Long-term Efficacy of Rituximab Treatment in Thrombotic Thrombocytopenic Purpura

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Abstract

The use of therapeutic plasma exchange has reduced mortality rates in thrombotic thrombocytopenic purpura (TTP) from 90 to 10–20%. However, TTP is a potentially lethal disorder, and management of patients with TTP refractory to plasma exchange or frequently recurrent disease is difficult. In those cases, rituximab might be a therapeutic option, although current data are based primarily on case reports and smaller case series. While initial response rates to rituximab are reported to be high, long-term follow-up data of patients treated with rituximab are rare; however, it is important to estimate the safety and benefit of this treatment. In this article we focus on current experience with rituximab in the treatment of TTP, including recent results with long-term follow-up.

Keywords

Thrombotic microangiopathy, thrombotic thrombocytopenic purpura, treatment, therapeutic plasma exchange, rituximab, follow-up, ADAMTS13, CD20

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Thrombotic thrombocytopenic pupura (TTP) is a life-threatening disease characterised by microangiopathic haemolytic anaemia, consumptive thrombocytopenia and various organ dysfunctions, such as neurological symptoms, renal damage and fever.[1] In order to ensure best treatment responses, early diagnosis and appropriate intervention are crucial. Therefore, it was proposed to reduce the diagnostic criteria to three conditions: thrombocytopenia and microangiopathic haemolytic anaemia in the absence of an alternative explanation for thrombocytopenia and microangiopathic hemolytic anaemia, thereby abandoning the previous pentad of symptoms.[2] The decreased diagnostic threshold has resulted in a sevenfold increase of TTP incidence.[3] The classification of TTP according to Sadler[4] distinguishes idiopathic (primary) TTP from secondary TTP following predisposing conditions such as cancer, eclampsia, drug toxicity or haematopoietic stem cell transplantation. The acquired form of idiopathic TTP is further distinguished from hereditary disease (Upshaw–Schulman syndrome).

Rationale for Rituximab Therapy in Thrombotic Thrombocytopenic Pupura

Much progress has been made in recent years in understanding the pathophysiology of TTP. Moake et al. described unusually large von Willebrand factor (vWF) multimers in the plasma of patients with relapsing, acquired or congenital TTP causing intravascular platelet aggregation and occlusion of the microvasculature.[5] vWF is a glycoprotein produced within the vascular endothelial cells and the megakaryocytes. In its multimer form, vWF has maximal capacity to aggregate and bind blood platelets. Under normal conditions, increased platelet aggregation is prevented by cleavage of the vWF multimers. Tsai et al.[6] and Furlan et al.[7] independently identified a vWF-cleaving protease (ADAMTS13) missing from the plasma of patients with congenital TTP[8] and severely deficient in patients with acquired idiopathic TTP. Mutations in the *ADAMTS13* gene were shown to cause congenital TTP,[9] so far more than 90 mutations of the *ADAMTS13* gene have been described.[3] Much more common than hereditary TTP is the idiopathic form of TTP caused by auto-antibodies. These inhibitory antibodies – mostly immunoglobulin G (IgG) antibodies – bind to the cystine-rich domain of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) and lead to a decreased function of the enzyme.[10,11]

The major role of B cells in the production of inflammatory cytokines and auto-antibodies, as well as the ability to act as antigen-presenting cells, is the basis for B-cell-depleting therapies in immune-mediated disorders. Due to the autoimmune nature of acquired idiopathic TTP, rituximab has been used as a second-line immunosuppressive intervention in TTP cases refractory to plasma exchange as well as in frequently relapsing patients.[12–21] Rituximab, a chimeric monoclonal antibody directed against the CD20 antigen present on B lymphocytes, is used in lymphoma therapy as well as in autoimmune diseases such as rheumatoid arthritis and immune thrombocytopenia. Its effect relies on clearance of B lymphocytes by complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity or directly by inducing apoptosis. However, several lines of evidence indicate that the T-cell compartment may also be modulated by these interventions.[22,23]

