Rituximab for acute plasma-refractory thrombotic thrombocytopenic purpura

A case report and concise review of the literature

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Summary

Thrombotic thrombocytopenic purpura (TTP) is a rare disease which responds well to plasma exchange treatment in the majority of patients. We report on a patient with acute TTP caused by severe autoantibody-mediated ADAMTS-13 deficiency, in whom remission was not achieved by initial treatment consisting of plasma exchange (PE), plasma infusion and corticosteroids, followed by vincristine and splenectomy. In view of the ongoing activity of TTP, treatment was initiated with rituximab, a chimaeric monoclonal antibody directed against the CD 20 antigen present on B lymphocytes. The patient received 4 weekly infusions of 375 mg/m², each administered after the daily PE session and withholding PE until 48 hours later. Three weeks after the last infusion of rituximab a complete clinical and laboratory remission of this first episode of acute refractory TTP was documented. A concise review of the literature on the role of rituximab in patients with a first episode of acute plasma-refractory TTP suggests that rituximab in that situation may produce clinical remission in a significant proportion of patients, result in a lowered plasma requirement and avoid the complications of salvage immunosuppressive therapy. The use of rituximab in acute refractory TTP appears to be safe, with no excess infectious complications. We conclude that rituximab should be considered in TTP patients with acquired ADAMTS-13 deficiency who fail to respond clinically after 7–14 days of standard treatment with daily PE and glucocorticoids.

Key words: acute refractory thrombotic thrombocytopenic purpura; TTP; ADAMTS-13; rituximab

Introduction

In 1924 Moschcowitz described the case of a sixteen-year-old girl who developed haemolytic anaemia, thrombocytopenia, neurological dysfunction and renal compromise. Death ensued from cerebral infarction and cardiac failure. Autopsy revealed widespread thromboses, particularly in the terminal arterioles [1], and later the name thrombotic thrombocytopenic purpura (TTP) was used to describe a clinical syndrome comprising five cardinal features – microangiopathic haemolytic anaemia, thrombocytopenia, fever, renal impairment and neurological dysfunction [2, 3].

Idiopathic acquired thrombotic thrombocytopenic purpura is a rare disease with a reported annual incidence of 4.5 per million [4]. Daily plasma exchange (PE) and replacement with fresh frozen plasma (FFP) has become the first-line therapy for TTP on the strength of clinical studies documenting a significant reduction in mortality from more than 90% to some 10%–20% [5]. The effectiveness of PE is generally attributed to the removal of circulating anti-ADAMTS-13 autoantibodies and the concomitant supplementation of ADAMTS-13 activity [6, 7]. However, PE may also be effective in patients without severely deficient ADAMTS-13 activity [8].

About 10% to 20% of TTP patients show an incomplete response to daily PE or are refractory. Generally, escalation of therapy should be considered after at least 7–14 days of adequate treatment with PE or if the clinical course deteriorates during that time. In these cases, plasma treatment should be intensified first. If response fails to materialise, additional immunosuppressive treatment is indicated.

Besides corticosteroids, various other immunosuppressive or immune-modulating agents

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have been given to patients with refractory or relapsing TTP. Case reports and small, uncontrolled series suggest that adding vincristine to the standard treatment may induce remission in refractory cases. Cyclophosphamide, cyclosporine, azathioprine and intravenous immunoglobulins have all been used successfully in small numbers of patients, but there are no clinical trials to guide the use of these immunosuppressive agents in the setting of acute refractory or chronic relapsing TTP [9–11].

For many years, splenectomy was performed empirically in patients with refractory or relapsing TTP, with reported remission rates in small case series of 50–100%. Relapses occur in a considerable proportion of patients and are significantly more frequent in patients with severe ADAMTS-13 deficiency [8, 12]. Resumption of plasma therapy is the treatment of first choice. Before the introduction of plasma therapy for TTP an improved survival rate was observed in splenectomised patients. Recently it was shown that splenectomy in refractory and in relapsing TTP associated with anti-ADAMTS-13 autoantibodies induced disappearance of the antibodies, normalisation of ADAMTS-13 activity and clinical remission [13]. Further, splenectomy reduced the frequency of relapses in a large cohort of patients [14].

