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Fixed-Schedule Maintenance Rituximab for Relapse Prevention in Recurrent Immune Thrombotic Thrombocytopenic Purpura in a Patient With a Previous Splenectomy

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Abstract

We report the case of a 53-year-old man with immune thrombotic thrombocytopenic purpura (iTTP) who presented with microangiopathic hemolytic anemia and thrombocytopenia. The diagnosis was confirmed by undetectable ADAMTS13 activity and the presence of anti-ADAMTS13 autoantibodies. The initial episode coincided with the diagnosis of classical Hodgkin lymphoma with splenic involvement. Over 11 years, five acute episodes occurred, corresponding to three clinical relapses and one early exacerbation. Treatment included plasma exchange, corticosteroids, caplacizumab, and several courses of rituximab in a previously splenectomized patient. Given the high cumulative disease burden, a multidisciplinary discussion led to the initiation of subcutaneous rituximab maintenance at 1,400 mg every two months, with a planned total duration of two years. At the time of this report, the patient had completed approximately one year of maintenance therapy, and treatment was ongoing. During this period, no further clinical relapses were documented, and ADAMTS13 activity remained above 50% in the available assessments. Fixed rituximab maintenance may represent an individualized relapse-prevention strategy in selected patients with recurrent iTTP, although further evidence is required to establish its efficacy and safety.

Categories: Hematology
Keywords: adamts13 protein, maintenance therapy, recurrence, rituximab, thrombotic thrombocytopenic purpura

Introduction

Immune thrombotic thrombocytopenic purpura (iTTP) is a rare and potentially fatal thrombotic microangiopathy characterized by severe ADAMTS13 deficiency, usually defined as activity <10%, caused by autoantibodies against this protease. Reduced cleavage of high-molecular-weight von Willebrand factor multimers promotes platelet adhesion and aggregation in the microcirculation, resulting in thrombocytopenia, microangiopathic hemolytic anemia, and organ ischemia [1-6]. Current acute treatment is based on therapeutic plasma exchange and corticosteroids, with caplacizumab and rituximab incorporated according to guideline recommendations and clinical context [1-3]. Despite therapeutic advances, 30%-50% of patients experience relapse, particularly when reduced ADAMTS13 activity persists during remission [1-3]. Rituximab may be used pre-emptively in patients in remission with severe ADAMTS13 deficiency, but evidence regarding fixed, prolonged maintenance regimens remains limited [1,7]. We report a case of recurrent iTTP in a splenectomized patient in whom fixed-schedule maintenance rituximab was selected because of the high cumulative disease burden and recurrence despite previous rituximab-associated recovery of ADAMTS13 activity, rather than waiting for a renewed severe ADAMTS13 decline to trigger pre-emptive treatment.

Case Presentation

A 53-year-old man, a smoker with a 25 pack-year history and no other relevant medical history, was admitted with transient dysarthria and paresthesia affecting the left side of the face and left upper limb. Laboratory findings included hemoglobin 6.3 g/dL, a platelet count of 14×10^9/L, schistocytes, lactate dehydrogenase (LDH) 1110 U/L, indirect hyperbilirubinemia, undetectable haptoglobin, and mild renal dysfunction (Table *1*). ADAMTS13 activity was 0%, with anti-ADAMTS13 autoantibodies, confirming iTTP. Plasma exchange was initiated. Following an initial response, an attempt to discontinue treatment was followed by worsening microangiopathy, prompting corticosteroid therapy and resumption of plasma exchange for a total of 30 sessions.

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Acute TTP Episode versus Laboratory Parameter (reference range)	Acute Episode 1 (Initial episode)		Acute Episode 2 (Relapse 1)		Acute Episode 3 (Relapse 2)		Acute Episode 4 (Exacerbation)		Acute Episode 5 (Relapse 3)	
	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge
Hemoglobin (13-18 g/dL)	6.3	11.19	13.54	13.62	13.2	12.8	12.7	12.8	13.6	13.7
MCV (87-103 fL)	107	96	102	102	100.8	105.4	101.9	100.8	100.5	102.2
Platelets (150-400×10⁹/L)	14	428	51	296	27	291	14	173	35	227
Reticulocytes (25-90x10⁹/L)	443	120	202	150	189	140	156	83	153	128
Lactate Dehydrogenase (135-225 U/L)	1110	231	578	223	611	234	1058	286	661	276
Haptoglobin (30-200 mg/dL)	0	183	-	106	0	121	-	78	0	67
Total Bilirubin (<1.2 mg/dL)	2.6	0.6	1.1	0.3	4.1	0.2	1.08	0.4	2	0.6
Direct Bilirubin (<0.3 mg/dL)	0.7	-	0.3	0.1	0.6	<0.1	0.2	0.2	0.8	0.2
INR	1.25	0.9	1.01	1.02	1.06	1.03	1.03	1	1.01	-
Urea (<50 mg/dL)	72	72	52	36	49	47	61	64	62	67
Creatinine (0.7-1.4mg/dL)	1.4	0.8	1	0.9	1.2	1.4	1.4	1	1.2	1.3
Troponin (<0.05 ng/mL)	0.02	-	-	-	-	-	0.105	-	0.023	-
D-dimer (<500 ng/mL)	1900	-	3050	-	-	-	6420	1330	-	-

TABLE 1: Changes in the patient's laboratory parameters at admission and discharge during each acute iTTP episode, with corresponding reference ranges.

