Review Article

The efficacy of rituximab in the treatment of inhibitor-associated hemostatic disorders

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Summary

Rituximab is a chimeric anti-CD20 monoclonal antibody active against normal and malignant B cells which has proven to be effective in the therapy of CD-20 positive lymphomas. Its B-cell cytotoxic action has also been exploited in many non-malignant autoimmune disorders in which it has been used with the aim of interfering with the production of pathologic antibodies. The present knowledge regarding the use of rituximab in antibody-associated disorders of hemostasis (i.e. idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, acquired hemophilia A, congenital hemophilia with inhibitors, acquired inhibitors against coagulation factors) is presented briefly in this review. The results suggest that rituximab can be useful in the treatment of disorders of hemostasis associated with inhibitor formation. Although collectively the number of patients treated is now quite substantial, most of the data are drawn from isolated case reports or descriptions of small, uncontrolled series. Large, prospective, randomized trials are, therefore, needed to confirm the positive, preliminary results.

Keywords

Rituximab, inhibitor, coagulation disorders

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Introduction

Rituximab is a chimeric monoclonal antibody against CD20, a transmembrane protein present on the surface of essentially all B cells but not on mature plasma cells. This monoclonal antibody, which depletes B cells in the circulation and lymphoid tissues, has demonstrated efficacy in the treatment of CD20-positive lymphoproliferative disorders (1). Recent preliminary studies have indicated that this agent may also be effective in a number of autoantibody-mediated diseases such as thrombotic thrombocytopenic purpura (2), systemic lupus erythematosus (3), rheumatoid arthritis (4), autoimmune hemolytic anemia (5–7), cryoglobulin disease (8, 9), acquired factor VIII antibodies (10), IgM polyneuropathies (11), glomerulonephropathies (12), and immune thrombocytopenic purpura (ITP) (13). Rituximab has also been used with success to induce immune tolerance in congenital hemophiliacs with alloantibodies against factor VIII and IX (14).

Based on a literature search, including PubMed, references from reviews and abstracts from the most important meetings on this topic, we present an overview of the current knowledge on rituximab therapy in disorders of hemostasis associated with inhibitor development.

Rituximab for the treatment of immune thrombocytopenic purpura

There are several reports on the successful use of rituximab, at the same dosage as that used for the treatment of lymphoma (375 mg/m^2 weekly for four weeks intravenously), as second-line therapy for patients with ITP (15–36). However, most of these are only anecdotal case reports. The first study involving a consistent number of patients was published in 2001 by Stasi and colleagues (19), who treated 25 patients with ITP resistant to two to five other therapeutic options with rituximab 375 mg/m^2 weekly for four weeks. Five patients showed a complete response and five others had a partial response. In seven of these patients the responses were sustained for over six months. However, in two patients with relapsed disease, repeat treatment with rituximab induced a new response. There was a suggestion that younger patients were more likely to respond. Interestingly, in a subsequent report of another seven cases (20), the authors identified two patterns of response: an early response in which the platelet count increase was seen after the first or second antibody infusion and a late response in which the rise in the platelet count was not observed during rituximab administration but only at

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weeks six to eight. As all of these patients had received previous courses of immunoglobulins, the authors hypothesized Fc receptor blockade of the macrophage system by the opsonized B cells. Zaja et al. (6) used rituximab to treat 20 patients with relapsed ITP or ITP refractory to standard therapies and obtained nine complete and four partial responses. After a median follow-up of 180 days, four patients had relapsed. More recently, Cooper et al. (28) treated 57 adults with chronic resistant ITP and observed a sustained response in 32% of them. The authors commented that rituximab compared favourably with other second-line therapies because of its lack of toxicity: indeed, all patients completed the treatment. Vesely et al. (37) recently published a systematic review on the management of adult patients with persistent idiopathic thrombocytopenic purpura following splenectomy and identified azathioprine, cyclophosphamide and rituximab as the three drugs giving the highest rate of complete responses (17–27%). There is also some evidence of the effectiveness of rituximab in refractory childhood ITP (23, 29, 32, 33). In a retrospective study of rituximab therapy in children with severe chronic ITP, 15 of 24 patients (63%) achieved a stable platelet count (>150 x 10^9/l) for four to 30 months without additional therapy (33). The largest study on rituximab in childhood chronic ITP is that recently conducted by Bennet et al. (29). In their prospective phase I/II study, the authors assessed the safety and efficacy of rituximab in 36 young ITP patients and found a good tolerability with a sustained response in 11 (31%) of the children. The clinical course of the published ITP cases treated with rituximab as a second-line therapy is reported in Table 1. As can be seen, sustained complete or partial responses were obtained in 39% of treated patients, a rate which appears to be among the best achieved by second line therapies. Based on these encouraging results, some experts are now advocating the use of rituximab as a first-line therapy for adults with ITP (38, 39). However, it should be emphasized that most of the above mentioned studies were uncontrolled and included small series of patients. Moreover, in some cases, concomitant immunosuppressive treatment was given, thus confounding an analysis of the real effectiveness of rituximab. In conclusion, in our opinion, prospective, randomized trials with large numbers of patients and an adequate follow-up are needed before this therapeutic option can be recommended for ITP patients at diagnosis.

