Rituximab for chronic recurring thrombotic thrombocytopenic purpura: a case report and review of the literature

Roslyn Yomtovian[1], **Waldemar Niklinski**[1], **Bernard Silver**[2], **Ravindra Sarode**[3], and **Han-Mou Tsai**[4]

[1]Department of Pathology, The University Hospitals of Cleveland, Case Western Reserve University School of Medicine, Cleveland, OH

[2]Department of Medicine, The University Hospitals of Cleveland, Case Western Reserve University School of Medicine, Cleveland, OH

[3]Department of Pathology, The University of Texas Southwestern Medical Center, Dallas, TX

[4]Division of Hematology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY, USA

Summary

Deficiency of von Willebrand factor (VWF) cleaving protease ADAMTS13 has been demonstrated to be the proximate cause of a subset of thrombotic microangiopathic haemolytic anaemias (MAHA) typical for thrombotic thrombocytopenic purpura (TTP). *ADAMTS13* gene mutations cause the hereditary form; acquired deficiency has been attributed to presence of an autoantibody, which may represent a specific subset of MAHA best termed 'autoimmune thrombotic thrombocytopenic purpura'. We describe a patient with relapsing TTP because of ADAMTS13 inhibitors, who failed to achieve sustained remission despite therapies with plasma exchange, steroids, vincristine, staphylococcal protein A and splenectomy. The ADAMTS13 inhibitor titre remained elevated and clinical stability was only maintained by plasma exchange every 2–3 d over a period of 268 d. The patient then received rituximab therapy (eight doses of 375 mg/m^2 weekly), during which she required five plasma exchanges in the first 10 d, two exchanges in the next 3 weeks, and none thereafter for 450 d and ongoing. The ADAMTS13 inhibitor titre decreased and enzyme activity increased. We compared this case with that of seven previously reported TTP cases also treated with rituximab; experience suggests that rituximab therapy deserves further investigation for patients with either refractory or relapsing TTP caused by ADAMTS13 inhibitors.

Keywords

thrombotic thrombocytopenic purpura; rituximab; plasma exchange

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Thrombotic thrombocytopenic purpura (TTP), a relatively uncommon but serious disease characterized by the development of von Willebrand factor (VWF)-platelet rich hyaline thrombi in the arterioles and capillaries, affects the brain, heart, pancreas, kidney and other organs (Bukowski, 1982). Complications from neurological or cardiac abnormalities are the most common cause of death.

Correspondence: Ravindra Sarode MD, Department of Pathology, University of Texas Southwestern Medical Center 5323 Harry Hines Blvd., CS3.114 Dallas, TX 75390-9073, USA. ravi.sarode@utsouthwestern.edu.

The use of plasma exchange has decreased the mortality rate of TTP from >90% to <10–30% (Rock *et al*, 1991). However, relapse of the disease occurs in more than one-third of the cases that achieve remission (Shumak *et al*, 1995; Bell, 1997). A subset of patients develop multiple relapses or persistent disease, which requires numerous sessions of plasma exchange; this is costly, technically demanding, often associated with serious complications such as infection, thrombosis and/or transfusion reactions, and is debilitating to the patients. Some of the cases that fail to achieve a sustained remission with plasmapheresis improve after the use of corticosteroids, vincristine, cyclophosphamide, azathioprine, high dose intravenous immunoglobulin, cyclosporin A, staphylococcal protein A immunoadsorption and/or splenectomy (Gaddis *et al*, 1997; Kwaan & Soff, 1997; Allford *et al*, 2003; Aqui *et al*, 2003). However, other patients are unresponsive to these therapies and require long-term plasma exchange to prevent a fatal outcome.

Recent studies demonstrate that a subset of thrombotic microangiopathic haemolytic anaemias (MAHA) is associated with severe deficiency of VWF-cleaving protease ADAMTS13. Mutations in the *ADAMTS13* gene have been detected in cases presenting as Schulman–Upshaw syndrome (Levy *et al*, 2001; Kokame *et al*, 2002; Schneppenheim *et al*, 2003). However, deficiency of the ADAMTS13 enzyme in adolescents and adults is most often due to an immunoglobulin (Ig)G autoantibody against the ADAMTS13 enzyme (Furlan *et al*, 1998; Tsai & Lian, 1998). The autoimmune cause of the deficiency suggests that these cases may respond to immunosuppressive therapies.

