

Rituximab for the treatment of acquired antibodies to factor VIII

Wolfgang R. Sperr, Klaus Lechner, Ingrid Pabinger

From the Department of Medicine I, Division of Haematology & Haemostaseology, Medical University Vienna, Austria.

Acknowledgments: we would like to thank Drs. Stasi, Aggarwal, Leahy, Abdallah, Holme, Ahn and Krause for providing follow-up data on their patients. We thank Miss Yen-An Chen for skillful assistance in the preparation of the manuscript.

Manuscript received July 19, 2006. Accepted November 7, 2006.

Correspondence: Wolfgang R. Sperr, MD, Department of Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Austria. A-1090 Waehringer Guertel 18-20, Vienna, Austria. E-mail: wolfgang.r.sperr@meduniwien.ac.at

ABSTRACT

Background and Objectives

Rituximab, a monoclonal chimeric antibody to the CD20 antigen, is an effective therapy for the treatment of non-Hodgkin's lymphomas. Moreover, rituximab has also shown to be effective in various autoimmune diseases including spontaneous antibodies to factor VIII. The aim of this study was to assess the efficacy of rituximab treatment of spontaneous inhibitors to factor VIII.

Design and Methods

We studied the efficacy of rituximab by analyzing the data of 42 previously published cases as well as one so far unpublished case. For comparison, we also analyzed 44 patients treated with cyclophosphamide/prednisone reported in the literature.

Results

Treatment with rituximab resulted in an overall rate of complete remission (CR) of 78.6%. Similar results were found when analyzing patients who had (75%) or had not (77%) received previous treatment with other immunosuppressive drugs. The median time to CR was 8.3 weeks. In follow-up 66% of the patients were still in CR after 2 years and the plateau in the Kaplan-Meier analysis suggests that a substantial number of patients had been cured. Among the 44 patients treated with cyclophosphamide/prednisone reported in the literature, the CR rate was 84.1%, which was slightly higher than that for rituximab. The median time to CR with cyclophosphamide/prednisone treatment was 6.3 weeks, which was similar to that in the rituximab-treated patients; the probability of continuous CR at 2 years was 94%.

Interpretation and Conclusions

All in all, both treatment schemes are effective therapies in patients with spontaneous antibodies to factor VIII. Our data analysis is only descriptive and no conclusions can be drawn as to the relative efficacy of the two regimens. However, these data may serve as a useful basis for planning randomized studies to definitively resolve these issues.

Key words: factor VIII antibody, treatment, rituximab, cyclophosphamide

Haematologica 2007; 92:66-71

©2007 Ferrata Storti Foundation

Acquired antibodies to factor VIII (*spontaneous factor VIII antibodies*) are a rare but serious coagulation disorder. Most of the patients with such antibodies present with severe, life-threatening bleeds which may be fatal, if untreated. In a series of 215 patients with spontaneous factor VIII antibodies observed before 1991 the mortality rate was 22%.¹ Since activated prothrombin complex concentrates² and recombinant factor VIIa³ have become available the acute bleeds can be controlled in the majority of patients. However, patients remain at a high risk of fatal bleeding, if the antibody cannot be eliminated by appropriate treatment.⁴ Therapy with prednisone and cyclophosphamide is regarded by the majority of clinicians as the most effective standard first-line immune suppressive therapy. Nevertheless, up to one third of patients are refractory to this therapy.⁵ Alternative treatment options that have become available are high-dose immunoglobulins,⁶ cyclosporine,⁷ and cladribine.⁸ However, all these treatment schemes have shown only limited efficacy.

Rituximab, a monoclonal chimeric antibody against the CD20 antigen has been proven to be an effective therapeutic agent in the treatment of follicular lymphoma⁹ and when combined with standard chemotherapy it improves the cure rate in diffuse large cell lymphoma significantly.¹⁰ Recently published data show that rituximab is also an effective treatment in several autoimmune diseases, such as immune hemolytic anemia,¹¹ autoimmune thrombocytopenia,¹² thrombotic thrombocytopenic purpura,¹³ rheumatoid arthritis¹⁴ and acquired antibodies to clotting factors, in particular spontaneous factor VIII antibodies. In this article, we analyze previously published data on the treatment of factor VIII antibodies with rituximab with particular reference to response rates, time to complete remission and duration of responses and compare these data with those obtained from patients who were treated with cyclophosphamide/prednisone.