Standard Treatment

The standard treatment of acquired idiopathic TTP consists of plasma exchange with fresh frozen plasma,[24,25] thereby removing large vWF

multimers as well as auto-antibodies to ADAMTS13 and replacing the vWF-cleaving protease activity.[26,27] Therapeutic plasma exchange is the only therapy for TTP with proven efficacy in prospective randomised clinical trials. The Canadian Apheresis Study Group compared plasma infusion (30ml/kg initially, then 15ml/kg daily) with plasma exchange (1.5 plasma volume/day for ten days, then one plasma volume/day) and demonstrated increased survival in the plasma exchange arm (78 versus 63%).[25] Other studies reported similar results.[28] As a result of this therapeutic intervention the overall survival could be improved from 10% to more than 80%.[29,30] However, up to one-third of patients relapse after successful treatment of an acute episode, and especially patients who present initially with severe ADAMTS13 deficiency have a significantly increased risk of relapsing TTP.[26,31] In case of plasma-refractory TTP, which is defined as persistent thrombocytopenia or lactate dehydrogenase elevation after a total of seven daily plasma exchange procedures, current guidelines advise to intensify plasma exchange and to add corticosteroids.[27] The advice of additional corticosteroids is mainly based on clinical experience and case series, but has not yet been proved in controlled clinical trials. Other additional therapy with immunosuppressive drugs such as azathioprine, cyclophosphamide or cyclosporine has not been proved to be beneficial.[32]

Rituximab as Second-line Treatment

No specific standard treatment schedule exists for second-line treatment of refractory or relapsing TTP. If rituximab was used as a treatment option in this situation, it was mainly administered at doses of 375mg/m^2 weekly for an average of four doses, in the same manner as the treatment schedule in non-Hodgkin's lymphoma. In most cases rituximab was administered in parallel to continued therapeutic plasma exchange. Using this regimen, the majority of patients with refractory or relapsing TTP achieved complete remission with complete clinical and laboratory responses including normal ADAMTS13 level and disappearance of anti-ADAMTS13 antibodies.[26,33] However, only a small number of patients have been reported worldwide.

The largest case series describing 25 patients with acute refractory and relapsing TTP treated with rituximab was published by Scully et al.[14] All patients initially achieved clinical remission; however, median follow-up was only 10 months (one to 33 months). Ling et al. reported 13 patients with refractory or relapsing TTP, of which 12 patients achieved complete response after rituximab treatment during median follow-up of 24 months.[34] Longer follow-up is reported by Jasti et al.,[35] describing 12 patients with TTP. Of the 11 patients with refractory TTP treated with rituximab during the acute episode, two patients died and nine were in ongoing complete remission after follow-up between one and 79 months. One patient with relapsed TTP was in remission for two years, and the subsequent relapse was again successfully treated with rituximab. Altogether, more than 100 patients have been reported to have received second-line treatment with rituximab, two-thirds because of refractory disease to standard treatment and one-third because of recurrent disease. More than 90% of patients achieved complete remission after rituximab. In the reported cases, only 10–13% of patients relapsed after rituximab treatment after a median follow-up of 11 months.[13,14] Further research should focus on long-term follow-up, especially when considering that B-cell recovery typically occurs nine to 12 months after rituximab application. Longer follow-up is required to address the possible long-term side effects of rituximab and the overall safety of this treatment.[36] Moreover, despite the initial high response rates after rituximab treatment, longer follow-up periods are required to assess the exact benefit of this therapy and also to take into account late relapses.