Rituximab, a chimaeric monoclonal antibody against CD20 that depletes B cells in the circulation and lymphoid tissues, has shown efficacy in the treatment of CD20-positive lymphoproliferative disorders (Boye *et al*, 2003). The agent has also been used with success in patients with immune thrombocytopenic purpura and other types of autoimmune diseases (Levine & Pestronk, 1999; Berentsen *et al*, 2001; Specks *et al*, 2001; Stasi *et al*, 2001; Dimopoulos *et al*, 2002; Mori *et al*, 2002; Motto *et al*, 2002; Perrotta *et al*, 2002; Remuzzi *et al*, 2002; Salopek *et al*, 2002; Zaja *et al*, 2002, 2003a,b; Renaud *et al*, 2003; Trape *et al*, 2003; Zecca *et al*, 2003). In preliminary studies, patients with refractory TTP have achieved sustained remission after rituximab therapy (Chemnitz *et al*, 2002; Gutterman *et al*, 2002; Tsai & Shulman, 2003; Zheng *et al*, 2003).

We describe the experience of using rituximab in a case of refractory TTP and compare the experience with previously reported cases.

Case report

The patient, an African American female, developed her first episode of TTP at the age of 26 years, when she presented with confusion and lethargy. Her platelet count was 8×10^9/l; haemoglobin, 6·0 g/dl; creatinine, 106 μmol/l and lactate dehydrogenase (LDH), 1275 IU/l (normal <250 IU/l). Blood smears contained schistocytes. A diagnosis of TTP was made and plasma exchange was started. Remission was achieved after 59 sessions of plasma exchange and four doses of vincristine over a period of 99 d (Fig 1). In the following 4 years, she experienced five relapses of TTP, each requiring eight to 91 plasma exchanges over 19 to 270 d respectively (Fig 1). During that period, she also received four treatments of immunoadsorption therapy with staphylococcal protein A columns (Prosorba®; Fresenius AG, Bad Homberg, Germany), a splenectomy and seven doses of vincristine. After her last relapse on day 268 before initiation of rituximab therapy, she became dependent on plasma exchange; whenever plasma exchange was withheld, her platelet count decreased to very low levels within 2–3 d (Fig 2). Cyclophosphamide, azathioprine or cyclosporin A was not used because of the patient's concern of potential adverse effects. On several occasions the patient had suffered adverse reactions, such as hives and rigours, associated with plasma

transfusion and complications of bleeding, and infection and thrombosis in or around the central lines.

On a compassionate use basis, rituximab (Genentech Inc., San Francisco, CA, USA), 375 mg/m², was initiated. Intravenous doses (eight) were administered weekly; each dose was accompanied by acetaminophen (650 mg) and diphenhydramine (25 mg). There were no adverse reactions in association with the drug administration. She required five plasma exchanges in 10 d following the first dose of rituximab and two additional plasma exchanges in the next 3 weeks. In each instance, rituximab was administered following plasma exchange. Plasma exchange was performed no sooner than 48 h following a dose of rituximab. Indeed, the second weekly dose of rituximab was held an additional week because of the need to continue five sessions of plasma exchange following the first dose. Since then, her platelet count has stabilized within the normal range. Her haemoglobin and LDH levels gradually normalized and the follow-up smear showed a mild postsplenectomy picture but is otherwise normal. She has not required plasma exchange for 450 d and this is ongoing (Fig 2). The patient has not presented any evidence of other autoimmune diseases; the human immunodeficiency virus, hepatitis B and C serology tests have been negative. She has no history of taking any medications known to be associated with TTP.

Materials and methods

With informed consent from the patient, plasma samples were obtained by centrifugation of whole blood in 3·2% sodium citrate and stored at −70°C. Determination of ADAMTS13 activity in a plasma sample was based on the generation of homodimers of the 176- and 140-kDa fragments of the VWF substrate as previously described (Tsai & Lian, 1998). A test plasma sample was mixed with a normal control sample to detect ADAMTS13 inhibitor activity. The Bethesda unit, originally defined for measuring the inhibitor titre of factor VIII (Tsai *et al*, 2001), was used to determine the inhibitor titre of ADAMTS13. One unit of inhibitor suppresses ADAMTS13 activity by 50% in an equal mixture of normal and patient plasma after 1 h of incubation at 37°C. VWF multimers were analysed by sodium dodecyl sulphate agarose gel electrophoresis (Tsai & Lian, 1998). The Institutional Review Boards at the participating facilities approved the study protocols.