Treatment with rituximab, a chimaeric monoclonal antibody directed against the CD 20 antigen present on B lymphocytes, leads to clearance of B lymphocytes responsible for antibody production by complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity or directly by inducing apoptosis. Rituximab has been used successfully to treat lymphoproliferative B-cell malignancies and several immune mediated diseases [15].

We describe a patient presenting with a first episode of acute refractory TTP who was successfully treated with rituximab. We also review the literature on the role of rituximab in a first episode of acute refractory idiopathic TTP.

**Case report and clinical course**

A 63-year-old female patient was admitted with a 3-day history of recurrent episodes of dysphagia, dysarthria and facial palsy, dyspnoea and generalised weakness. Haemoglobin was 64 g/L (normal range 115–148 g/L) and platelet count 9 × 10^9/L (130–330 × 10^9/L). The peripheral blood smear revealed fragmented red cells with polychromasia. Levels of LDH (2237 U/L, normal range 240–480 U/L) and bilirubin (168 μmol/L, normal range <17 μmol/L) were elevated and serum haptoglobin was undetectable, reflecting a considerable degree of intravascular haemolysis. Direct Coombs’ test was negative. There was laboratory evidence of myocardial ischaemia and tachyarrhythmia on the ECG, and echocardiography revealed a dilatative cardiomyopathy with an ejection fraction of 15%. Marked hyperthyroidism was noted with TSH <0.01 mU/L (0.27–4.2 mU/L) and free T4 >100 pmol/L (10–23 pmol/L) in the presence of anti-TSH receptor antibodies and anti-thyroid peroxidase antibodies. Two years earlier the patient had been treated for stage IV B peripheral T-cell lymphoma. Treatment consisted of high-dose chemotherapy and autologous stem cell transplantation. Present staging evaluation showed a sustained complete remission.

The clinical diagnosis of acute acquired TTP was confirmed by the finding of severely deficient ADAMTS-13 activity (<3% of the normal) in the presence of circulating anti-ADAMTS-13 inhibitory antibodies (Figure 1). Measurement of ADAMTS-13 activity and of inhibitory antibodies was performed as previously described [6, 16]. Therapy with PE and plasma infusion (PI) was promptly instituted and glucocorticoids were added (1 mg prednisone per kg bodyweight daily).

**Figure 1**

ADAMTS-13 activity determination by immunoblotting of plasma-purified vWF substrate degraded by BaCl2-activated ADAMTS-13 in the patient’s plasma during both the course of treatment and follow-up period (patient samples 1–11). Assay calibration by normal plasma dilutions of 1:20 (100% activity), 1:40 (50%), 1:80 (25%), 1:160 (12.5%), 1:320 (6.25%), 1:640 (3%), and buffer control (0%) (calibration curve).
Despite treatment with daily PE, PI and glucocorticoids and transiently increasing ADAMTS-13 activity, TTP activity was ongoing 10 days after initiation of therapy, with haemoglobin of 90 g/L, platelet count 64 × 10^9/L and recurrent severe ADAMTS-13 deficiency (<5%). Treatment was therefore supplemented with vincristine infusions (2 mg intravenously on each occasion) on days 11, 21 and 37. However, remission was not achieved by that day (haemoglobin 74 g/L and platelet count 59 × 10^9/L). Splenectomy was therefore performed next day. Four weeks later haemoglobin was 93 g/L, platelet count 89 × 10^9/L and hence TTP activity was still present despite daily PE and PI in combination with glucocorticoids.