Design and Methods

Patients

To collect data on therapy with rituximab or cyclophosphamide/prednisone of patients with spontaneous factor VIII antibodies we screened the Medline, abstracts of the meetings of the American Society of Hematology and of the congress of the International Society of Thrombosis and Haemostasis. All together we were able to identify ten published articles or short reports,¹⁵⁻²⁴ eight abstracts²⁵⁻³² and one unpublished observation.³³ These reports presented the results of treatment with rituximab in a total number of 43 patients. To receive more information on these patients, in particular their follow-up (i.e. duration of

Table 1. Pretreatment demographic, clinical and laboratory data of the patients analyzed.

	Rituximab	Prednisone-cyclophosphamide
Number of patients with any data	43	44
Median age (range), years	70 (8-94) (n= 37)	65 (30-85) (n=13)
Sex (female, male, unknown)	18/16/8	4/9/31
Underlying disease (yes/no/unknown)	14/13/15	14/13/15
Inhibitor titer* (median, range), all patients	30 BU/mL (n=38) (1.5-660) (n=38)	27 (0.5 -1350) (n=42)
Inhibitor titer* (median, range), untreated	23 BU/ML (1.6-525) (n=15)	
Inhibitor titer* (median, range), previously treated	47 BU/mL (2.3-660) (n=16)	
Previously untreated, previously treated, unknown	20/21/1	All untreated
Additional treatments	Prednisone (n=11) Cyclophosphamide(n=2) Immunoglobulins (n=1)	
Number of doses of rituximab	6-8 (n=2) 4 (n=30) 1-3 (n= 6) Unknown (n=4)	

*Immediately before rituximab treatment.

complete remission) we contacted the first and/or co-authors of these reports. Additional information was provided by Drs. Stasi, Aggarwal, Leahy, Abdallah, Holme, Ahn and Krause. We are greatly indebted to these colleagues. The characteristics of the patients are summarized in Table 1.

Additionally, patients who had been treated with a *conventional regimen* (cyclophosphamide and prednisone) were analyzed for response rate, time to complete remission (CR) and duration of CR. The original data of individual patients were described in the articles by Herbst,³³ Lian,³⁴ Bayer,³⁵ Shaffer³⁶ and Huang.³⁷ The characteristics of these patients are also shown in Table 1.

Treatment regimen

Rituximab was given in most patients according to the standard treatment protocol which had been developed for treatment of follicular lymphoma,⁹ i.e. four weekly cycles of rituximab at a dose of 375 mg/m² as an infusion. The majority of patients received four cycles of rituximab (range: 1-8 cycles).

Definitions and data analyses

Complete remission was defined as complete disappearance of the antibody and normalization of factor VIII activity. Patients with partial remission were classified as having no remission. In order to analyze the significance of differences of BU levels among patients achieving a complete remission and patients without remission the Mann-Whitney-U-test was applied. To compare the CR rate among different treatment groups the χ^2 test was used. The product limit method of Kaplan and Meier was applied to analyze the probability of CR and the probability of a continuous CR in patients treated with rituximab, rituximab with or without pretreatment, and cyclophosphamide/prednisone. To calculate the significance of differences between the various treatment groups, the log rank test was applied. Differences were considered statistically significant when the p value was <0.05 .

Results

BU before treatment

Information on antibody levels before therapy was available for 38 patients treated with rituximab and 43 patients treated with cyclophosphamide/prednisone. Similar levels were found in both treatment groups. The median BU levels were 30 BU/mL (range, 1.5-660) in the group of patients treated with rituximab and 27 (range, 0.5-1350) in the patients treated with cyclophosphamide/prednisone.

Response rate and time to response after initiation of immune suppressive therapy

The response to rituximab was documented in 42/43 patients. A CR was achieved in 33 out of these 42 (78.6%) patients. The CR rate was 75% (12/16) in untreated patients and 77% (17/22) in previously treated patients. All patients who received cyclophosphamide/prednisone were previously untreated. The CR rate in these patients was 84.1% (37/44). No significant difference was found between the patients treated with rituximab and those treated with cyclophosphamide/prednisone. When comparing antibody levels in non-responders and responders, the median antibody level was higher in non-responders than in responders in both groups (rituximab: 160 BU/mL versus 20 BU/mL, respectively; with cyclophosphamide/prednisone: 50 BU/mL versus 23 BU/mL, respectively; $p < 0.05$) (Figure 1).