Long-term Follow-up After Rituximab Treatment

To address these concerns in our patient cohort, we re-evaluated all patients with non-familial idiopathic TTP refractory to plasma exchange or with recurrent disease treated with rituximab between 2000 and 2008 at the University Hospital of Cologne with a median follow-up of almost 50 months, reflecting the longest follow-up period after rituximab treatment reported to date.[37]

Diagnosis of TTP was based on clinical and laboratory findings – including consumptive thrombocytopenia, haemolytic anaemia and elevated schistocytes in the peripheral blood smear – irrespective of ADAMTS13 activity. All patients were initially treated with standard treatment including daily plasma exchange with fresh frozen plasma (1.5 times plasma volume) and corticosteroids. The decision to initiate rituximab treatment was made in the case of non-response to daily plasma exchange, severe allergic reactions to plasma exchange leading to treatment discontinuation or relapse after initial successful therapy. In the period 2000 to 2008, 30 patients with an acute episode of non-familial idiopathic TTP were treated at the University Hospital of Cologne. Twelve patients receiving treatment with rituximab were identified and re-examined. Due to different pathophysiology, patients with TTP secondary to bone marrow transplantation, rheumatological diseases or active cancer were excluded.

In most cases, the treatment schedule consisted of rituximab at a dose of 375mg/m^2 per week for four consecutive weeks administered in parallel to daily plasma exchange, except for two patients with intolerance to plasma exchange after a total of 22 and 10 exchange procedures respectively, leading to plasma exchange therapy disruption. After application of rituximab, plasma exchange was interrupted for 24 hours. In general, plasma exchange was continued until clinical remission and platelet count above 150 x 10^9/l for longer than 48 hours.

At the time of initial TTP diagnosis, the median age of the 12 patients was 42.5 years, and 75% of patients were female. At presentation, the mean platelet count was decreased to 19.8 x 10^9/l and mean lactate dehydrogenase (LDH) was elevated to 1018U/l (reference <250U/l). All patients had plasma exchange with fresh frozen plasma and steroid treatment prior to rituximab, and four patients had been additionally treated with vincristine (2mg intravenous). Seven patients were treated during the first episode of acute TTP, among whom five received rituximab because of an insufficient response to standard therapy with plasma exchange: two patients suffered from severe allergic reaction leading to disruption of plasma exchange after 22 and 10 exchange procedures, respectively. Five patients received rituximab because of relapse after at least one prior episode of acute TTP initially successfully treated with standard therapy. Baseline characteristics of all patients are shown in *Table 1*. Due to assay availability, unfortunately only in a minority of patients, ADAMTS13 activity was analysed before initiation of rituximab therapy. After application of rituximab, no severe acute side effects were noted and all patients responded with complete remission. This is in line with previous data reporting acute response rates of >90%.[26,34]

After nearly 50 months follow-up, three of 12 patients had relapsed. Previous reports have estimated the relapse rate after rituximab at

Table 1: Follow-up of 12 Patients Treated with Rituximab by Authors

Case Number	Age (Years)	Sex	Prior TTP episodes	Reason for Rituximab Initiation	Number of Rituximab Applications 375mg/m^2	Follow-up (Months)	Relapse after Rituximab
1	57	Male	–	Allergy to PE	4	36	–
2	34	Female	–	Allergy to PE	4	40	–
3	36	Female	–	Refractory to PE	4	41	–
4	46	Female	3	Relapse	4	52	–
5	26	Female	1	Relapse	4	67	4
6	22	Male	1	Relapse	4	11	1
7	45	Male	3	Relapse	4	46	–
8	41	Female	–	Refractory to PE	4	46	–
9	72	Female	–	Refractory to PE	7	22	–
10	51	Female	–	Refractory to PE	4	67	–
11	44	Female	1	Relapse	4	70	–
12	36	Female	–	Refractory to PE	2	97	1

PE = plasma exchange; TTP = thrombotic thrombocytopenic purpura.