The documented autoimmune aetiology of TTP in this patient provided the rationale for the use of the monoclonal antibody rituximab. This was given as 4 weekly infusions (week 10, 11, 12, 13) at a dose of 375 mg/m², each administered after the daily PE session and withholding PE until 48 hours later. Three weeks after the last infusion of rituximab, 16 weeks after initial presentation, PE and PI could be withdrawn. At that time haemoglobin was 104 g/L, platelet count 142 × 10^9/L and ADAMTS-13 activity 20%. Haemoglobin and platelet count rose steadily until the last follow-up visit at week 34, with values of 138 g/L and 394 × 10^9/L respectively (Figure 2), when complete clinical and laboratory remission of TTP was documented.

TSH and free T4 values returned to normal within two weeks after initiation of therapy with PE, PI and glucocorticoids, and remained within normal limits without treatment at the last follow-up visit at week 34.

Treatment of TTP was complicated by a left-sided subphrenic abscess post-splenectomy, necessitating drainage, and a left-sided pleural empyema, for which a thoracotomy with debridement had to be performed at week 21. Furthermore, the patient developed pulmonary embolism at week 26 and had to be orally anticoagulated with a target INR of 2.0–3.0.

Two weeks after the last follow-up visit, 23 weeks after the last administration of rituximab, the patient died suddenly at home and unfortunately a post-mortem examination was not agreed on. In view of the dilatative cardiomyopathy with a severely reduced ejection fraction on admission, which was attributed to the prior high dose chemotherapy and autologous stem cell transplantation but could have also been due to the TTP itself, and which had caused multiple episodes of ventricular tachycardia during plasma exchange therapy with persistent impairment of the ejection fraction even after remission of TTP, sudden cardiac death is the most likely explanation.

Review of the literature

The role of rituximab in relapsing TTP has recently been reviewed [17]. Our review focused on cases with a first episode of acute refractory idiopathic TTP. We carried out a concise review of the literature covering publications between the first case report in 2002 up to April 2007. We searched in the PubMed database of the U.S. National Library of Medicine for “acute refractory”, “thrombotic thrombocytopenic purpura”, “TTP” and “rituximab”. While reviewing these articles we focused on case reports and case series reporting on rituximab in the treatment of a first episode of acute refractory idiopathic TTP. We defined refractoriness of TTP as failure of standard treatment with PE and addition of other therapeutic modalities such as immunosuppressive agents and/or splenectomy to induce remission. Eight case reports or case series were identified which fulfilled these criteria [18–25]. The results of the published studies are summarised in Table 1.

Chemnitz et al. [18] reported on two patients with a first episode of acute refractory TTP. The first was a 39-year-old female patient in whom ADAMTS-13 activity before treatment was <1% in the presence of inhibitory antibodies against ADAMTS-13. Treatment consisted of PE and glucocorticoids. In view of clinical deterioration, treatment with vincristine was added. After 12 days of treatment with no significant response, rituximab was started and repeated weekly. After 4 courses of rituximab the patient’s condition improved gradually and laboratory values nor-
malised completely, with ADAMTS-13 activity of 100% without a detectable inhibitor.

The second was a 37-year-old female patient who received vincristine after unsuccessful treatment with PE and glucocorticoids. After 11 days it was decided to treat the patient with rituximab. She received two cycles, after which a response was noted, and was discharged on day 45. The laboratory values completely normalised after 77 days. The patient remained in complete remission for almost one year after treatment.

Sallah et al. [19] published five cases with refractory TTP, at least one patient fulfilling the criteria of a first episode of acute refractory TTP. The treatment of this 32-year-old patient prior to administration of rituximab consisted of prednisone, PE, vincristine and splenectomy. After 3½ months of treatment and ongoing TTP, rituximab was given and resulted in complete remission of TTP with normalisation of ADAMTS-13 activity and a response lasting for 13 months.

Koulova et al. [20] reported on a 40-year-old male who was initially treated with glucocorticoids concurrently with PE. After 5 consecutive plasma exchanges with persistent low platelet count, therapy with vincristine was initiated. After 14 days of unsuccessful treatment rituximab was started, although the platelet count began to rise even before the initiation of rituximab. Because of proteinuria on admission a renal biopsy was obtained and a chronic membranous “lupus-like” glomerulonephropathy was diagnosed with a stable clinical course.