Data on the time to achieve CR were available for 28 patients. The median time to CR in all patients treated with rituximab was 8.3 weeks (range, 2-76). In previously treated patients ($n=15$) the time to reach CR was shorter (4 weeks; range, 2-76 weeks) than that in untreated patients ($n=9$; 11 weeks; range, 2-21 weeks), but the differences were not statistically significant ($p=0.55$, Figure 2). For four of the 28 patients it was not

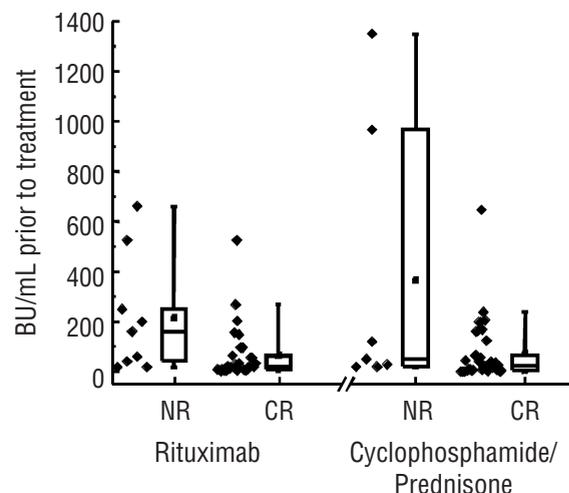


Figure 1. Levels of factor VIII (BU/mL) inhibitor in patients (R) achieving a complete remission (CR) after therapy with rituximab or cyclophosphamide/prednisone and patients with persistence of disease despite therapy (NR). Inhibitor titers were found to be higher in the NR group than in the CR group ($p < 0.05$ as assessed by the Mann-Whitney U-test). The boxes represent 25-75%, the whiskers minimum and maximum, the mean is represented by the square (\square) and the median by the line within the boxes.

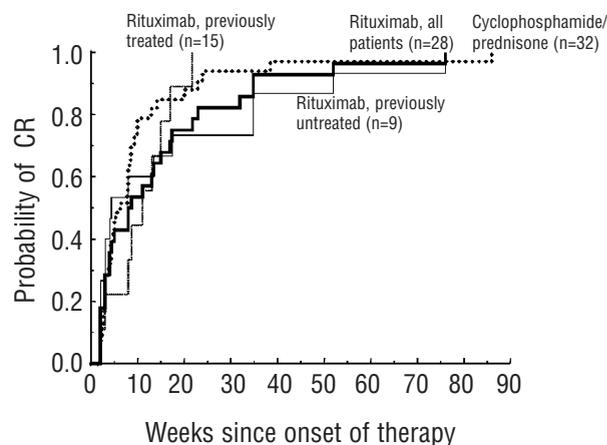


Figure 2. Time to complete remission (CR) in patients treated with rituximab (bold line) or cyclophosphamide/prednisone (bold dotted line). The fine line represents patients treated with rituximab who had received a previous treatment, the fine dotted line represents patients treated with rituximab who were previously untreated.

stated whether they were untreated or had had prior immunosuppressive therapy. The median time to CR in patients treated with cyclophosphamide/prednisone was 6.3 weeks (range, 2.0-86).

Duration of CR

Data on the duration of CR were available for 24 patients (for four of whom it was not stated whether they were untreated or had had prior immunosuppressive

