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Role of Rituximab in the Treatment of Different Hematological Disorders

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ABSTRACT

Rituximab (anti-CD20 antibody) has been approved as a treatment for B-cell associated hematological disorders. CD20 expression and its complement regulatory proteins and membrane binding structures play a crucial role in rituximab efficacy. Complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity are the major mechanisms by which rituximab eliminates B cells. The efficacy of anti-CD20 varies in different diseases. Rituximab was approved as a successful treatment in diseases such as non-Hodgkin lymphomas, particularly diffuse large B-cell lymphoma and follicular lymphoma. In addition, rituximab has recently shown promising results with several autoimmune diseases; it was approved for rheumatoid arthritis as well as being used for other diseases such as systemic lupus erythematosus. Likewise, rituximab was successfully used for incompatible ABO organ transplantation instead of the invasive splenectomy procedure. This review will discuss the use of rituximab for different hematological diseases.

Keywords: Rituximab, Hematological disorders, Regulatory proteins, Lymphoma

INTRODUCTION

Antibody-dependent therapeutic approaches have considerably influenced the treatment of hematological disorders. Rituximab (RTX) is a chimeric IgG1 monoclonal antibody targeting B-lymphocyte antigen CD20 [1-24]. It was the first monoclonal antibody treatment approved by the US Food and Drug Administration in 1997 for the treatment of non-Hodgkin lymphoma (NHL) [1,6,18,20,22,24].

The effectiveness of the drug depends on three main factors: the expression of CD20, the membrane-binding receptor, and the expression of complement regulatory proteins (CRP). Therefore, if the expression of CD20 is weak, the drug will not be effective 3. In addition, if there is any mutation in the membrane-binding receptor, the drug will not bind properly to the B cells, and RTX will be rendered ineffective [3]. Furthermore, the over-expression of CD46, CD55, and CD59, which are all CRPs, negatively impacts RTX efficacy [6,12].

The drug RTX eliminates the malignant B cells by four different mechanisms [6]. The major mechanism of RTX, complement-dependent cytotoxicity (CDC), kills the malignant targets by activating complement C3 and the membrane attack complex, through binding of the Fab region of RTX to four amino acid sequences located on a large extracellular loop on the B cells that express CD20 [1,6,7,9,10,12,15-18,22,23,25]. The second mechanism, antibody-mediated cellular cytotoxicity (ADCC), is triggered upon binding of the Fc portion to binding receptors FcγR [1,6,7,9-12,15-18,22,23,25-27]. Lastly, RTX also depletes B cells by inducing apoptosis and inhibiting direct growth [1,7, 9,15,16].

Although RTX has generally been well received for the treatment of various hematological diseases associated with CD20 expression, opinions have varied. It has been shown that RTX plays a fundamental role in the treatment of lymphomas, leukemias, and autoimmune diseases [6,7,9,12,16]. Studies focusing on the use of RTX, particularly in NHL, chronic lymphocytic leukemia (CLL), and autoimmune diseases, will be evaluated and analyzed in this review.

Rituximab in Non-Hodgkin's Lymphoma

NHL is the most common hematological malignancy 17. CD20 is expressed in about 90%-95% of all NHL cases [9,11,17]. Follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) are presented in 70% of NHL cases

[9,14,17]. RTX positively affects the treatment of these diseases [3,6-11,14-16, 21,25,28-31]. The impact of RTX will be reviewed below for each common type of NHL.

Diffuse large B-cell lymphoma: DLBCL are considered the most common form of NHL 14. RTX plus chemotherapy including treatment with cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP) has been approved to be the "gold standard" treatment for DLBCL patients regardless of patient age [1,3,6,9, 11,14,17,28,32]. In addition, studies that focused on the use of RTX revealed that RTX and CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) are not effective when used alone [1,3,9,11,14]. Research by Pfreundschuh, et al. on 824 patients with DLBCL, where patients were treated by both CHOP and R-CHOP therapy, indicated that the latter was more effective than CHOP alone.

Similarly, Niitsu, et al. reported that a patient with intravascular large B-cell lymphoma, a rare DLBCL, responded very well to RTX [33]. They reported an overall survival rate of 66% for patients undergoing R-CHOP therapy and 46% for patients undergoing only CHOP [33].

The efficacy of RTX is associated not only with CHOP but also with other kinds of chemotherapy. In a study by Saito et al., 34 two groups of patients with DLBCL received two different treatment regimens; the first group received TCOP (cyclophosphamide, therarubicin, vincristine, and prednisolone) between 1997 and 2002, while the second group received RTX plus TCOP (R-TCOP) from 2001 to 2005; the overall response in these two groups was 58% and 92%, respectively [34]. Overall survival was also greater in the second group. R-TCOP demonstrated impressive efficacy in the treatment of DLBCL, suggesting that both apoptosis and the inhibition of proliferation are responsible for RTX's effectiveness [34]. In addition, RTX maintained its significant efficacy under different physiological conditions, such as pregnancy.

Interestingly, RTX is safe for pregnant women [5]. In a study by Rey, et al. on a pregnant woman with DLBCL, RTX was shown to be effective and safe in the patient's third trimester [5]. Although a high titer of RTX was measured in the baby's blood, the baby exhibited normal growth and good health. However, a single case is insufficient to prove the safety of RTX in these circumstances, and more studies are needed to support the use of RTX in pregnancy to avoid any risk to both mother and child.