Rituximab for the treatment of thrombotic thrombocytopenic purpura (TTP)

TTP is a relatively uncommon but serious disease characterized by the development of von Willebrand factor (VWF)-platelet rich hyaline thrombi in the arterioles and capillaries affecting the brain, heart, pancreas, kidney and other organs (40). Recent studies have demonstrated that a subset of thrombotic microangiopathic hemolytic anemias is associated with severe defi-

Table 1: Results of the largest published studies on second-line treatment with rituximab of patients with idiopathic thrombocytopenic purpura.

Author	Year	Reference	Patients treated	Age years	Sex M/F	Response[a] n (%)	Relapse n (%)	Patients in CR n (%)	Follow-up months
Perotta *et al.*	1999	15	10	NI	1/9	6/10 (60)	2/6 (33)	6/10 (60)[b]	1–14
Grossi *et al.*	2000	16	5	NI	NI	1/5 (20)	0/1 -	1/5 (20)	6
Saleh *et al.*	2000	17	13	21–77	5/8	3/13 (23)	0/3 -	3/13 (23)	3–6
Stasi *et al.*	2001	19	25	22–74	9/16	13/25 (52)	6/13 (46)	9/25 (36)[c]	6–27
Stasi *et al.*	2002	20	7	20–66	1/6	5/7 (71)	0/5 -	5/7 (71)	2–12
Giagounidis *et al.*	2002	21	12	28–71	5/7	9/12 (75)	2/9 (22)	9/12 (75)[d]	6–15
Zaja *et al.*	2003	13	20	16–76	5/15	13/20 (65)	4/13 (31)	9/20 (45)	2–16
Shanafelt *et al.*	2003	22	12	22–79	8/4	6/12 (50)	1/6 (17)	5/12 (42)	1–11
Braendstrup *et al.*	2003	24	35	17–82	17/18	17/39[e] (44)	0/17 -	17/39 (44)	47
Shenov *et al.*	2003	25	20	3–18	NI	14/20 (70)	0/14 -	14/20 (70)	1–20
Wiley *et al.*	2003	26	19	3–19	8/11	15/19 (79)	9/15 (60)	6/19 (32)	1–27
Cooper *et al.*	2004	28	57	21–79	18/39	31/57 (55)	13/31 (42)	18/57 (32)	6–41
Narat *et al.*	2005	30	6	19–74	4/2	5/6 (83)	0/6 -	5/6 (83)	2.5–20
Taube *et al.*	2005	31	22	2–15	8/14	13/22 (59)	5/13 (38)	8/22 (36)	NI
Bennet *et al.*	2005	32	36	2–18	21/15	11/36 (31)	0/11 -	11/36 (31)	NI
Wang J *et al.*	2005	33	24	2–19	10/14	17/24 (71)	8/17 (47)	9/24 (38)	4–30
Garcia-Chavez *et al.*	2005	34	14	17–70	NI	13/14 (93)	3/13 (23)	10/14 (71)	NI
Ahn *et al.*	2005	35	12	22–87	3/9	10/12 (83)	0/10 -	10/12 (83)	4–29
Case *et al.*	2005	36	22	24–83	5/17	13/22 (59)	1/13 (8)	12/22 (54)	2–48
Total			371			215/375 (25)	54/215 (25)	167/375 (44)	