Millward et al. [21] reported the case of a 20-year-old female who was treated with prednisone and daily PE. After 17 daily PE sessions, which had been complicated by an anaphylactic reaction and renal failure necessitating haemodialysis, the platelet count gradually declined again. At that point rituximab was administered. Approximately six hours after the rituximab infusion the patient developed acute respiratory failure and cardiogenic shock and was transferred to the intensive care unit, where the clinical condition was stabilised. After four additional plasma exchanges the platelet count increased and LDH declined to normal values. The patient was discharged four weeks after initial presentation.

The case report by Scott et al. [22] describes a 21-year-old woman treated by daily PE. On days 12, 18, and 29 after diagnosis PE was discontinued, and on each occasion a rapid drop in platelet count and elevation of LDH occurred. She was therefore treated by intravenous prednisolone on days 32, 33 and 34 after diagnosis, and was given rituximab on days 39, 47, 54 and 60. Daily plasma exchange was discontinued on day 49. There was no evidence of relapse 150 days after diagnosis.

Fakhouri et al. [23] reported two patients with absent remission of TTP after at least 3 weeks of PE, who therefore received 4 weekly infusions of rituximab. In both patients PE was discontinued before treatment with rituximab and was not resumed afterwards. PI was continued for at least 3 weeks and progressively tapered after the induction of clinical remission, which was defined by both the regression of visceral ischaemic signs if initially present and normalisation of standard blood parameters (platelet count >150×10⁹/L and haemoglobin level >120 g/l). Both pa-

### Table 1

Results of published studies on rituximab in patients with a first episode of acute refractory TTP.

<table>
<thead>
<tr>
<th>Authors, Year of Publication, Reference</th>
<th>Number of patients treated (n)</th>
<th>Age</th>
<th>Sex</th>
<th>ADAMTS-13 activity &lt;5% (n)</th>
<th>Time from diagnosis to rituximab therapy (days)</th>
<th>Rrituximab doses, cycles (n)</th>
<th>Clinical remission (n)</th>
<th>Serious rituximab related side effects</th>
<th>Follow-up months (median: 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemnitz et al., 2002, 18</td>
<td>2</td>
<td>37–39</td>
<td>0,2</td>
<td>1* PE, Steroids, V</td>
<td>11–12 days</td>
<td>375 mg/m², 2</td>
<td>2</td>
<td>none</td>
<td>2 to 12</td>
</tr>
<tr>
<td>Sallah et al., 2004, 19</td>
<td>1</td>
<td>32</td>
<td>NR</td>
<td>1 PE, Steroids, V, SPE</td>
<td>NR</td>
<td>375 mg/m², 1</td>
<td>1</td>
<td>none</td>
<td>13</td>
</tr>
<tr>
<td>Koulova et al., 2005, 20</td>
<td>1</td>
<td>40</td>
<td>1,0</td>
<td>NR PE, V</td>
<td>14 days</td>
<td>375 mg/m², 1</td>
<td>1</td>
<td>none</td>
<td>5</td>
</tr>
<tr>
<td>Millward et al., 2005, 21</td>
<td>1</td>
<td>20</td>
<td>0,1</td>
<td>NR PE, Steroids, V</td>
<td>18 days</td>
<td>375 mg/m², 1</td>
<td>1</td>
<td>acute respiratory failure, cardiogenic shock</td>
<td>NR</td>
</tr>
<tr>
<td>Scott et al., 2005, 22</td>
<td>1</td>
<td>21</td>
<td>0,1</td>
<td>PE, Steroids</td>
<td>59 days</td>
<td>140 mg/m², 1</td>
<td>1</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Fakhouri et al., 2005, 25</td>
<td>2</td>
<td>21–58</td>
<td>0,2</td>
<td>PE, Steroids, V, Pi</td>
<td>at least 21 days</td>
<td>375 mg/m², 2</td>
<td>2</td>
<td>none</td>
<td>9</td>
</tr>
<tr>
<td>Darabi et al., 2006, 24</td>
<td>2</td>
<td>39–62</td>
<td>0,2</td>
<td>PE, Steroids, V, SPE</td>
<td>11–42 days</td>
<td>375 mg/m², 2</td>
<td>2</td>
<td>none</td>
<td>NR</td>
</tr>
<tr>
<td>Scully et al., 2006, 26</td>
<td>14</td>
<td>23–65</td>
<td>4,10</td>
<td>12** PE, Steroids, V</td>
<td>at least 7 days</td>
<td>375 mg/m², 4</td>
<td>14</td>
<td>none</td>
<td>1 to 25</td>
</tr>
<tr>
<td>This report</td>
<td>1</td>
<td>63</td>
<td>0,1</td>
<td>PE, PE, Steroids, V, PE, Pi</td>
<td>67 days</td>
<td>375 mg/m², 4</td>
<td>1</td>
<td>none</td>
<td>4</td>
</tr>
</tbody>
</table>

