Rituximab in the treatment of acquired factor VIII inhibitors.

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Brief Report

Words: abstract 146, text 1277

Running head: Rituximab for acquired factor VIII inhibitors

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Autoantibodies against factor VIII (FVIII) are rare but can cause life-threatening bleeding requiring costly factor replacement and prolonged immunosuppression. We report four consecutively treated patients whose acquired FVIII inhibitors responded rapidly to immunosuppressive regimens that included rituximab, a monoclonal antibody against CD20+ B cells. Three patients had spontaneously occurring inhibitors. The fourth, a patient with mild hemophilia A, developed both an autoantibody and an alloantibody following recombinant FVIII treatment. Pretreatment FVIII activities ranged from <1% to 4% and inhibitor titers from 5 to 60 Bethesda units (BU). One patient with polymyalgia rheumatica who developed the inhibitor while receiving prednisone responded to single agent rituximab. The hemophilia patient had rapid resolution of the autoantibody whereas the alloantibody persisted for months. Responses continue off treatment from 7+ to 12+ months. This report adds to the growing evidence that rituximab has efficacy in immune disorders due to autoantibody formation.

Introduction

Autoantibodies against FVIII develop in less than one individual per million per year and have a reported mortality between 6 and 22%. Most cases are idiopathic; up to 50% are associated with autoimmune diseases, malignancies, drugs or the postpartum period. Human or porcine FVIII, prothrombin complex concentrates, or recombinant human FVIIa may be required to control bleeding. To suppress inhibitor formation most patients receive immunosuppressive drugs, such as prednisone, cyclophosphamide, azathioprine or cyclosporine.
The anti-CD20 monoclonal antibody rituximab rapidly eliminates a majority of circulating B cells suggesting that it could be beneficial in autoantibody-mediated diseases by targeting the autoreactive B cells. Early reports of responses in immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) appear to confirm this notion prompting consideration of its use for FVIII inhibitors.

**Study Design**

Four consecutive patients diagnosed with acquired FVIII inhibitors at our institutions received either 4 (Patients 1-3) or 2 (Patient 4) weekly infusions of rituximab 375 mg/m². Except for patient 3, each patient received a brief course of prednisone at 1mg/kg/d which was rapidly tapered (figure 1 and 2). All patients gave informed consent. FVIII inhibitors were titered by the Bethesda assay. The STACLOT LA test by Diagnostica Stago (Asnieres-sur-Seine, France) was used to detect lupus anticoagulants.

Patient 1, a 69-year-old man with chronic renal failure presented with melena, bleeding from an arthrocentesis site, Hb 5.6 g/dL, PTT 94 sec, FVIII activity (FVIIIc) 4% and inhibitor titer 5 BU. He required 7 units of red cells. Bleeding resolved following treatment with recombinant human FVIII (100 U/kg loading, 10 U/kg/hr maintenance), desmopressin acetate (DDAVP) and premarin. Prednisone was started on day 1, rituximab on day 3. Pretreatment serum electrophoresis revealed a very small monoclonal IgG lambda paraprotein. Total gamma globulin level was 0.92 gm/dL (0.6-1.6).

Patient 2, a 38-year-old man with ascites and lymphadenopathy of unknown etiology, a PTT of 67 sec, FVIIIc <1%, inhibitor titer 23 BU and a lupus anticoagulant developed a large hematoma at a venepuncture site and a 2 g% fall in hemoglobin. One week after treatment with FEIBA 50
IU/kg qid, 1 g cyclophosphamide i.v. and prednisone, FVIIIc was 3%, and treatment with rituximab was initiated due to lack of clinical improvement. FEIBA was safely discontinued 1 week after rituximab was initiated.

Patient 3, a 79-year old woman on prednisone and azathioprine for polymyalgia developed spontaneous giant ecchymoses, the largest 20x25 cm. Investigations revealed a PTT of 58 sec, FVIIIc 2%, inhibitor titer 8 BU and a lupus anticoagulant. Azathioprine was discontinued, prednisone maintained, and weekly rituximab initiated. Within 1 week, the ecchymoses resolved.

Patient 4, a 39-year old man with mild hemophilia A, factor VIII level 15%, due to an Arg2150His mutation received recombinant human FVIII perioperatively. Six days postoperatively, on a regimen of FEIBA and DDAVP, an inhibitor of 60 BU was detected but FVIIIc was unchanged at 15%. Two weeks later FVIIIc fell to 2% with only a minimal increase following DDAVP prompting treatment with rituximab and prednisone.

**Results and Discussion**

Our patients who presented with bleeding had rapid clinical improvement following initiation of immunosuppressive treatment that included rituximab. This was most striking in patient 3 whose giant ecchymoses resolved rapidly following the first dose of rituximab, her sole treatment. In patients 1-3 FVIIIc normalized and the inhibitor became undetectable between 3 and 12 weeks from the start of rituximab (figure 1). Patient 1 had a normal FVIIIc within 2 weeks and resolution of the inhibitor at 3 weeks. The antigenic stimulation by the factor VIII infusions patient 1 received may have had a role in his rapid response.\(^{10}\) In patient 4 (figure 2) endogenous
FVIIIc returned to baseline within one week, indicating resolution of the autoantibody, while antibody directed against wild type FVIII persisted for more than two months. All patients remain in remission between 7 and 12 months from the start of treatment.

