Sustained response with rituximab in patients with thrombotic thrombocytopenic purpura: A report of 13 cases and review of the literature

Huichung T. Ling,1 Joshua J. Field,1 and Morey A. Blinder1,2,*

Idiopathic thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease mediated by autoantibodies directed against ADAMTS-13. A number of small series and case reports have shown promising results with rituximab in refractory or relapsed TTP. In this report, we present 13 patients with TTP treated with rituximab. Twelve of the 13 patients (92%) achieved complete response; no subsequent relapses occurred with median follow-up of 24 months (range, 13–84 months). The addition of rituximab to standard therapy appears to be effective in sustaining long-term remission in TTP. However, the optimal dosing and timing of rituximab warrant further investigation. Am. J. Hematol. 84:418–421, 2009. © 2009 Wiley-Liss, Inc.

Introduction
Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease characterized by thrombocytopenia and microangiopathic hemolytic anemia, in addition to clinical features such as fever, neurological symptoms, and renal failure. The introduction of plasmapheresis has increased survival in patients with TTP from less than 10% to ~80% [1]. However, a small portion of patients remain refractory to plasmapheresis, and up to a third of patients experience subsequent relapses [2]. Most cases of idiopathic TTP are found to be mediated by autoantibodies against ADAMTS-13, a protease that cleaves von Willebrand factor thus limiting the thrombus growth [3]. The discovery of the autoimmune nature of TTP has led to renewed interest in immunosuppressive therapy. Rituximab has demonstrated promising results in a number of small series and case reports [4–18]. However, prior studies have limited follow-up and lack consistency in treatment regimen. In this report, we present 13 patients with TTP treated with rituximab who had an unsatisfactory response to standard therapy.

Results
Of the 13 patients treated with rituximab, six patients presented during their first TTP episode while seven patients had relapse of their TTP (Table I). Among the relapsed individuals, the median duration from their prior episode was 4 years (range, 4 months–5 years). Nine of the 13 patients were female; 10 of the 13 patients were African-American. The median age was 42 years old (range, 23–71).

During this current TTP episode, five patients presented with a neurological complaint, five patients complained of abdominal pain or vomiting, one had chest pain, and one presented with generalized weakness. One patient was asymptomatic and received rituximab for chronic TTP with inability to wean off plasmapheresis. Five of the 13 patients also had evidence of acute renal failure. The mean laboratory parameters on presentation were hematocrit 25.7%, platelets 22 × 10^9/L, and LDH 1318 IU/L.

After the addition of rituximab, 12 of the 13 patients (92%) achieved complete hematological and clinical remission. Of the responders, only one required additional plasmapheresis after completion of rituximab. No major adverse events due to rituximab were noted. All of the 12 patients who responded to rituximab remained in sustained remission with no further relapses with median follow-up of 24 months (range, 13–84 months).

All 13 patients had documented ADAMTS-13 deficiency. Twelve patients showed severely decreased activity (<10%) with detectable inhibitor level prior to rituximab. Of the eight patients with available ADAMTS-13 data postrituximab treatment, seven patients had recovery of their ADAMTS-13 activity with resolution of detectable inhibitor. One patient did not respond to rituximab (Table I, case 13). This patient was diagnosed with TTP at age 21 who responded to plasmapheresis and steroids. She relapsed after 4.5 years but this time remained refractory despite plasmapheresis, steroids, vincristine, and rituximab; she subsequently died of bleeding complications. Because of concern about possible removal of rituximab with ongoing plasmapheresis, flow cytometry was performed which demonstrated depletion of CD20+ B-cells from her circulation indicating the efficacy of rituximab (data not shown). Of note, she had a high titer of ADAMTS-13 inhibitor prior to rituximab that improved with treatment. However, her ADAMTS-13 activity remained undetectable during her relapse.

Discussion
Rituximab is a chimeric monoclonal antibody against CD20 that depletes B-cells in the circulation and lymphoid tissues. Current FDA-approved indications include treatment of non-Hodgkin lymphoma (NHL) and rheumatoid arthritis. Rituximab has also been used with variable success in several autoimmune diseases. For instance, published studies have demonstrated an ~50% response rate in refractory/relapsed ITP and in autoimmune hemolytic anemia; however, the response duration is variable ranging from 2 weeks to 95 months [19]. In acquired hemophilia, the

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Conflict of interest: Nothing to report.