INR: international normalized ratio; MCV: mean corpuscular volume; iTTP: immune thrombotic thrombocytopenic purpura

Computed tomography revealed generalized lymphadenopathy, hepatosplenomegaly, and splenic microinfarcts. Because the lymphadenopathy was not amenable to biopsy, diagnostic splenectomy was performed. Histopathologic examination revealed classical Hodgkin lymphoma, mixed cellularity subtype, with splenic involvement. Following chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), complete remission of both the lymphoma and iTTP was achieved.

The first relapse occurred approximately five years after the initial episode and presented with mild epistaxis, a platelet count of 51×10^9/L, reticulocytosis, schistocytes, LDH 578 U/L, and undetectable ADAMTS13 activity with positive anti-ADAMTS13 autoantibodies. Treatment with plasma exchange and corticosteroids was initiated, requiring a total of 16 plasma exchange sessions.

A further five-year period of clinical remission preceded the second relapse, which was identified during preparation for endobronchial ultrasonography to investigate pulmonary parenchymal abnormalities. Laboratory findings included a platelet count of 27×10^9/L, schistocytes, LDH 611 U/L, and indirect hyperbilirubinemia without anemia. ADAMTS13 activity was 0%; anti-ADAMTS13 autoantibodies, initially below the positivity threshold, subsequently became positive. Seven days after discharge, an early exacerbation occurred, with a platelet count of 14×10^9/L, LDH 1058 U/L, ADAMTS13 activity of 0%, and anti-ADAMTS13 autoantibodies of 101 U/mL. Daily plasma exchange, corticosteroids, caplacizumab, and rituximab 375 mg/m² weekly for four weeks were initiated, with subsequent recovery of ADAMTS13 activity to >50%. Troponin I was elevated to 0.105 ng/mL, and echocardiography showed an ejection fraction of 51%, regional wall motion abnormalities, and grade I diastolic dysfunction.

The disease relapsed again approximately 11 years after the initial presentation, when the patient was 64 years old. This third relapse was characterized by a platelet count of 35×10^9/L, indirect hyperbilirubinemia, proteinuria, and schistocytes, followed by headache, dizziness, sixth cranial nerve paresis, and worsening renal function. ADAMTS13 activity was again 0%, with positive anti-ADAMTS13 autoantibodies. Treatment consisted of plasma exchange, high-dose corticosteroids, and a further course of rituximab. ADAMTS13 activity subsequently recovered to 59%, with resolution of the thrombotic microangiopathy. The longitudinal clinical course, including the timing of acute episodes, serial ADAMTS13 activity, and the subsequent maintenance rituximab period, is summarized in Figure *1*.

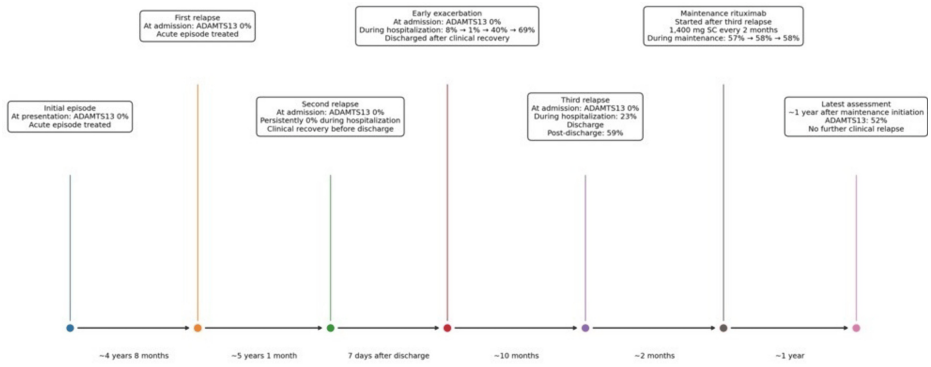


FIGURE 1: Longitudinal clinical course and ADAMTS13 activity in recurrent iTTP

Longitudinal clinical course of immune thrombotic thrombocytopenic purpura, showing the timing of the initial episode, three clinical relapses, one early exacerbation, serial ADAMTS13 activity measurements, and the subsequent maintenance rituximab period. Maintenance rituximab was initiated after the third relapse and administered subcutaneously at a fixed dose of 1,400 mg every two months.