Spontaneous resolution of FVIII inhibitors occurs in up to 30% of patients, most frequently when the inhibitors develop postpartum. Since the median time to spontaneous resolution is 21 months most patients are treated with immunosuppressive drugs to induce more rapid resolution. Single agent prednisone has a reported response rate of 30% and could have accounted for the responses seen in three of our patients. However patients who respond to prednisone frequently require long term maintenance therapy to prevent relapse. In contrast, we were able to taper prednisone rapidly without relapse in our patients.

The combination of prednisone with cyclophosphamide is effective in 70 to 100% of patients and inhibitors resolve within 3 to 37 weeks. The time to response in our rituximab treated patients appears shorter, and potential complications associated with combination prednisone and cyclophosphamide therapy such as neutropenic fever, herpes zoster, myelodysplasia, and cataracts were avoided.

Inhibitor titers in our patients were of intermediate strength and comparable to those reported in many studies. Although patients with low level inhibitors respond more easily to immunosuppressive treatment, inhibitor titer is not directly related to bleeding complications and even patients with low titer inhibitors can have fatal bleeding.
The addition of short courses of prednisone to rituximab may have enhanced the response in our patients. A preliminary report found only partial remissions in 3 patients with FVIII inhibitors treated with rituximab alone and a complete remission in a patient who also received prednisone. However, the complete response of our patient 3 indicates that single agent rituximab can suffice. Two of our patients (patient 1 and 2) may have had an underlying lymphoproliferative disorder possibly accounting for a better response.

Rituximab was well tolerated in our study. Gamma globulin levels decreased by 16% at 3 months in patient 1 and returned to pre treatment levels by 7 months. In the context of recent reports on viral infections following rituximab it is noteworthy that we observed no worsening of pre-existing hepatitis C in patient 4, who was on a course of ribavirin and interferon when rituximab was started.

FVIII inhibitors have been reported in several kindreds with mild hemophilia due to missense mutations, usually arising after factor replacement and causing a bleeding pattern similar to acquired hemophilia. Patient 4’s course was similar to these previously reported experiences (figure 2); Consistent with an alloresponse the high titer inhibitor initially spares the endogenous FVIII, but a subsequent drop in the FVIII level indicates the formation of autoantibodies. In our patient prednisone and rituximab led to a rise in FVIIIc back to his baseline level within a week. However, measurable antibody against wild type FVIII persisted for more than 2 months, suggesting that rituximab eliminated autoreactive B cells more effectively than alloreactive B cells.
Rituximab has been used with varying success in other autoantibody-mediated disorders. Reported response rates range from 30% in ITP\textsuperscript{15} to 100% in childhood AIHA.\textsuperscript{16} Different response rates may be due to differences in pathogenesis or expression levels of CD20 on the antibody-producing B cell population.\textsuperscript{14} During maturation of B cells to plasma cells CD20 expression is down regulated. Therefore, timing may be critical for response since rituximab may not be effective if a CD20 negative plasma cell population has become established. The ITP patients received rituximab a median of 15 months from diagnosis,\textsuperscript{15} while patients in our study were treated within weeks of diagnosis. Early reports also suggest that rituximab may have efficacy in rheumatoid arthritis\textsuperscript{24} and Wegener’s granulomatosis.\textsuperscript{25} Our patient’s polymyalgia unfortunately did not improve following treatment with rituximab. However, the lupus anticoagulants in patient 2 and 3 and the monoclonal gammopathy in patient 1 resolved after treatment.

We conclude that rituximab appears to be an effective and safe treatment for patients with factor VIII inhibitors and merits further study. Early treatment and combination with prednisone may be required for maximal benefit.
References:


Figure 1.
Figure 2.
Figure Legends

Figure 1. Response to treatment in 3 patients with acquired FVIII inhibitors.

Upper half of the figure shows FVIII activity (FVIIc) in %. Lower half shows inhibitor titer in Bethesda units (BU). Rituximab 375mg/m², open arrows, was started at week 0 and repeated weekly for four doses. Prednisone at 1 mg/kg/d is indicated by a solid line; broken line indicates prednisone taper. Solid arrow indicates cyclophosphamide 1 gm i.v. In patient 3 azathioprine (A) was stopped and prednisone 30 mg qd was continued unchanged as indicated by the broken line.

Figure 2. Response to treatment in a patient with mild hemophilia A and an acquired FVIII inhibitor.

Upper half of the figure shows FVIII activity (FVIIc) in %. Lower half shows inhibitor titer in Bethesda units (BU). Rituximab 375mg/m², open arrows, was given at week 0 and week 1. Prednisone at 1 mg/kg/d is indicated by a solid line; broken line indicates prednisone taper.
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