about 10%.[13,14,26] However, this data was based on a few patients with short follow-up, thus limiting the validity of the estimate. The higher relapse rate of 25% in our cohort is probably due to the longer follow-up period reported in the present study, and possibly reflects the gradual reversal of B-cell depletion and subsequent formation of new antibodies directed against ADAMTS13. Notably, from five patients suffering from partly frequent relapses before initiation of rituximab treatment, three have remained disease-free even after long-term follow-up. Only one patient relapsed after rituximab treatment during the initial TTP episode. All relapsing patients responded to subsequent rituximab therapy. Interestingly, the two patients treated with rituximab during the initial TTP episode, after stopping plasma exchange due to severe allergic reaction, had a sustained response without recurrence of TTP after a follow-up of 36 and 40 months. Both patients had not responded until the end of plasma exchange. Therefore, rituximab as a single agent is able to produce long-term remissions in TTP without continuous plasma exchange. However, the individual contribution of plasma exchange or rituximab to the treatment success remains open to question in the majority of patients. In two patients a maintenance therapy with rituximab was initiated consisting of 375mg/m^2 every four weeks. One patient remains disease-free with ongoing maintenance therapy, the other is in sustained complete remission despite the cancellation of maintenance therapy after three months.

Treatment of Further Relapse after Rituximab Treatment

Treatment decision-making in the case of further relapse after rituximab is difficult and not evidence-based. Rituximab has been used as pre-emptive treatment in patients with anti-ADAMTS13 auto-antibodies,[38] and rituximab maintenance may be an option in these patients. However, this has to be weighed against potential long-term side effects, such as progressive multifocal leucoencephalopathy.[39] An alternative treatment would be a splenectomy, which is supported by data provided by Kappers-Klunne et al.[40] Thirty-three patients with TTP were retrospectively reported who were splectomised due to refractory or relapsing disease. After median follow-up of 109 months the 10-year relapse-free survival was 70%. As these data were generated without rituximab being a treatment alternative, one has to balance the risks of the operation procedure, post-operative complications and infectious complications post-splenectomy against the consequences of long-term B-cell depletion during rituximab maintenance therapy.

Safety Considerations

In our patient collective, no treatment-related, especially infectious, complications were reported. In all but two patients, B-cell counts had recovered at the end of follow-up, and one of these two patients is currently treated with rituximab maintenance therapy. This is congruent with previous reports using rituximab in relapsing or refractory TTP. Rituximab is usually well tolerated and acute reactions are usually mild without causing discontinuation of the drug.[33] Infusion-related hypersensitivity adverse events including fever and hypotension are in most cases seen during the first infusion and mostly controlled with pre-medication and by slowing or temporary interruption of the infusion. However, rarely, potentially life-threatening complications have been reported. Progressive multifocal leukencephalopathy, a mostly fatal infection caused by the JC virus was described in lymphoma patients pre-treated with rituximab as well as in rare cases of immune-mediated disorders following rituximab treatment.[41] Other viral infections, such as reactivation of cytomegalovirus[42] or hepatitis B[43] are more frequently reported. Cardiovascular events, delayed interstitial pneumonitis[44] and renal toxicity were also described following rituximab treatment. Especially when considering rituximab maintenance in frequently relapsing patients it is necessary to balance the risks and benefits of different treatment options. The risk of long-term B-cell depletion and the associated risk of potential infectious complications need to be weighed against the risks of complications associated with therapeutic plasma exchange including catheter thrombosis, infection of the venous access and transfusion reactions. The Oklahoma Registry group reports a 26% risk per patient for major complications of plasma exchange including a 2.8% fatality rate.[45]

Conclusion

Currently, data on rituximab treatment in refractory or relapsing TTP are based on case reports or smaller case series. Questions remain, such as timing of initiation of rituximab treatment, duration of treatment and treatment schedule and the schedule of concomitant therapeutic plasma exchange. With these limitations in mind, it appears that rituximab is an effective second-line treatment option for patients with idiopathic TTP, with some patients achieving sustained responses even after long-term follow-up. Prospective multicentre studies are required to determine whether rituximab can be safely used just as salvage therapy or even initially in addition to plasma exchange to decrease the relapse rate after first-line treatment.[46,47] ■

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