Original Article

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Rituximab for Treatment of Hemophilia A with High-Responder Inhibitors

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Abstract

Background: The development of inhibitors is a complication factor replacement therapy in hereditary factor VIII deficiency. Several management options are available for the treatment of inhibitor. Rituximab, a monoclonal antibody against CD20, reduces inhibitor level in rare bleeding disorders. The aim of this study was to evaluate the effectiveness of rituximab in lowering or eliminating the levels of factor VIII inhibitors in patients with severe hemophilia A.

Materials and Methods: This cross sectional study was conducted on ten male patients with severe hemophilia A with inhibitor titer ≥5 Bethesda Units/ml (BU) during 100 weeks in comprehensive hemophilia care center in Imam Khomeini Hospital. The recruitment period began in September 2010 and continued through November 2012. Patients received rituximab 375 mg/m² weekly from week 1 through 4. Inhibitor titer was measured monthly on week 6 to 22, Then on week 24, 36, 52, and 100. All patients received four doses of rituximab.

Results: Major response occurred on four patients (40%).Three patients had a minor response and three patients with no response to treatment. Adverse events were included renal impairment, headache and increase liver transaminase. No severe allergic reaction was observed.

Conclusion: Rituximab is useful for eradication or lowering inhibitor titer in severe hemophilia A with high-titer inhibitor. Further clinical trials studies need to evaluate efficacy and safety of the rituximab as an adjunctive therapy in combination immune tolerance induction strategies.

Keywords: Hemophilia A, Rituximab, Inhibitor, High responder, Therapeutics, CD20 antibody

Introduction

Severe hemophilia A is a hereditary bleeding disorder due to factor VIII deficiency (1). Its clinical manifestations may include hemarthrosis, bruising, and bleeding from any site (2). Severe hemophilia A can be treated through replacement of intravenous factor VIII replacement with prophylaxis or on-demand protocol (3). Some patients, who received intravenous factor VIII, may develop alloantibody against factor VIII. Alloantibodies bind to the replaced factor in a variety of ways and interfere to its function (4). About 20-30% of patients with severe and 5-15% of patients with mild to moderate form of hemophilia A develop inhibitors against the replacement therapy (5, 6). The patients with Hemophilia B, inhibitor development occurs in about 2-3% (5, 6, 7). The risk of an inhibitor in hemophilia increases with the occurrence of some genetic mutations, exposure to high purity and recombinant products early in life and family history of inhibitor development (8). Inhibitor development is associated with increased

morbidity and cost. The main goal of treatment in such patients is decreasing inhibitor titer by immune tolerance induction (ITI), bypassing agents such as rFVIIa (Novo seven/Aryoseven) or factor VIII inhibitor bypassing activity (FEIBA) products for bleeding episodes although these procedures are not always effective (9,10,11). Moreover, most of the protocols that had been used demonstrate similar failure (17-37%) but differ appreciably with respect to dose and the time required for success (12). On the other hand, the up-front costs that are associated with currently used ITI regimen present a financial challenge to patients and ministry of health. Rituximab is a chimeric whole monoclonal antibody against the CD20 antigen expressed on B lymphocytes that are used to treat non-Hodgkin's lymphoma, chronic lymphocytic leukemia, transplant rejection, and autoimmune disease (13). Rituximab removes most CD20 circulating B cells (normal and malignant), and recovery of B cell counts occurs 6 to 12 months after last dose of rituximab (14). Reducing B cells may be successful in the treatment of immune conditions such as rheumatoid arthritis (15). Reports showed some evidence for off-label use of rituximab with improvement of symptoms and laboratory tests in multiple sclerosis , systemic lupus erythematous, and autoimmune anemia (16, 17). More recently, the combination of rituximab with immune tolerance induction (ITI) has been reported to be successful in patients who had previously failed ITI protocol treatment alone (18). A prospective investigation is ongoing for rituximab in hemophilia A with inhibitor. The inhibitors against factor VIII are antibodies and primarily Immune globulin G (IgG) (19, 20). The rituximab has successfully been used to control the symptoms, and the treatment of acquired FVIII inhibitors with refractory bleeding (20,21). Evidence by small series and some case reports showed that rituximab has efficacy in autoimmune coagulopathy due to antibody formation against coagulation factor (20-23). Some case reports and case series showed benefit of rituximab in high responder inhibitor in congenital hemophilia A (24-25). No randomized clinical trials were identified in the literature on efficacy of rituximab in hereditary hemophilia with inhibitor (26).
Over 4000 hemophilia A registered in Iran and near 300 patients have inhibitor (21), but we didn't find any report in Iran for rituximab in the treatment of inhibitor. Some reports in abroad didn't show effect of rituximab permanently. The purpose of this study was to evaluate the effectiveness of rituximab in lowering or eliminating of factor VIII inhibitors serum levels in severe hemophilia A with high responder.