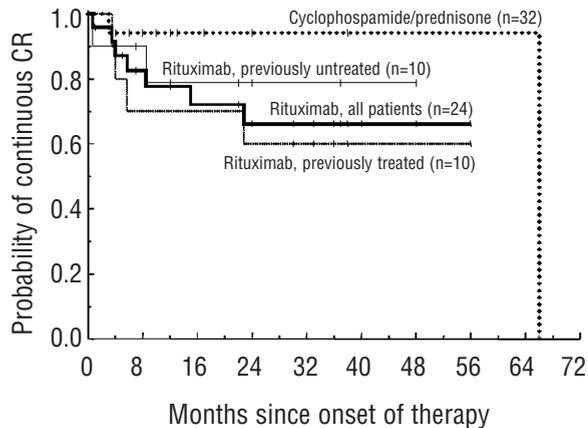


Figure 3. Probability of patients treated with rituximab (bold line) or cyclophosphamide/prednisone (bold dotted line) remaining in continuous complete remission. The fine line represents patients treated with rituximab who had received a previous treatment, the fine dotted line represents patients treated with rituximab who were previously untreated.

therapy). In patients treated with rituximab the probability of a continuous CR was 66% at 2 years (Figure 3). No relapse occurred after 23 months. Similar results were found when analyzing the duration of CR in patients who had (n=10) or had not (n=10) received pre-treatment ($p=0.46$, Figure 3). In three patients who had relapsed and received salvage treatment with rituximab and cyclophosphamide the second remission was longer than the first CR (*Stasi, personal communication*).

In patients receiving cyclophosphamide/prednisone the probability of continuous CR at 2 years was 94% (Figure 3).

Discussion

The optimal treatment for patients with acquired factor VIII antibodies has not yet been established. The only randomized study (of limited size) showed that in one third of the patients a response could be achieved with steroids alone and that steroid-resistant patients responded well to cyclophosphamide/prednisone.⁵ However, one third of patients were resistant to the combination regimen.

In this study we analyzed data from published series or case reports on patients treated with rituximab and patients treated with cyclophosphamide/prednisone. The combined data show that rituximab has a high efficacy for treatment of acquired factor VIII antibodies in untreated and previously treated patients. However, as already noted by Aggarwal,²¹ the efficacy of rituximab is lower in patients with higher antibody levels (>100 BU/mL). It is of interest that some patients achieved a CR only a long time after treatment with rituximab.

It is tempting to speculate that these patients had late spontaneous remissions as described by Lottenberg.⁴ About two-thirds of the rituximab-treated patients remained in CR and the Kaplan-Meier analysis shows a plateau at 66% which suggests cure or at least long-term remission. It is also noteworthy that some relapsed patients had a second remission with rituximab which was longer than the first remission.

A comparison of the *standard therapy* prednisone/cyclophosphamide (as first-line treatment) and rituximab (as first- or second-line treatment) revealed that cyclophosphamide/prednisone might be slightly more effective than rituximab. Based on our analysis a larger proportion of patients treated with cyclophosphamide/prednisone achieved a CR compared to those treated with rituximab. The time to CR was similar, but the duration of CR was longer with cyclophosphamide/prednisone. However, none of the differences was found to be statistically significant. Similar data on the efficacy of cyclophosphamide/prednisone were reported by Delgado *et al.* in their meta-analysis.³⁸

Our analysis has a number of limitations. Data were not derived from prospective studies with pre-defined inclusion and exclusion criteria, defined time points of post-treatment monitoring and standardization of concurrent therapies. The follow-up was rather short with a few exceptions.²⁰ Importantly, many patients on rituximab also received concomitant immunosuppressive therapy (Table 1) and this could have affected the evaluation of the efficacy of rituximab. On the other hand it should be mentioned that almost all patients received the same dose schedule of rituximab, that a uniform method for measuring the antibody activity (Bethesda method) was used in all studies and that the criteria for CR were uniform. Thus, despite all the limitations our analysis provides important information on the value of this new treatment.

Since rituximab monotherapy is effective in both malignant diseases (follicular lymphoma) and in autoimmune diseases, including factor VIII antibody and autoimmune thrombocytopenia, it is of interest to compare the efficacy of this monoclonal antibody in these two types of disease. Considering the published data it is obvious that rituximab is more effective for the treatment of factor VIII inhibitors than for follicular lymphoma. In particular, the rate of CR is much higher in patients treated for factor VIII antibodies, whereas the time to response seems to be similar in both conditions. There is a continuous relapse rate over time in follicular lymphomas and no cures, whereas two-thirds of patients with factor VIII antibodies may be potentially cured. The rate of CR following rituximab treatment is much lower in patients with autoimmune thrombocytopenia than in patients with factor VIII antibodies, but only very few patients relapse after having achieved CR.³⁹

