn et al.	2003	[42]	USA	Chronic GVHD	375 mg/m^2/wk ×4	8	4	9–28	NA

Marcelin et al.	2003	[43]	France	Castleman disease	375 mg/m^2/wk ×4	5	3	4–14	40 (mean)
Zaja et al.	2003	[44]	Italy	Type II mixed cryoglobulinemia	375 mg/m^2/wk ×4	15	[a]	9–31	64 (mean, 43–69)
Sansonno et al.	2003	[45]	Italy	Type II mixed cryoglobulinemia	375 mg/m^2/wk ×4	20	16	12	NA
Roccatello et al.	2004	[46]	Italy	Cryoglobulinemic glomerulonephritis	375 mg/m^2/wk ×4 → 375 mg/m^2/mo ×2	6	6	12–18	70 (37–76)

*Other concomitant treatments are not recorded. The author's interpretation of response attributable to rituximab is accepted. NA, data not available.
[a]Rituximab was effective in controlling skin vasculitis (purpura [11/12 pts], skin ulcers [5/6 pts]), subjective symptoms of peripheral neuropathy (7/7 pts) but not electrodiagnostic findings, arthralgia (4/4 pts), and fever (2/2 pts).
[b]Includes the 32 patients from 2 previous case series by Stasi et al. [47,48].
[c]Randomized controlled trial.
[d]A previous report decribed the same 8 patients [49].

TABLE IV. Case Reports That Describe Rituximab Treatment of TTP-HUS

Author	Year	Reference	Country	Regimen	Patients	Responded	Relapsed	Response duration (months median range)	Age (years, median [range])	Response duration (months, median [range])
Chemnitz et al.	2002	[50]	Germany	375 mg/m^2/wk ×4 and ×2	2	2	0	2,12	39,37	2,12
Gutterman et al.	2002	[11]	USA	375/mg/m^2/wk ×8 and ×4	3	3	1	23,17[a],2	54 (40–62)	23,17[a],2
Zheng et al.	2003	[51]	USA	375/mg/m^2/1–2 wk ×4	1	1	0	10	42	10
Tsai and Shulman	2003	[52]	USA	375/mg/m^2/wk ×4	1	1	0	16	36	16
Ahmad et al.	2004	[10]	USA	375/mg/m^2/wk ×2–4	4	3	1	13,13[a],14	56.5 (53–61)	13,13[a],14
Yomtovian et al.	2004	[53]	USA	375/mg/m^2/wk ×8	1	1	0	15	30	15
Stein et al.	2004	[54]	Israel	500/mg/m^2/wk ×4	1	1	0	6	37	6
Sallah et al.	2004	[55]	USA	375/mg/m^2/wk ×4	5	4	0	11 (9–13)	32 (25–52)	11 (9–13)
Fakhouri et al.	2004	[56]	France	375/mg/m^2/wk ×4	1	1	0	7	38	7
Reddy et al.	2005	[57]	USA	375/mg/m^2/wk ×4	5	5	0	15 (10–21)	37 (27–70)	15(10–21)
Koulova et al.	2005	[58]	USA	375/mg/m^2/wk ×5 and 4	2	2	0	11,5	45,40	11,5
Galbusera et al.[b]	2005	[59]	Italy	375/mg/m^2/wk ×4	1	1	1	16[a]	60	16[a]

[a]Denotes the time interval in months when relapse occurred.
[b]The case report by Galbusera et al. describes prophylactic treatment with rituximab to prevent relapse; relapse at 16 months denotes reappearance of ADAMTS13 inhibitors and recurrent loss of protease activity.

TABLE V. TMH Registry and Randomized Clinical Trial for Thrombotic Thrombocytopenic Purpura

Registry	
Objective:	To evaluate the clinical features of TTP related to measurements of ADAMTS13 and its inhibitor.
Randomized clinical trial	
Objective:	To determine if rituximab, in addition standard treatment, decreases early treatment failure rates and the frequency of subsequent relapse.
Protocol:	Plasma-exchange and glucocorticoids, plus either Rituximab (375 mg/m^2/ week for 4 weeks) or placebo.

be to determine if the efficacy of rituximab was related to the presence of severe ADAMTS13 deficiency caused by autoantibodies.