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<td>&lt;5%</td>
<td>&lt;4%</td>
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ADAMTS-13 activity reference range >67%; ADAMTS-13 inhibitor reference range <0.4 inhibitor unit.
AAF, African-American female; AAM, African-American male; AMS, altered mental status; ARF, acute renal failure; C, cytotoxic agents (vincristine or cyclophosphamide); CTD-NOS, connective tissue disease not otherwise specified; ITP, idiopathic thrombocytopenic purpura; MCTD, mixed connective tissue disease; NA, not available; NR, no response; NSIP, nonspecific interstitial pneumonitis; P, prednisone; PP, plasmapheresis; R, rituximab; S, splenectomy; WF, white female; WM, white male.

a Case 12 was previously reported (Ref. 6); she received an abbreviated course of rituximab (2 doses) during a prior relapse.
b Number of PP before initiation and completion of 4-week course of rituximab.
c Inhibitor levels not indicated when ADAMTS-13 activity >30%.
pooled response rate is as high as 86% with follow-up of 2 weeks to 41 months [5]. In contrast, preliminary observations have failed to show a significant clinical response with rituximab in systemic lupus erythematosus and multiple sclerosis. The reason behind this variable response is not well understood. One postulation is that autoantibodies have various degree of pathogenicity in different autoimmune disorders, and hence the depletion of B-cells alone may not be the entire answer [20]. Another possible explanation is that in those diseases where immunosuppressive agents are heavily used, there is down-regulation of the CD20 receptor which leads to decreased efficacy of rituximab.

Of our 13 TTP patients treated with rituximab, 12 achieved complete and sustained remission with median follow-up of 24 months (range, 13–84 months). Our response rate was 92%, which is comparable to the 95% reported in the literature [3]. None of our patients relapsed, which is similar to the low relapse rate of ~10% based on previous studies including many patients with a short follow-up [3]. In contrast, the relapse rate for plasmapheresis alone is as high as 37% [2]. Most of our patients also had severe ADAMTS-13 deficiency with detectable inhibitor, which has been associated with a more complicated clinical course and increased risk of relapse [21,22]. Therefore, rituximab appears to be a reasonable therapeutic option in patients with TTP who had an unsatisfactory response to standard therapy.

A review of the literature identified 12 articles with 42 cases of refractory or relapsed idiopathic TTP treated with rituximab that had more than 1-year follow-up (Table II). ADAMTS-13 activity pre-rituximab treatment was severely decreased (<10%) in 29 of the 37 patients with available ADAMTS-13 data. The course of rituximab varied between patients, ranging from 1 to 13 weekly doses at 375 mg/m². Thirty-eight of the 42 patients (90%) achieved complete remission with median response duration of 23.5 months (range, 13–79 months). Of the 38 patients who responded to rituximab, subsequent relapses occurred in eight patients (21%) after 13 to 46 months. As in our study, no early relapses were observed. Of the eight relapsed patients, five responded to a repeat course of rituximab, two died during relapse, and one was lost to follow-up.

Despite the apparent clinical benefit, many questions remain to be answered regarding the use of rituximab in idiopathic TTP. One unresolved issue is the dosage of rituximab. The current dose of 375 mg/m² administered weekly is based on experience with the treatment of NHL. However, there are some data to suggest that a lower dose may be as effective because the CD20+ B-cell burden is much lower than NHL [23]. Courses ranging from 1 to 13 doses have been used in the reported series, with 4 doses being the most common. In those patients who did not respond, it is unclear whether a longer course of rituximab would have induced remission. Another key question is when to incorporate rituximab into the therapeutic regimen of TTP. Currently, it is primarily used as a salvage therapy for chronic, refractory, or relapsed cases. However, in patients with severe ADAMTS-13 deficiency due to an inhibitor, early addition of rituximab during the course may be beneficial in decreasing the need for plasmapheresis and sustaining long-term remission. There may also be a role for rituximab during remission as a maintenance therapy. Another common concern is whether ongoing plasmapheresis removes rituximab from the blood. Although limited to one patient, our data suggests that CD20+ B-cell depletion occurs despite ongoing plasmapheresis. The binding of rituximab to CD20 receptor may be protective against its removal from the circulation.

In summary, the addition of rituximab to standard therapy for TTP has shown long-term efficacy in patients who had an unsatisfactory response to standard therapy either during the initial course of treatment or during relapse. However, confirmation of this finding would require a large prospective study. A multicentered randomized control trial has been proposed to evaluate whether the addition of rituximab to standard therapy decreases early treatment failure and the frequency of subsequent relapses [4]. In the interim, the role of rituximab in the treatment of TTP will continue to evolve.

### Methods

We reviewed all the patients with idiopathic TTP treated with rituximab at Barnes-Jewish Hospital/Washington University; 13 cases were identified from 2001 to 2007. The diagnosis of TTP was based on the clinical criteria irrespective of ADAMTS-13 status. Samples for ADAMTS-13 testing were collected immediately before the first plasmapheresis and again after 3–6 months as stable outpatient; assays were performed at the Blood Center of Wisconsin. The decision to initiate rituximab was made by the hematology service in patients with either refractory disease to standard therapy or patients with history of one or more relapses. Patients with an unsatisfactory response to standard therapy either during the initial course of treatment or during relapse. However, confirmation of this finding would require a large prospective study. A multicentered randomized control trial has been proposed to evaluate whether the addition of rituximab to standard therapy decreases early treatment failure and the frequency of subsequent relapses [4]. In the interim, the role of rituximab in the treatment of TTP will continue to evolve.
tion of symptoms, normalization of platelet count (>150 × 10^9/L), and cessation of all therapy. All the patients were followed in the hematology clinic at Washington University monthly for the first 6 months then yearly thereafter.

References