In conclusion, rituximab is an effective drug for the treatment of spontaneous factor VIII antibodies but so far the data are too immature for a final statement concerning the definite place of rituximab in the treatment algorithm of factor VIII antibodies. In case of failure of cyclophosphamide/prednisone, rituximab may be a useful salvage treatment. However, based on our data a randomized study should be done, despite all the difficulties due to the rarity of the disease. In such a study an add-on design (cyclophosphamide/prednisone vs. cyclophosphamide/prednisone+rituximab) might be the best choice. After 8 weeks responders and non-

responders could be randomized to continuous treatment with cyclophosphamide/prednisone or four cycles of rituximab.

Author Contributions

WS: data management, statistical analysis, interpretation of data, writing of the manuscript; KL: idea, collection of data, interpretation, writing of the manuscript; IP: treatment and report on unpublished case, interpretation of the data, writing of the manuscript. All authors approved the final version. 1. Table 1: created by WRS, KL and IP; all figures created by WRS and KL.

Conflict of Interest

The authors reported no potential conflicts of interest.

References

- Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to factor VIII. *Thromb Haemost* 1981;45:200-3.
- Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. *Haemophilia* 2004;10:169-73.
- Scharrer I. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VII deficiency. *Haemophilia* 1999;5:253-9.
- Lottenberg R, Kentro TB, Kitchens CS. Acquired hemophilia. A natural history study of 16 patients with factor VIII inhibitors receiving little or no therapy. *Arch Intern Med* 1987;147:1077-81.
- Green D, Rademaker AW, Briet E. A prospective, randomized trial of prednisone and cyclophosphamide in the treatment of patients with factor VIII autoantibodies. *Thromb Haemost* 1993;70:753-7.
- Schwartz RS, Gabriel DA, Aledort LM, Green D, Kessler CM. A prospective study of treatment of acquired (autoimmune) factor VIII inhibitors with high-dose intravenous gammaglobulin. *Blood* 1995;86:797-804.
- Hart HC, Kraaijenhagen RJ, Kerckhaert JA, Verdel G, Freen M, van de Wiel A. A patient with a spontaneous factor VIII:C autoantibody: successful treatment with cyclosporine. *Transplant Proc* 1988; 20: 323-8.
- Sallah S, Wan JY. Efficacy of 2-chlorodeoxyadenosine in refractory factor VIII inhibitors in persons without hemophilia. *Blood* 2003; 101:943-5.
- McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998; 16: 2825-33.
- Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235-42.
- Berentsen S, Ulvestad E, Gjertsen BT, Hjorth-Hansen H, Langholm R, Knutsen H, et al. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. *Blood* 2004; 103:2925-8.
- Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. *Blood* 2001;98:952-7.
- Sallah S, Husain A, Wan JY, Nguyen NP. Rituximab in patients with refractory thrombotic thrombocytopenic purpura. *J Thromb Haemost* 2004;2:834-6.
- Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; 350: 2572-81.
- Kain S, Copeland TS, Leahy MF. Treatment of refractory autoimmune (acquired) haemophilia with anti-CD20 (rituximab). *Br J Haematol* 2002;119:578.
- Wiestner A, Cho HJ, Asch AS, Michelis MA, Zeller JA, Peerschke EI, et al. Rituximab in the treatment of acquired factor VIII inhibitors. *Blood* 2002;100:3426-8.
- Jy W, Gagliano-DeCesare T, Kett DH, Horstman LL, Jimenez JJ, Ruiz-Dayao Z, et al. Life-threatening bleeding from refractory acquired FVIII inhibitor successfully treated with rituximab. *Acta Haematol* 2003;109:206-8.
- Fischer KG, Deschler B, Lubbert M. Acquired high-titer factor VIII inhibitor: fatal bleeding despite multimodal treatment including rituximab preceded by multiple plasmaphereses. *Blood* 2003; 101: 3753-4.
- Mathias M, Khair K, Hann I, Liesner R. Rituximab in the treatment of alloimmune factor VIII and IX antibodies in two children with severe haemophilia. *Br J Haematol* 2004; 125:366-8.
- Stasi R, Brunetti M, Stipa E, Amadori S. Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. *Blood* 2004;103:4424-8.
- Aggarwal A, Grewal R, Green RJ, Boggio L, Green D, Weksler BB, et al. Rituximab for autoimmune haemophilia: a proposed treatment algorithm. *Haemophilia* 2005;11:13-9.
- Marietta M, Pozzi S, Luppi M, Bertesi M, Cappi C, Morselli M, et al. Acquired haemophilia in HIV negative, HHV-8 positive multicentric Castleman's disease: a case report. *Eur J Haematol* 2003;70:181-2.
- Abdallah A, Coghlan DW, Duncan EM, Chunilal SD, Lloyd JV. Rituximab-induced long-term remission in patients with refractory acquired hemophilia. *J Thromb Haemost* 2005;3:2589-90.
- Holme PA, Brosstad F, Tjonnfjord GE. Acquired haemophilia: management of bleeds and immune therapy to eradicate autoantibodies. *Haemophilia* 2005;11:510-5.
- Mazj S, Li H, Lichtman SM, Budman D, Donahue L, Akhund B, et al. Successful treatment of acquired factor VIII inhibitor with rituximab in 4 patients [abstract]. *Blood* 2003; 102 (Suppl 1):798a[abstract].
- Low BG, Cohen AJ. Complete remission in high-titer acquired factor VIII inhibitor after rituximab therapy. *Blood* 2003; 102 (Suppl 1): 101b[abstract].
- Karwal MW, Schlueter AJ, Zenk DW, Davis RT. Treatment of acquired factor VIII deficiency with rituximab. *Blood* 2000; 96 (Suppl 1):84b[abstract].
- Karwal MW, Schlueter AJ, Zenk DW, Davis RT. Treatment of acquired factor VIII deficiency with rituximab. *Blood* 2001; 98 (Suppl 1): 533a[abstract].
- Tamponi G, Schinco P, Borchellini A, Valpreda A, Pollio B, Boccadoro M. Acquired factor VIII deficiency: rapid and complete remission after immunosuppressive therapy with high dose cyclophosphamide and rituximab. *Blood* 2002; 100 (Suppl 1):101b[abstract].
- Huth-Kühne A, Lages P, Zimmermann R. Successful inhibitor-elimination with rituximab in acquired hemophilia A and a patient with a carrier status for hemophilia A—two