Results

ADAMTS13 analysis

ADAMTS13 activity was determined on 22 occasions before rituximab was initiated. It was 0–0·1 U/ml (normal range 0·79–1·27 U/ml) on eight occasions when her platelet count was below 50×10^9/l or decreased by 50% from a previously stable level. The protease level was 0·1–0·8 U/ml on 13 occasions when she had received plasma exchange and her platelet count was rising, and was 0·13 U/ml on one occasion when she was in remission.

The course of her ADAMTS13 activity level and the inhibitor titre from the day she received the first dose of rituximab are depicted in Fig 3. During the first 31 d, the protease activity level was measured on five occasions. It was less than 0·1 U/ml except on one occasion, 4 d after plasma exchange was completed, when it was 0·14 U/ml. On day 36, the ADAMTS13 activity level increased to 0·22 U/ml and, thereafter, has been consistently higher than the levels measured prior to rituximab therapy initiation ($P < 0·001$ by ANOVA). The ADAMTS13 inhibitor titre was 0·56 U/ml before treatment with rituximab. It decreased to 0·29 U/ml ($P < 0·01$ by ANOVA) on day 36 and on subsequent determinations has remained between 0·22 and 0·35 U/ml (normal <0·2 U/ml).

Review of the literature

Four previous reports have described the use of rituximab in seven cases of TTP (Chemnitz *et al*, 2002; Gutterman *et al*, 2002; Tsai & Shulman, 2003; Zheng *et al*, 2003). The clinical features and the response to rituximab of these and the present case are summarized in Tables I and II. In all instances the patients were females, aged 31–62 years.

One report describes the use of rituximab in two cases during their first episodes of TTP (Chemnitz *et al*, 2002); the other six (including this case) had multiple relapses over a period of 2·3–10 years. They all had failed other modalities of treatment, including corticosteroids, azathioprine, cyclophosphamide, cyclosporin A, intravenous immunoglobulins, protein A immunoadsorption, splenectomy and vincristine. The indications for use of rituximab included: (i) failure to respond to plasma exchange (two cases, both in their first episodes), (ii) multiple relapses (one case), (iii) long-term plasma exchange (four cases requiring 42–102 exchanges over a period of 50–223 d) and (iv) recurrent episodes of cerebral ischaemia (one case). The patient treated for recurrent episodes of cerebral ischaemia had normal blood cell counts for 455 d preceding the treatment. All seven patients demonstrated ADAMTS13 deficiency because of the presence of inhibitors prior to rituximab therapy (Table III). Intravenous rituximab was administered at a dose of 375 mg/m^2/week for 2–8 weeks. No serious adverse reactions were reported. In five cases rituximab was the only therapy during the course of treatment. In the two cases treated during the first episode and the case with relapsing TTP additional therapies were administered during the course of rituximab therapy (vincristine and corticosteroids in the two acute cases and cyclophosphamide in the case treated for multiple relapses).

Seven cases achieved remission. Time to remission with sustained normal platelet counts was 2–5 weeks. The one case that did not achieve remission nevertheless responded with an increased platelet count and also required less-intensive plasma exchange. This case received four doses of rituximab, and plasma exchange was continued throughout the course of treatment.

Among the patients who achieved remission, the duration of response was 1·7 years in one case and 10–36 months and ongoing in the remaining five cases. One case was lost to follow up at 2 months.

A direct comparison of the response of ADAMTS13 activity level and its inhibitor among these reports is not possible because different types of assays were used, as recently reviewed (Tsai, 2003). Nevertheless, evidence of lower inhibitor titres following rituximab therapy was observed in all six cases that were investigated both pre- and postrituximab therapy (Table III). Among these six cases, five had evidence of increased ADAMTS13 activity levels. The only case that did not show evidence of increased ADAMTS13 activity levels also did not achieve remission. Notably, none of the patients with chronic TTP had a sustained normalization of ADAMTS13 activity levels.