Materials and Methods

Study Design

The study was designed as an interventional type to evaluate safety and efficacy of rituximab in hemophilia A patients with inhibitors over 5 Bethesda unit. The model was in single group assignment in one center.

Patients Characteristics

This study enrolled male individuals with severe hemophilia A (FVIII<1%), who diagnosed during childhood. Inclusion criteria included inhibitor titer profile to factor VIII of at least 5 BU/mL, inhibitor level greater than or equal to 5 BU/mL about 5 to 14 days after initial factor VIII exposure during screening and age over 5 years. The exclusion criteria were known hypersensitivities or allergies to murine and/or humanized antibodies, currently participating in investigational hemophilia studies, HIV infected, any immunodeficiency disorder, liver disease and serum Alanine transaminase (ALT) or Aspartate transaminase (AST) greater than three times the upper limit of normal, albumin less than 2.5g/dl, and/or INR greater than 1.7, received interferon or other immune-modulatory drugs such as steroids or cytotoxic therapy 30 days prior to study, history of cardiac arrhythmias,

any active febrile illness, kidney insufficiency or pulmonary infiltrates, previously received rituximab treatment, currently undergoing immune tolerance therapy, and evidence of hepatitis B (HBV) infection.

Ten patients were eligible to the study according to the inclusion criteria. None of them had received immune tolerance. Patients were hospitalized at comprehensive hemophilia care center of Imam Khomeini Hospital Complex. The recruitment period began in September 2010 and continued through November 2012.

Primary Outcome Measures

1. Presence or absence of a major response in each participant

Major response is determined by decreasing inhibitor level to less than 5 BU/mL between weeks 6 to 22 and remaining stable below 5 BU/mL at 14 days following re-challenge with FVIII infusion.

Secondary Outcome Measures

1. Presence or absence of at least a minor response in each patient

Inhibitor level decrease to <5 BU/mL between weeks 6 to 22 and either remaining stable <5 BU/mL 14 days following FVIII infusion re-challenge or titer following FVIII re-challenge is 5-10 BU/mL and <50% of original peak.

2. Number of adverse events to rituximab infusions was reported during four weeks

Dose

The dose of rituximab (Roche Pharmaceuticals Company) was as follows:

For participants greater than or equal to 10 kg, the dose is 375 mg per m2 BSA weekly for 4 weeks; and for participants less than 10 kg, is 12.5 mg/kg weekly for 4 weeks. The drug was administered as standard schedule.

Time Frame

Participants with peak inhibitor level above 5 Bethesda units (BU)/mL were d rituximab intravenously once a week for 4 weeks. Blood samples were collected at each visit for laboratory testing. Two weeks after the treatment, participants were tested for inhibitor; this test was repeated every 4 weeks up to 22weeks. Participants who received a repeated dose of factor VIII, and decrease inhibitor level below 5 BU/mL, and then blood test was conducted 14 days later for inhibitor level assay. Follow-up visits occurred at weeks 36, 52, and 100 included physical examination, blood collection, and monitoring of bleeding events and infections. Participants were visited at weeks 64, 76, and 88 to monitor bleeding events, physical examination, and viral infections (Human Immune-Deficiency Virus, Hepatitis B Virus & Hepatitis C Virus).

Ethical Consideration

This study was approved by Ethics Committee of Hematology-Oncology and Stem Cell Transplantation Research Center in agreement with Declaration of Helsinki and good clinical practice. Written informed consent was signed by all patients or their legal guardians. Consenting patients who met these criteria were assigned to the intervention.

Laboratory Methods

The FVIII inhibitor was measured by classic ‘‘Bethesda assay,’’ by Stago company reagent and the inhibitor titer was reported in ‘BU’.

Statistical Analysis

Data were collected using the case report forms during the study. Data were analyzed by SPSS (version 16.0; SPSS Co, Chicago, Illinois) and Stata (version 11). Quantitative data were expressed as mean ± standard deviation, and qualitative data were expressed as frequency and proportion (percentage). The standard level of statistical significance was considered as P<0 .05.