iTTP: immune thrombotic thrombocytopenic purpura

Given five acute episodes over approximately 11 years, corresponding to three clinical relapses and one early exacerbation, despite splenectomy and multiple courses of immunosuppressive therapy, the case was discussed by a multidisciplinary team. A fixed-schedule regimen of subcutaneous maintenance rituximab, 1,400 mg every two months, was initiated with a planned total duration of two years because of the high cumulative disease burden and previous ADAMTS13 responses to rituximab. Amoxicillin prophylaxis was instituted because of asplenia and the additional infection risk associated with cumulative immunosuppression. One dosing interval was extended because of hospitalization for decompensated heart failure and community-acquired pneumonia. At the time of this report, the patient had completed approximately one year of the planned two-year maintenance regimen, and treatment was ongoing. During this period, no further clinical relapses occurred. ADAMTS13 activity was 57%, 58%, 58%, and 52% at 12 days, 31 days, 38 days, and approximately 13 months after maintenance initiation, respectively. No anti-ADAMTS13 autoantibody results were available during the maintenance period.

Discussion

This case demonstrates the chronic, relapsing nature of iTTP, with three clinical relapses and one early exacerbation according to consensus definitions [8]. The initial coexistence of Hodgkin lymphoma may have acted as a trigger. Although cancer-associated microangiopathic hemolytic anemia is a recognized entity [9], severe ADAMTS13 deficiency with anti-ADAMTS13 autoantibodies established a specific immune mechanism in this patient. Furthermore, subsequent relapses during lymphoma remission support a disease course independent of active lymphoproliferative disease.

Serial monitoring of ADAMTS13 activity, complemented by autoantibody assessment, is central to follow-up, as changes in these markers during remission are associated with a higher risk of relapse, although they do not allow the timing of an episode to be predicted [7,10,11]. In this patient, recovery of ADAMTS13 activity to >50% after rituximab was not associated with lasting protection, illustrating that a single measurement does not equate to sustained immunologic remission.

The strategy used differs from conventional pre-emptive rituximab therapy, which is usually guided by a renewed significant reduction in ADAMTS13 activity during remission. A fixed, scheduled regimen was chosen with the aim of prolonging B-cell depletion and delaying reconstitution of the autoimmune response. Saleem et al. described maintenance treatment every three months for two years in a pediatric case, with no further relapses; Barba et al. observed recovery of ADAMTS13 activity in 10 of 13 patients receiving an intensified and prolonged regimen; Delrue et al. demonstrated the feasibility of subcutaneous rituximab in an ADAMTS13-guided pre-emptive setting [12-14]. A recent review considers prolonged strategies in selected cases, particularly in the setting of an inadequate response or recurrent iTTP after rituximab [15]. Although these data do not validate the regimen used, they support its clinical plausibility [12-15].

Cumulative immunosuppression, together with asplenia and the episode of pneumonia, prompted surveillance for infections and monitoring of immunoglobulin levels. Episodes of decompensated heart failure occurred during maintenance treatment; given pre-existing cardiac abnormalities and previous exposure to doxorubicin, no direct causal relationship with rituximab was established.

At the time of this report, approximately one year of the planned two-year maintenance regimen had been completed, and treatment remained ongoing. The absence of clinical relapses during this period and the maintenance of ADAMTS13 activity >50% are encouraging findings but do not establish treatment efficacy. Importantly, the approximately one-year relapse-free observation period during maintenance remains substantially shorter than the approximately five-year intervals that preceded the first and second clinical relapses; therefore, the current follow-up is insufficient to determine whether fixed-schedule maintenance has altered the natural relapse pattern of the disease.

This report is limited by its single-patient nature and by the fact that the planned two-year maintenance regimen had not yet been completed at the time of reporting. The absence of a comparator also precludes distinguishing the effect of scheduled rituximab maintenance from the natural variability of the disease course. Longer follow-up, including assessment after completion of maintenance therapy, will be necessary to determine the durability of both clinical and immunologic remission.

Conclusions

Recurrent iTTP may remain clinically challenging despite splenectomy and repeated courses of immunosuppressive therapy. In this patient, a fixed-schedule regimen of subcutaneous rituximab at 1,400 mg every two months, planned for a total duration of two years, was selected as an individualized strategy for relapse prevention after multiple acute episodes and previous responses to rituximab. At the time of this report, approximately one year of maintenance therapy had been completed, and treatment remained ongoing. The absence of further clinical relapses during this period, together with ADAMTS13 activity remaining above 50% in the available assessments, was encouraging but should be interpreted cautiously.

Fixed-schedule rituximab maintenance is not an established standard of care in iTTP but may represent an individualized therapeutic option in selected patients with recurrent disease and a high cumulative disease burden. Further studies are needed to establish its efficacy, safety, optimal dosing interval, and treatment duration.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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