Discussion

Stabilization of platelet counts and cessation of haemolysis occurred after rituximab therapy in a patient with relapsing TTP, who had previously required plasma exchange every 2–3 d, over a period of 9 months, for treatment of the disease. The patient required five exchanges in the first 10 d after the first dose of rituximab, two exchanges between days 11 and 31, and has not required treatment thereafter (>450 d).

Analysis of ADAMTS13 activity detected a severe deficiency of the protease and the presence of an IgG inhibitor throughout her course. Her inhibitor titre was in the range

typically observed in patients with TTP (Tsai *et al*, 2001). Before rituximab therapy, her protease activity level was persistently ≤0·10 U/ml when she was not being treated with plasma exchange. After rituximab therapy, her inhibitor titre decreased, accompanied by an increase in ADAMTS13 activity levels. Nevertheless, during her long period of remission, ADAMTS13 inhibitor activity remained detectable and the enzyme activity remained subnormal, suggesting that rituximab therapy induced clinical remission in this case by diminishing, but not eliminating, the autoantibody against ADAMTS13.

A review of the literature revealed that the response of this case to rituximab is similar to that of previously reported cases of chronic TTP (Gutterman *et al*, 2002; Tsai & Shulman, 2003; Zheng *et al*, 2003). From all reported cases treated with rituximab, two had acute TTP, and rituximab was introduced within 2 weeks of the initial presentation (Chemnitz *et al*, 2002). Because remission is common when acute TTP is treated with plasma exchange for 7–14 d, the response of these two patients to rituximab is difficult to evaluate. In a third patient, the concurrent use of cyclophosphamide soon after a relapse also diminishes the confidence that remission was due to rituximab. However, anecdotal experience suggests that a response to cyclophosphamide is uncommon within a few weeks. The remaining five cases suffered multiple relapses over a course of 2·3–10 years and active or relapsing disease lasting from 50 d to 15 months preceding the use of rituximab. Among these, a coincidence of remission independent of rituximab therapy in each case is extremely unlikely, although not completely impossible.

Role of other therapies

Previously, because the pathogenesis of TTP was unknown, patients with relapsing TTP were empirically treated with corticosteroids, vincristine, cyclophosphamide, azathioprine, splenectomy, cyclosporin A, intravenous immunoglobulins or staphylococcal protein A columns (Prosorba®) (Gaddis *et al*, 1997; Kwaan & Soff, 1997; Allford *et al*, 2003; Aqui *et al*, 2003). However, the efficacy of these treatments has not been systemically evaluated. Among these eight reported cases, excluding the two cases with their initial episodes of TTP and one case that was treated concurrently with cyclophosphamide, all had failed other modalities of treatment before the introduction of rituximab as the only treatment. The experience of these cases suggests that rituximab therapy is effective among patients who have failed other modalities of therapies, although the role of rituximab and other modalities in the treatment of TTP remains to be determined in future studies.

Dosage and administration

Rituximab is generally administered as four weekly doses for the treatment of lymphoproliferative diseases. However, eight weekly doses have been used with no additional adverse reactions (Piro *et al*, 1999). The number of doses used in patients with TTP ranged from two to eight. Although removal of the administered agent during plasmapheresis is a concern, data of serum rituximab levels among patients undergoing plasma exchange are not available, and it is not clear whether plasma exchange on day 1 or a few days after the intravenous administration of rituximab has a negative impact on the therapeutic efficacy of the antibody. Notably, the present case received multiple plasma exchanges beginning 2 d after the first dose of rituximab. Nevertheless, she required only two exchanges after the second dose. The experience of this case suggests that perhaps because of a rapid extravascular distribution, plasma exchange one or a few days after completion of rituximab administration may not have a major negative impact. However, the only case that did not achieve remission also happened to receive plasma exchange throughout her period of rituximab therapy, raising the suspicion that removal of the administered antibody might have contributed to her failure to respond. Until more data are available to address the concern of a potentially negative impact, it seems reasonable to

postpone plasma exchange as long as possible after the rituximab dose. However, plasma exchange should not be withheld if it is deemed clinically necessary. Clearly, further studies are needed to determine whether supplemental doses of rituximab after plasma exchange are needed to compensate for the loss of the antibody during plasma exchange and, thus, promote clinical response.