M = males; F = females; CR = continuous remission ; NI = not indicated.
[a]Complete or partial response. Complete response was defined as a platelet count ≥100 x 10^9/L in absence of concomitant steroid therapy. A partial response was defined as a platelet level ≥50 x 10^9/L in absence of concomitant steroid therapy.
[b]Two patients relapsed but retreatment resulted in a new, durable response.
[c]In two patients with relapsed disease, repeat treatment with rituximab induced a new response.
[d]Two patients who relapsed after initially successful rituximab therapy, were retreated with rituximab and achieved a new CR.
[e]Since four patients were treated twice, 39 outcomes were evaluated.

ciency of the VWF-cleaving protease ADAMTS13 (41). Although mutations in the ADAMTS13 gene have been implicated in hereditary forms of TTP, more frequently the deficiency of the ADAMTS13 enzyme is acquired as the result of the development of an autoantibody against this protease. Given the autoimmune cause of this disease, many investigators have tested the effects of immunosuppressive therapies in association with the standard therapeutic approach of plasma exchange (42). Based on the positive results in other autoimmune diseases, rituximab has been employed in some patients with refractory TTP and several recent studies have documented the effectiveness of this agent in terms of increasing ADAMTS13 activity, eradicating the inhibitor and improving clinical parameters (43–63).

Sallah et al. (49) described three patients with refractory TTP and severely deficient ADAMTS13 activity secondary to an antibody inhibitor who achieved remission after the addition of rituximab to plasma exchange. ADAMTS13 activity normalized a median of 35 days after the first dose of rituximab and this normalization coincided with suppression of the inhibitor. Yomtovian et al. (47) reported similar findings in a patient with relapsing TTP who was able to become independent of plasma exchange after treatment with rituximab. This patient had some suppression of the inhibitor and an increase in ADAMTS13 activity, although during long-term remission ADAMTS13 activity remained subnormal and inhibitors detectable. Reddy et al. (53) treated five patients with relapsed TTP by adding rituximab to plasma exchange. Four of the five patients with documented inhibitors and decreased ADAMTS13 activity prior to therapy had suppression of inhibitors and normalization of ADAMTS13 activity after treatment with rituximab.

Table 2 summarizes the recent literature data on the use of rituximab in TTP. Interestingly, Fakhouri et al. (52), who studied six cases of TTP in the acute phase and five in remission, found that rituximab was effective not only in inducing a clinical remission in active cases but also in preventing relapses by restoring significant ADAMTS13 plasma activity (> 10%). Similar results were obtained by Galbusera et al. (55) in a patient with recurrent TTP. As a cautionary note, Millward et al. (54) described a patient in whom the successful treatment of rituximab was complicated by cardiogenic shock. Thus, these authors advised a particularly careful assessment of risks and benefits before using rituximab in patients with TTP. Nevertheless, from the data presented in Table 2, it is clear that rituximab is potentially very useful in the treatment of refractory TTP as well as in the chronic relapsing form of the disease. More data are needed to evaluate the long-term effectiveness of this therapy targeting antibody inhibitors of ADAMTS13.

Rituximab for the treatment of acquired hemophilia A

Acquired hemophilia A is a rare but often severe bleeding diathesis caused by the spontaneous development of autoantibodies against coagulation factor VIII (10). Treatment strategies in patients with acquired hemophilia have two major objectives: i) ef-

Table 2: Results of the published studies on rituximab treatment in patients with thrombotic thrombocytopenic purpura.