Results

During the study, 10 patients were enrolled in the project. All patients were male. The mean age was 22.50 ± 10.66 years (range:

6-41 years). Three patients were under 18 years old. Mean ± SD baseline inhibitor level was 32.20 ± 25.11 BU (range: 8.5-83 BU). Other factors, such as vital signs (respiratory rate, heart rate, blood pressure and body temperature), liver and renal function tests, and blood count were normal. Four weekly infusions of rituximab were tolerated well in all patients.

Response to treatment

Four out of 10 patients achieved a major response at first but the titer of inhibitor rose again after weeks of 102; three patients had minor response but had a significant clinical improvement, and three patients had no response. The results of the rituximab treatments are shown in Figure1. Proportion of patients with major and minor response was 0.4 (CI: 0.066-0.652) and 0.3 (CI: 0.121 - 0.737), respectively. Table 1 shows the main finding of the cohort. The mean inhibitor level showed in Figure 2 after treatment. Patients younger than 5 years old showed better response to treatment in comparison with patients older than 5 years old (Figure 3).

Bleeding Episode

During the study, all the patients had bleeding in knee joint, also four patients had in the ankle and shoulder and two had epistaxis. The mean ±SD of bleeding episodes was 28.8±7.61 (Range: 18-37) during the treatment and follow-up period and it was 32.1±9.64 (Range: 22-49) before the treatment. The numbers of bleeding events decreased during the trials without any change in physical activity, but it wasn't significant. The patients didn't report any serious bleeding episodes. All patients were treated on bleeding events by on demand protocol using FVIII from 50 -100 IU/kg.

Adverse events

One patient experienced mild and transient renal impairment (increased in creatinine level, 1.7, normal: 1.5), nausea, and headache at the time of the first rituximab infusion, and these adverse effects were resolved without any sequel after 24 hours. Liver enzyme increased mildly in two patients and returned to normal level after two weeks. One patient had transient palpitation after first dose of rituximab, who respond rapidly to symptomatic treatment and it was resolved without any treatment. One patient had minor allergic reaction, and pruritus, which was resolved by antihistamine. There were no major complications, and any infectious adverse event.

Table I: Patient characteristics and outcome after using rituximab in patients with hemophilia A with inhibitor

Patient	Age (year)	Severity	Time to lowest inhibitor titer (wk)	Bleeding episodes	Outcome	Adverse Effects
1	22.0	severe	6	26	Major	N
2	23.0	severe	3	18	Major	Renal
3	41.0	severe	2	18	Major	N
4	27.0	severe	6	20	Major	L
5	6.0	severe	10	32	Minor	Palpitation
6	33.0	severe	14	35	Minor	pruritus
7	19.0	severe	4	37	Minor	No
8	29.0	severe	10	35	NR	No
9	16.0	severe	3	32	NR	No
10	9.0	severe	2	35	NR	L