Next, the issue of defining "standard care" was addressed. In light of the variability in management of TTP across the United States [14], it was important to define an algorithm for care that could be generally adopted. Thus, it was determined that plasma exchange with either fresh frozen plasma or cryoprecipitate-poor plasma would be appropriate, since both appear equally efficacious [15,16]. To allow for some variation in individual institutional practice, and to allow for plasma exchange adjustments related to severity of the clinical course, the range of 1.0–1.5 plasma volumes per exchange was accepted. It was acknowledged that the volume of exchanged plasma may be a critical determinant of patient response, but variation of the plasma volume exchanged within this range seemed the most practical compromise to adjust to community standards of practice. It was also determined that glucocorticoid treatment, equivalent to prednisone, 1 mg/kg/day, was acceptable and would be given to all patients. Finally, it was decided not to taper plasma exchange treatments after achievement of remission, defined as a platelet count $\geq$150,000/μL for 2 consecutive days and an LDH level $<$1.5-times the upper limit of normal. This decision was based on the lack of data supporting the efficacy of tapering plasma exchange treatments [14] and the anticipation that rituximab may decrease the risk for exacerbation.

A major issue was to determine when the course of rituximab treatment should begin. Should the clinical trial be reserved for patients who had no initial response to standard therapy, or should rituximab begin early in the clinical course? It was decided that early intervention with rituximab was most appropriate, which would provide an opportunity to observe the greatest potential benefit for the most patients. It was also decided that patients would be eligible for this clinical trial either at the time of their initial presentation or at the time of presentation with a recurrent episode. Patients presenting with a recurrent episode of TTP would be analyzed separately; these patients may have the greatest potential benefit from rituximab.

The primary endpoint will be a measure of early treatment failure, described by a composite of specific measures, such as failure to achieve a continuous complete remission within an early defined time, need for intervention with other treatment modalities, and mortality. Secondary endpoints will include the occurrence of relapses over 3 years of follow-up as well as analysis of ADAMTS13 activity and inhibitors.

A survey of participating sites suggested that 35–40% of patients who are treated for TTP and who would meet our eligibility criteria would fail to achieve a remission at 21 days with standard care according to the definitions of our protocol. We estimated that adjunctive treatment with rituximab may decrease this failure rate by 50%. This effect, a 50% reduction in the failure rate, could be detected with 80% power if 110 patients were enrolled in each arm of the study. This is a feasible number of patients for the TMH Clinical Trials Network since it was estimated that the sites can enroll 75 patients per year.

DISCUSSION

Although rituximab was initially developed for treatment of B-cell malignancies, its use in immune-mediated disorders has expanded rapidly over the past 6 years. Rituximab appears to have efficacy that is at least equivalent to other immunosuppressive agents, and its targeted effect on B-cells appears to diminish the risk of opportunistic infections. Our systematic review documents the extraordinary variety of conditions for which rituximab has been used (Table II) and its apparent efficacy in immune-mediated disorders (Table III), including TTP (Table IV). Among all of these reports, only one randomized clinical trial has been performed, in patients with rheumatoid arthritis [9]. From this background information, and from the emerging concept that TTP may be an autoimmune disorder, a randomized clinical trial of rituximab for management of TTP is important and timely.

The formation of the TMH Clinical Trials Network provides an ideal setting to design and execute a clinical trial of rituximab as adjunctive treatment for TTP. The network provides 17 institutions to study uncommon disorders, which could not be studied in an individual institution. Although the primary research question of our protocol is whether early addition of rituximab to standard care (plasma exchange and glucocorticoid) will decrease early treat-

ment failure rates, there will be many additional benefits from this clinical trial. Protocol development has required standardization of patient characteristics to define inclusion criteria, and these criteria will provide a consistent case definition of TTP. Protocol development has also required precise definition of outcome measures. If these outcome measures become an established standard, they will allow better comparison of future clinical data among different case series. In addition to the randomized controlled trial, all patients will be asked to participate in a registry, even if they are not subsequently randomized or if they choose not to participate in the randomized trial. This registry will provide important new information on the clinical course of TTP across the 17 participating institutions. Furthermore, patients will be followed for a period of 3 years, thus providing important new information on long-term clinical outcomes.

This experience highlights the valuable role of the TMH Clinical Trials Network to study important questions and to provide evidence for improved management of patients with uncommon hematologic disorders.

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