Authors	Year	Reference	Patients treated	Age years	Sex M/F	Rituximab doses 375 mg/m^2	Clinical remission[a] n (%)	Follow-up months
Gutterman *et al.*	2002	43	3	40–54	0/3	4–8	2/3 (67)	17–36
Chemnitz *et al.*	2002	44	2	37–39	0/2	2–4	2/2 (100)	2–12
Zheng *et al.*	2003	45	1	42	0/1	6	1/1 -	10
Tsai *et al.*	2003	46	1	36	0/1	8	1/1 -	24
Yomtovian *et al.*	2004	47	1	31	0/1	8	1/1 -	15
Ahmad *et al.*	2004	48	4	57–61	2/2	2–4	3/4[b] (75)	6–13
Sallah *et al.*	2004	49	5	25–52	NI	4	4/5 (80)	9–13
Stein *et al.*	2004	50	1	37	0/1	4	1/1 -	6
Fakhouri *et al.*	2005	52	11	21–60	6/5	4	6/6[c] (100)	6–11
Reddy *et al.*	2005	53	5	27–70	2/3	4	5/5 (100)	10–21
Millward *et al.*	2005	54	1	20	0/1	1	1/1 -	9
Alcaraz *et al.*	2005	56	3	21–35	0/3	6	3/3 (100)	9–33
Bortolheiro *et al.*	2005	57	1	NI	0/1	NI	1/1 -	11
Giuffrida *et al.*	2005	58	1	50	0/1	4	1/1 -	6
Scully *et al.*	2005	59	11	NI	3/11	2–8	11/11 (100)	1–27
Scott *et al.*	2005	60	1	21	0/1	4	1/1 -	5
Koulova *et al.*	2005	61	2	40–45	2/0	4–5	2/2 (100)	5–11
Kosugi *et al.*	2005	62	1	69	1/0	4	1/1 -	7
Gianfaldoni *et al.*	2005	63	1	58	1/0	11[d]	1/1[d]	NI
Total			56				48/51 (94)	

M = males; F = females; CR = clinical remission ; NI = not indicated.
[a]Defined as normal platelet count, stable hemoglobin level, and no symptoms or signs potentially caused by TTP.
[b]One responder relapsed after 13 months; a second course of rituximab and prednisone resulted in an unmaintained complete remission (follow up 6 months).
[c]Five patients received rituximab prophylactically during remission.
[d]This patient relapsed one year after the first course of rituximab (4 infusions) and was retreated (7 infusions), achieving a new clinical remission.

Table 3: Results of the published studies on the treatment with rituximab of patients with acquired hemophilia A.

Authors	Year	Reference	Patients treated	Age years	Sex M/F	Inhibitor titer BU/mL	Rituximab doses 375 mg/m^2	Response[a] n (%)	Follow-up months
Karwal *et al.*	2001	65,66	4	73–79	2/2	19–525	4	2/3[b] (67)	0.5–13
Wiestner *et al.*	2002	67	4	38–79	3/1	5–60	2–4	4/4 (100)	7–12
Kain *et al.*	2002	68	1	28	1/0	268	4	1/1 -	24
Fischer *et al.*	2003	69	1	71	1/0	633	2	0/1 -	-
Marietta *et al.*	2003	70	1	71	0/1	2.3	3	0/1 -	-
Jy *et al.*	2003	71	1	81	0/1	400	4	1/1[c] -	6
Low *et al.*	2003	72	1	32	0/1	600	11	1/1 -	3
Mazj *et al.*	2003	73	4	24–70	1/3	2–34	2–4	4/4 (100)	1–12
Stasi *et al.*	2004	74	10	27–78	5/5	4–250	4–8	10/10[d] (100)	12–41
Grimley *et al.*	2004	75	2	31–83	0/2	10–16	4	2/2 (100)	3–4
Riess *et al.*	2004	76	2	60–72	0/2	38–40	4	2/2 (100)	14–24
Krause *et al.*	2005	77	4	70–81	2/2	9–156	4	4/4 (100)	NI
Abdallah *et al.*	2005	78	2	47–80	0/2	5–148	4	2/2 (100)	18–30
Aggarwal *et al.*	2005	79	4	60–81	2/2	7–525	4–8	4/4[e] (100)	3.5–10
Holme *et al.*	2005	80	2	64–94	1/1	42–1350	4	1/2 (50)	3
Maruscak *et al.*	2005	81	1	59	1/0	108	12	1/1 -	21
Fiedl *et al.*	2005	82	4	40–71	1/3	249–836	4	1/4 (25)	19
Hut-Kuhne *et al.*	2005	83	2	47–70	0/2	1.6–3.6	4	2/2 (100)	NI
Total			50					42/49 (86)	