* one case not reported
** one case ADAMTS-13 activity 12%, one case ADAMTS-13 activity 64%
PE = plasma exchange, PI = plasma infusion, SPE = splenectomy, V = vincristine, NR = not reported
The largest case series involving a first episode of acute refractory TTP was published by Scully et al. [25]. Acute refractory TTP was defined as failure to achieve either a normal platelet count following 7 days of PE, or deterioration in clinical symptoms despite standard therapy during the first episode of TTP. Remission was defined as sustained normal platelet count, absence of clinical manifestations of TTP and cessation of PE. On admission all patients received i.v. methylprednisolone daily for three days. In total, 14 cases have been reported which fulfilled the criteria of acute refractory TTP; 12 cases had ADAMTS-13 activity <5%, one case had 12% enzyme activity and one case had no measured baseline ADAMTS-13 activity but had normal ADAMTS-13 activity following 6 weeks’ treatment elsewhere with PE and prednisolone. Thirteen patients had evidence of an inhibitor to ADAMTS-13 and/or IgG antibodies to ADAMTS-13 on admission. All patients received a weekly i.v. rituximab infusion for four weeks immediately following PE. The median ADAMTS-13 activity following 4 weekly rituximab treatments was 90% (range: 29–109%). There was a significant decrease in IgG antibody titre with no evidence of an inhibitor in any patient following treatment with rituximab and at 3 months’ follow-up. Treatment with rituximab was associated with rapid normalisation of clinical features and laboratory parameters within a median of 11 days after initiation of therapy. No relapse of TTP was recorded after treatment with rituximab, and treatment was well tolerated.

Discussion

The mainstay of treatment of acute acquired TTP is daily PE and replacement with FFP. The effectiveness of this treatment approach has been clearly established and has recently been reviewed [26]. PE should be instituted soon after presentation, since delay in initiating treatment may increase treatment failure and mortality [27]. It is empirically recommended that daily PE should continue for a minimum of two days after achievement of remission, defined as a normal platelet count and LDH value, rising haemoglobin and a normal neurological status [28]. Measuring ADAMTS-13 activity and/or ADAMTS-13 inhibitory antibody levels in addition to the clinical categories idiopathic TTP and non-idiopathic TTP are predictive of the outcome and may be useful in tailoring treatment [29].

Despite the considerable improvement in survival with the early institution of daily PE in patients with TTP, there is a subset of patients with either an incomplete, delayed or absent response to this standard treatment. Although there is no generally accepted definition of refractory disease, escalation of therapy should be considered after 7–14 days of adequate treatment with daily PE and corticosteroids if the clinical course deteriorates during that time. In such cases, intensification of PE or the addition of immunosuppressive drugs such as vincristine, cyclophosphamide or cyclosporine has been recommended.