N: no, wk.: week, NR: No Response, L: increase Liver transaminase

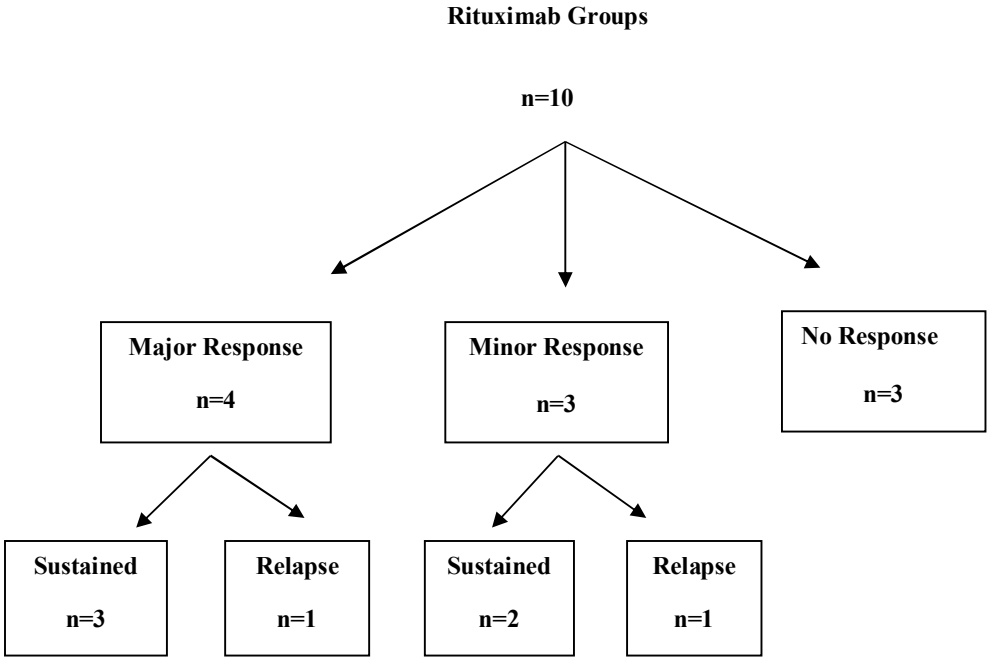

Figure 1.The outcome of ten patients treatment with severe hemophilia A treated by rituximab for an inhibitor eradication protocol for a period of 100 weeks.

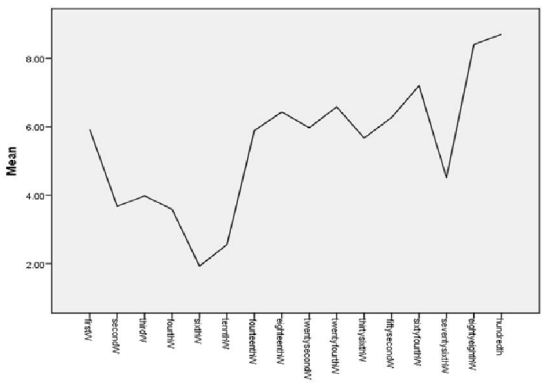

Figure 2. Mean inhibitor level during observation period

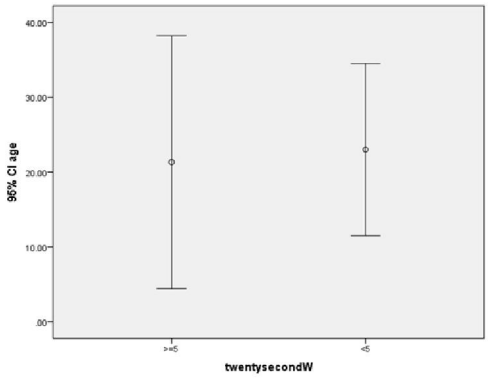

Figure 3. Age group and response to rituximab at week twenty after treatment

Discussion

Immune Tolerance Induction (ITI) is successful in only two thirds of patients with inhibitor. The remainders of patients need alternate way to control inhibitor production and bleeding episodes (21-22). Immunosuppression by rituximab is a way to reduce antibody formation (20). Several studies showed all cases who took rituximab had a complete success rate of

33-63% (24-25). The main findings in previous studies were rituximab decrease inhibitor levels against factor VIII in most patients, but long-term and sustained eradication of the inhibitor is uncommon (23-27). In addition, long-term follow up is very important issue for safety, efficacy, relapse and infection rate, and late adverse effects of rituximab (25). Repeated course with rituximab are under question (28-29). Rituximab suppress B cell type immune system for at least six months, and its effect to prevent relapse is not generally accepted by the experts (25-26).

The present study was a report of a cohort, in patients with hereditary severe hemophilia A with inhibitor were treated with rituximab in one center. In this study, overall response rate was 70% and complete response was 40% (4 out of ten). One of them has sustained complete response after long–term follow up (24 months) and 3 patients (30%) had minor response. No serious complications were seen during course of treatment and follow-up adverse events of treatment with rituximab were few in most reports (27-29). Hypersensitivity reaction and other allergic reaction were common in most studies (23) but the allergic reaction occurred only in one patient in our study. Due to the administration of steroids and antihistamine before rituximab, less allergic complications were observed before during study. The study didn't find any severe infection after rituximab but some reports showed infection in patients with central venous catheter (25-27). Included patients didn't implant central venous catheter.

The important issues are relapse and long-term effect of rituximab on immune system (26). Another important question is about the number of injection and courses of treatment that research group can use rituximab alone or in conjunction other immune suppressive agents to reach better results (25-26). These questions remain unanswered and need further studies.

Conclusion

In conclusion, the findings of current investigation suggest the efficacy of rituximab in treatment of high responder FVIII inhibitor but ITI remains the standard for the first line therapy. Multi centers, prospective, randomized studies in future are needed to measure the effect of rituximab on treatment of inhibitor in hemophilia.

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Conflict of interest

The authors state that they have no conflict of interest. The study supported by Roche Company in Iran.

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