- case reports. *J Thromb Haemost* 2005; 3 (Suppl 1):P1830[abstract].
31. Malato A, Siragusa S, Anastasio R, Bonifacio G, Lo Coco L, Abbadessa V. Successful treatment of acquired haemophilia with FEIBA and rituximab. *J Thromb Haemost* 2005;3 (Suppl 1):P1398[abstract].
 32. Krause M, Königs C, Kessel C, von Auer C, Kreuz W, Scharrer I. Epitope mapping of inhibitory antibodies and inhibitor elimination with rituximab in patients with acquired haemophilia. *J Thromb Haemost* 2005; 3 (Suppl 1): P0201 [abstract].
 33. Herbst KD, Rapaport SI, Kenoyer DG, Stanton W, Feinstein DI. Syndrome of an acquired inhibitor of factor VIII responsive to cyclophosphamide and prednisone. *Ann Intern Med* 1981;95:575-8.
 34. Lian EC, Villar MJ, Noy LI, Ruiz-Dayao Z. Acquired factor VIII inhibitor treated with cyclophosphamide, vincristine, and prednisone. *Am J Hematol* 2002;69:294-5.
 35. Bayer RL, Lichtman SM, Allen SL, Budman DR, Buchbinder A, Fettes J, et al. Acquired factor VIII inhibitors--successful treatment with an oral outpatient regimen. *Am J Hematol* 1999;60:70-1.
 36. Shaffer LG, Phillips MD. Successful treatment of acquired hemophilia with oral immunosuppressive therapy. *Ann Intern Med* 1997;127:206-9.
 37. Huang YW, Saidi P, Philipp C. Acquired factor VIII inhibitors in non-haemophilic patients: clinical experience of 15 cases. *Haemophilia* 2004;10:713-21.
 38. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol* 2003;121:21-35.
 39. Cooper N, Stasi R, Cunningham-Rundles S, Feuerstein MA, Leonard JP, Amadori S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. *Br J Haematol* 2004;125:232-9.