There is increasing evidence that the use of rituximab, a chimeric monoclonal antibody against the CD20 antigen depleting B cells in the circulation and lymphoid tissues, has a role in the treatment of acute refractory and relapsing autoimmune TTP due to ADAMTS-13 inhibitory antibodies. However, there is still a lack of reliable data on the optimal time schedule and dose, duration of therapy, possible risk stratification according to the level of inhibitory antibody-titre, long term maintenance of remission and side effects in patients with acute refractory and relapsing TTP.

Placing rituximab in that setting, it is necessary to balance the risks and benefits of different
Rituximab for acute plasma-refractory thrombotic thrombocytopenic purpura

Hand, with the above-mentioned exception rituximab necessitating haemodialysis. On the other hand, with the above-mentioned exception rituximab was well tolerated and did not cause infectious complications despite low levels of B lymphocytes when measured. There is evidence from the largest case series published to date that treating acute refractory TTP patients with rituximab as early as 7 days after admission will induce a rapid and high rate of remission and is associated with very few short term side effects [25]. This will also lead to a reduction in plasma requirement and increase patient safety by diminishing potential side effects of the plasma exchange procedure. We therefore suggest using rituximab fairly early, within 7–14 days of admission, in patients with acute refractory TTP.

The optimal dose of rituximab in acute refractory and relapsing TTP has not been defined. In the majority of cases a dose of 375 mg/m² once weekly for four weeks is given, which is the accepted dose schedule for the treatment of lymphoproliferative B-cell malignancies. Reviewing the literature on cases with a first episode of acute refractory TTP, it may be noted that patients achieve remission even with a single dose or two weekly doses of rituximab [16, 19]. Whether a dose of 375 mg/m² once or twice or a reduction of the single administered dose would be sufficient in refractory or relapsing TTP patients needs further study.

In all published case reports addressing the first episode of acute refractory TTP the follow-up period was short, ranging from 1–25 months [18–25]. There is thus little information about the duration of the TTP remission and the rate of late relapses after treatment with rituximab in patients with acute refractory TTP. The majority of the reported cases achieved clinical remission and improved ADAMTS-13 activity. These encouraging results argue in favour of conducting multi-centre, randomised controlled trials evaluating the optimal time schedule and dose, duration of therapy, possible risk stratification according to the level of inhibitory antibody-titre, and long-term effects and side effects of rituximab in patients with a first episode of acute refractory TTP [31].

A literature review based on several case reports has of course its limitations. Firstly, there is strong potential for publication bias. Thus these case reports on successful treatment of acute refractory TTP with rituximab should be interpreted with caution as far as firm new clinical evidence is concerned. Secondly, there is no universally accepted definition of refractory disease or of disease remission. These terms have therefore not been uniformly used in different case reports and case series, and this renders comparison of study results difficult.

To our surprise, our patient had not only detectable circulating anti-ADAMTS-13 inhibitory antibodies but also anti-TSH receptor and antithyroid peroxidase antibodies with marked hyperthyroidism. With the administration of glucocorticoids and the initiation of daily PE, presumably removing the highly protein-bound T4 and T3 molecules as well as the anti-TSH receptor and antithyroid peroxidase antibodies, TSH and free T4 became normal within two weeks and remained within normal limits during the follow-up period. Hence the simultaneous occurrence of multiple autoantibodies causing such different diseases as TTP and hyperthyroidism further emphasises the association of autoimmune mediated TTP with other autoimmune disorders. To the best of our knowledge this is the first description of the concomitant occurrence of thyrotoxicosis and TTP.

In summary, rituximab has a role in the treatment of patients with a first episode of acute refractory autoantibody-induced TTP, as shown in this and previous cases. Induction of remission by rituximab is associated with the disappearance of ADAMTS-13 inhibitors and normalisation of ADAMTS-13 activity. Treatment with rituximab appears to be both effective and safe, possibly leading to a significant reduction in plasma requirement and complications of salvage immunosuppressive therapy. We conclude that, on the basis of the literature review, rituximab should be considered in TTP patients who fail to respond after 7–14 days of standard treatment with daily PE and glucocorticoids.

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