M = males; F = females; BU = Bethesda Units; NI = not indicated.
[a]Complete or partial response. A complete response was defined as the attainment of a normal factor VIII level and an inhibitor level of < 1 BU/ml and a partial response was defined as a decrease of at least 50% in inhibitor titer with a factor VIII level of at least 25% and no further bleeding.
[b]Three patients were valuable.
[c]The patient obtained a partial remission with persistence of a low-titer inhibitor but without clinical bleeding.
[d]Three relapsed patients obtained a new sustained response with rituximab at the same dosage. Two high-titer inhibitor patients not responding to rituximab alone, achieved a completer remission after rituximab plus cyclophosphamide.
[e]Both relapsed patients responded to a second course of rituximab and prednisone.

fective control of acute bleeding through bypassing agents (activated prothrombin complex concentrates [APCC] and recombinant factor VII activated [rFVIIa]), and ii) long-term eradication of inhibitors by using immunosuppressive treatments (64). Rituximab has recently been employed for the latter objective (65–83). Wiestner et al. (67) reported the cases of four patients with acquired factor VIII high-titer inhibitors who obtained rapid and sustained responses following immunosuppressive regimens including prednisone and rituximab. In 2004, Stasi et al. (74) reported the largest series of patients so far. Rituximab was given intravenously at the dose of 375 mg/m^2 once weekly for four consecutive weeks. Eight patients with an inhibitor titer less than 100 Bethesda units (BU)/ml achieved a complete response. Three relapsed patients obtained a new sustained response with retreatment with rituximab at the same dosage. The remaining two patients with inhibitor titers higher than 100 BU/ml experienced only a partial and transient decrease of the inhibitor following rituximab, but they obtained a complete and sustained response to combination therapy with rituximab plus pulsed intravenous cyclophosphamide. Similar results were recently observed by Aggarwal et al. (79) in four patients with autoimmune hemophilia treated with rituximab and prednisone. All four patients responded: complete sustained responses were obtained in two while the other two relapsed but then both responded to second courses of rituximab and prednisone. Similar positive experiences on few patients have been reported by other investigators. Table 3 summarizes the published data. Once again it should be emphasized that most of the reports are isolated cases and, as positive outcomes may be preferentially reported, there may be a bias in these data. Furthermore, an analysis of the literature data reveals a dearth of cases treated with rituximab as a single eradicating agent, since most patients received concomitant immunosuppressive regimens. However, it appears that patients with high titers can respond to treatment with rituximab, although the responses may be only partial or require a long time to become complete. A complete and sustained response may be obtained in such patients by increasing the number of doses of rituximab (72) or by adding immunosuppressive therapy to rituximab (74). In the light of these results, Aggarwal et al. (79) proposed a treatment algorithm for acquired hemophilia A, according to which patients with a low inhibitor titer (< 5 BU/ml) and minimal bleeding should be treated only with prednisone, while patients with higher inhibitor titers should also receive rituximab (if their titer is < 30 BU/ml or there is serious bleeding) or rituximab plus cyclophosphamide (if their titer is ≥ 30 BU/ml). In our opinion this approach is reasonable as it should accelerate patients' responses and produce more favorable outcomes.

Rituximab in congenital hemophilia with high titer inhibitors

The development of inhibitors in patients with hemophilia A is a serious complication associated with increased morbidity and

Table 4: Published studies on the use of rituximab in congenital hemophilia with high titer inhibitors.

Authors	Year	Reference	Patients treated	Age years	Diagnosis	Rituximab doses 375 m/m^2	Response[a] n (%)	Relapse n (%)	Patients in CR n (%)	Follow-up months
Linde *et al.*	2001	85,86	1	14	1 SHA	7	1/1 -	1/1 -	0/1 -	13
Medeiros *et al.*	2002	87	1	41	1 MHA	5	1/1 -	0/1 -	1/1 -	4
Escobar *et al.*	2002	88	1	58	1 MHA	4	1/1 -	0/1 -	1/1 -	3
Mathias *et al.*	2004	14	2	11–13	1 SHA, 1 SHB	4	1/2 (50)	0/1 -	1/2 (50)	11
Curtin *et al.*	2004	89	4	1.2–15	4 SHA	4–10	3/4 (75)	0/3 -	3/4 (75)	3–12
Pruthi *et al.*	2005	90	2	19–66	1 SHA, 1 HAM	5	1/2 (50)	0/1 -	1/2 (50)	15
Dunkley *et al.*	2005	91	1	51	1 HAM	4	1/1 -	0/1 -	1/1 -	NI
Carcao *et al.*	2006	92	5	6–65	4 SHA, 1 HAM	4–8	3/5 (60)	0/3 -	3/5 (60)	11–24
Moschovi *et al.*	2006	93	2	5–15	2 SHA	4	1/2 (50)	0/1 -	1/2 (50)	20
Total			19				13/19 (68)	1/13 (8)	12/19 (63)	