Time to response

In this patient, a diminished need for plasma exchange was apparent within 2 weeks after the first dose of rituximab; she required five plasma exchanges in the first 10 d after rituximab was initiated, but only two plasma exchanges in the next 20 d. An evaluation of the responses observed in other cases suggests that, within 2–5 weeks after administration of the first dose of rituximab, alleviation of disease activity and a decrease in the need for plasma exchange are observed.

Duration of response and risk of relapse

Previous studies show that rituximab administration is followed by depletion of B cells in the circulation and in the lymphoid tissues (Kneitz *et al*, 2002; Zaja *et al*, 2002, 2003a,b). Recovery of the B cells is typically apparent by 6–12 months. In TTP patients treated with rituximab, one case had a relapse at 17 months. Another case showed a gradual decrease in the ADAMTS13 activity level starting from month 14 after the treatment was started, although she remains in remission for 3 years and on going (H. M. Tsai, unpublished observations). This pattern suggests that relapse is possible. As relapse can be devastating or fatal, further investigation is needed to delineate whether and when retreatment should be considered.

Risks and benefits

A prolonged course of plasma exchange is expensive, debilitating to the patients, and often associated with the development of infection or other complications related to venous access lines. Adverse reactions to plasma are also common. Although rituximab may be associated with serious reactions, most adverse events, including chills, fever and rigours, are infusion-related and can be avoided or alleviated by following appropriate guidelines. Serious cardiopulmonary or mucocutaneous reactions have been also been reported. Therefore, the risk of rituximab therapy should be carefully evaluated against the risk of plasma exchange or alternative therapies.

Potential role of rituximab in the management of acute TTP

Some patients with acute TTP are refractory to plasma exchange, resulting in a fatal outcome. Other patients develop relapses after achieving an initial remission. It is tempting to speculate that rituximab, by suppressing the B-cell immune response, may also facilitate remission among patients with acute TTP and diminish the risk of subsequent relapses. However, the course of TTP is typically unpredictable and remission in anecdotal cases that receive rituximab therapy cannot be considered with certainty as a response to the treatment. A randomized control study would be needed before rituximab could be recommended as an adjuvant to plasma exchange.

In summary, the experience of this and previous cases demonstrates that rituximab treatment is followed by sustained remission in two cases of acute TTP and five of six cases of chronic TTP. Rituximab increased the ADAMTS13 levels and decreased, but did not eliminate, the inhibitor of ADAMTS13 among patients with chronic TTP. Thus, patients with chronic refractory TTP appear to be good candidates for treatment with rituximab because a small increase of the ADAMTS13 activity level is apparently sufficient for inducing long-term

clinical remission. Based on these preliminary results, a systematic clinical trial designed to determine the precise role and efficacy of rituximab in the treatment and management of refractory TTP is urgently needed. Such a trial would, for example, provide data on the utility of whether serial ADAMTS13 assays are predictive for response or subsequent risk of TTP relapse. In the interim, based on the compilation of reported cases and our experience, the use of rituximab appears to be a reasonable strategy in otherwise highly refractory cases of TTP.

Acknowledgments

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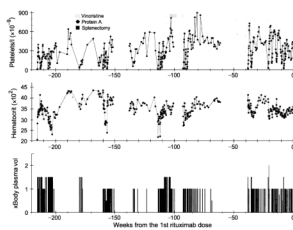
Fig 1.
Platelet count, haematocrit and plasma exchange (× body plasma volume) data prior to the initiation of rituximab therapy. The use of vincristine or staphylococcal protein A columns and the date of splenectomy are indicated.
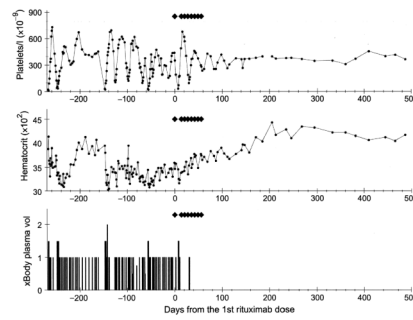
Fig 2.
Platelet count, haematocrit and plasma exchange data immediately prior to the initiation of rituximab and subsequent follow-up. Each ◆ indicates one dose of rituximab (375 mg/m²).
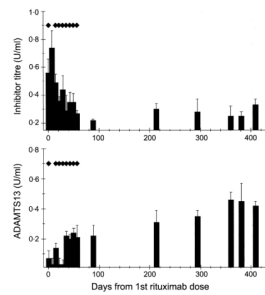
Fig 3.
ADAMTS13 inhibitor titres and activity levels (mean ± SD) after the initiation of rituximab therapy. Each ◆ indicates one dose of rituximab (375 mg/m^2). The inhibitor titre first showed a decrease by day 21 $P < 0.05$), while the ADAMTS13 activity level first increased by day 35 and remained in the range of 0·2–0·4 U/ml ($P < 0.01$).