M = males; F = females; NI = not indicated; HA = hemophilia A; SHA = severe hemophilia A; HB = hemophilia B; SHB = severe hemophilia B; MHA = moderate hemophilia A; HAM = mild hemophilia A.
[a]Complete or partial response. According to Carcao and colleagues[92] a partial response (PR) was defined as post-rituximab inhibitor negativization and a complete response (CR) was defined as PR + normal recovery and normal factor VIII half-life.

mortality. Among the several therapeutic modalities used for treating inhibitors in hemophilia A patients (high doses of human factor VIII, porcine factor VIII, bypassing agents such as APCC and rFVIIa) only immune tolerance therapy (ITT) has been proven to eradicate the inhibitor in 60–80% of patients (84). Various ITT regimens have been used, differing according to the dose and frequency of factor VIII infusion and whether immunosuppressive agents are included. However, in the last few years, investigators have tested other less conventional ITT regimens designed in order to reduce the potentially toxic effects of the chemotherapeutic agents used (cyclophosphamide, vincristine, corticosteroids, etc.), also taking into consideration that most patients with inhibitors are children. The experience with rituximab in patients with congenital hemophilia and inhibitors is limited to only a few case reports and case series (Table 4) (85–93) and the rituximab was usually only given after several courses of conventional ITT had failed. Most of the patients described have not been followed for a sufficiently long period of time to draw conclusions regarding the long-term effect of this agent in eradicating inhibitors in congenital hemophiliacs. The largest series is that recently reported by Carcao et al. (92). In their five cases rituximab, in combination with concurrent daily factor VIII infusions, appeared to be beneficial in four of the five cases, reducing (one case) or eradicating (three cases) inhibitors. The only patient who did not experience any drop in inhibitor titer was treated with rituximab alone. On the basis of their own experience and the existing literature data, the authors hypothesized that the use of rituximab may be indicated for all patients with high titer inhibitors in order to reduce the inhibitor titer rapidly prior to starting conventional ITT, thus improving the chance of successful inhibitor eradication.

Rituximab for the treatment of other inhibitor-associated hemorrhagic disorders

Due to the rarity of other inhibitor-associated hemorrhagic disorders, few reports are available on the use of rituximab in such diseases (60, 61). On the whole, these reports testify to the positive effect of rituximab in antibody-mediated hemorrhagic disorders. Lian et al. (94) reported the case of a 43-year- old female who developed a factor V inhibitor associated with liver transplantation. As an initial course of high dose immuno-globulin was ineffective, rituximab therapy was started. The patient responded partially to four weekly doses of rituximab, and when an additional six doses were given, the factor V inhibitor was eradicated. Miesbach (95) reported the case of a 77-year-old woman with an antibiotic-associated factor XIII inhibitor in whom treatment with rituximab was followed by a marked increase in factor XIII activity.

Conclusions

There are increasing data in the literature regarding the effectiveness of rituximab as second-line treatment for patients with acquired or inherited hemostatic disorders associated with inhibitor development. Approximately one third of patients with autoimmune thrombocytopenia who are resistant to standard therapy have been shown to respond to rituximab. The promising results obtained in ITP have led to the use of rituximab in several other disorders in which a pathogenic role for autoantibodies has been demonstrated, such as TTP, acquired hemophilia A and other autoantibody-associated hemorrhagic disorders. Finally, recent observations suggest that rituximab may be useful in eradicating inhibitors also in congenital hemophiliacs, especially when administered concomitantly with factor VIII as immune tolerance treatment.

In conclusion, this analysis of the literature reveals the potential benefit of rituximab in inhibitor-associated hemorrhagic disorders, although most of the data should be interpreted cautiously as they are drawn from case reports or small series of patients followed for only short periods of time. The risk of a reporting bias in this context is obviously high. Thus, long-term, multicenter, prospective randomized trials are now needed in order to determine the real role of rituximab in the treatment of inhibitor-related hemostatic disorders.

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