Table I

Features of the cases of TTP treated with rituximab.

Study	Case no.	Age (years)	Sex (M, F)	Duration of TTP (years)	Other therapies[*]	Active disease leading to rituximab	
						Duration (d)	Plasma exchange (no.)
Gutterman *et al* (2002)	1	54	F	4·75	1, 2, 4, 7, 8	166	102
	2	62	F	10	1, 2, 7, 8	223	44
	3	40	F	3	2, 3, 5, 7, 8	50	42
Chemnitz *et al* (2002)	1	39	F	12 d	–	12	12
	2	37	F	7 d	–	7	7
Zheng *et al* (2003)	1	42	F	2·3	7, 8	10	10
Tsai and Shulman (2003)	1	36	F	9·3	2, 3, 8	455	0
This report	1	31	F	4·1	2, 6, 7, 8	270	94
Overall	8	31–62	M: 0	Acute: 7–12 d	Six cases	Acute: 7–12	Acute: 7–12
			F: 8	Chronic: 2·3–10		Chronic: 10–455	Chronic: 10–102

[*] In addition to plasma exchange.

1, azathioprine (two cases); 2, corticosteroids (five cases); 3, cyclophosphamide (two cases); 4, cyclosporin A (one case); 5, intravenous immunoglobulins (one case); 6, protein A columns (one case); 7, splenectomy (five cases); 8, vincristine (six cases).

TTP, thrombotic thrombocytopenic purpura.

Table II

Dose of rituximab and clinical response.

Study	Case no.	Rituximab dose (375 mg/m^2)	Concurrent therapies	Clinical remission[*]	Remission duration (months)
Gutterman *et al* (2002)	1	8	None	Yes	36+
	2	8	None	Yes	17[†]
	3	4	None	No[‡]	–
Chemnitz *et al* (2002)	1	4	Vincristine	Yes	2[§]
			Corticosteroids	Yes	12+
	2	2	Vincristine		
			Corticosteroids		
Zheng *et al* (2003)	1	6	Cyclophosphamide	Yes	10+
Tsai and Shulman (2003)	1	8	None	Yes	24+
This report	1	8	None	Yes	15+
Overall	8	2–8	Three cases	Seven cases	2–36

[*] Defined as normal platelet count, stable haemoglobin level, and no symptoms or signs that are potentially caused by thrombotic thrombocytopenic purpura.

[†] Platelet count increased and required less-intensive plasma exchanges.

[‡] Relapse.

[§] Lost to follow-up.

Table III

ADAMTS13 and its inhibitors before and after rituximab therapy.

| Study | Case no. | ADAMTS13 activity and inhibitors | | | | |
| | | Before rituximab | | After rituximab | | |
		Activity	Inhibitor	Activity	Inhibitor titre
Gutterman *et al* (2002)	1	ND	ND	–	–
	2	Deficiency	Yes	Increased	Decreased
	3	Deficiency	Yes	Unchanged	Decreased
Chemnitz *et al* (2002)	1	Deficiency	Yes	Increased	Decreased
	2	ND	ND	ND	ND
Zheng *et al* (2003)	1	Deficiency	Yes	Increased	Decreased
Tsai and Shulman (2003)	1	Deficiency	Yes	Increased	Decreased
This report	1	Deficiency	Yes	Increased	Decreased
Overall	8	Deficiency: 6/6	6/6	Increased: 5/6	Decreased: 5/5

ND, not done. Subsequent investigation revealed the presence of ADAMTS13 deficiency because of inhibitors.