Samochatova, et al. [35] evaluated the efficacy of RTX when administered to children in a study on 11 children (8 boys and 3 girls) with DLBCL; MabThera, and chemotherapy plus RTX were administrated to the patients. Ten patients showed complete remission, whereas one showed partial remission [35]. Although the combination therapy elicited considerable improvement in these cases, further investigation should be done to understand the reasons underlying patients' resistance to this combination therapy.

In contrast to previous studies, Sar et al. studied 11 patients who did not respond to RTX [3]. However, the attempts by this study group to identify the reasons underlying the ineffectiveness of RTX were unsuccessful; genetic tests were conducted to establish if there was any mutation in the binding site; however, no mutation was detected and the low CD20 expression was ruled out as a factor 3. Further studies are necessary to understand the reasons behind the ineffectiveness of RTX in a minority of patients.

Follicular lymphoma: The aim of treating FL is to increase the survival rate for this incurable disease [9,29,30,36]. As 75%-100% of patients respond to RTX plus CHOP [36], R-CHOP is recommended for the treatment of advanced-stage FL [9,17,29,30,36,37]. A study of four randomly selected patients revealed prolonged survival with good prognostic signs following R-CHOP therapy 9, 10. Similarly, the results of a large study including 1000 patients with FL supported the use of RTX with chemotherapy, either CHOP or Cyclophosphamide, Vincristine, and Prednisolone (CVP). A significant increase was noted in survival rates for patients administered RTX with CHOP or CVP [11,30,36]. The survival time for the patients treated with the only CVP was 15 months, while that for patients treated with a combination of CVP and RTX was 32 months. Similar results were obtained for patients treated with CHOP and R-CHOP, where the survival time was 2.6 years and 4 years, respectively [11,36]. Furthermore, a 470-patient study in Europe illustrated that the survival time increased by 36 months with the use of RTX 11. This emphasizes the importance of RTX in increasing survival time. In Slovakia, Kafka et al. studied 10 patients treated by R-CHOP, and their findings supported the use of the combined treatment rather than CHOP alone [37].

RTX in chronic lymphocytic leukemia: Chronic lymphocytic leukemia (CLL) is a clonal malignancy of undefined etiology marked by the accumulation of mature B cells in the blood, spleen, liver, bone marrow, and lymph nodes 38. It is considered the most common form of leukemia in the Western world, with an annual incidence rate of 3-5 cases per 100,000 individuals [11,26,38]. CD20 is expressed on almost all B cells in B-CLL patients [38]. However, its expression was lower in CLL patients than in NHL patients [19,31,38]. Therefore, the effectiveness of RTX in B-CLL cases should be reviewed.

O'Brien, et al. reported that CLL patients treated with 500 mg/week of RTX for 4 weeks showed an overall response of 36%, and all responses were partial. However, Robak, et al. reported an overall response of 45% in 88 patients treated with 250 mg RTX, 3 times a week for 4 weeks [38]. Although the response was better in the latter study, side effects such as rigors, hypotension, bronchospasms, fever, and chills observed owing to an increase in the RTX dose [38]. Therefore, further studies are required to analyze the toxicity of RTX in CLL patients, and the dose must be fixed in these cases. In addition, it is important to determine if there is any correlation between dose toxicity and the patients' age and/or health status.

Several studies have evaluated the combined use of RTX and chemotherapy for CLL treatment [38]. Robak, et al. presented a study involving patients treated with fludarabine (FA) for 4 cycles. RTX was given to the patients in the third and fourth cycles in combination with FA; their overall response was 90%. Similar results were obtained in previous studies that used only FA (without RTX); thus RTX did not offer any advantage [38]. In contrast, Robak, et al. demonstrated that RTX is beneficial when it is added to the main treatment regime [38]. A combination of RTX and FA treatment was administered to randomized patients, and an impressive 90% overall response (OR) and a 47% complete response (CR) was obtained, as compared to previous studies that used only FA, wherein the OR was 77% and CR was 28% [38]. However, a major side effect was granulocytopenia. The positive results obtained in the second study support the initial use of RTX in combination with chemotherapy in CLL cases. The reduced expression of CD20 in these cases necessitates the need for longer-term RTX treatment to eliminate the B cells effectively. In the former study, RTX treatment might not have given for sufficient duration to show its efficacy.

Other studies examined the use of multiple antibody-dependent treatments. Zent, et al. evaluated the combined use of RTX and anti-CD52 Alemtuzumab on 30 untreated patients with CLL [26]. Alemtuzumab had a limited effect on the malignant cells and RTX was found to be ineffective. Intrinsic factors were suggested to be responsible for the resistance to RTX cytotoxicity [26]. Furthermore, the low expression of CD20 in CLL patients could be one of the causes of resistance [26]. Addition of RTX to Alemtuzumab did not increase the efficacy of the treatment [26]. ADCC was claimed to be the major action mechanism of RTX, although other studies have shown that CDC is another fundamental action mechanism of RTX [18,26]. More studies dissecting the mechanism of RTX action and its role in killing B cells are strongly recommended. These studies may also illustrate the reasons for RTX resistance.

Some additive therapies and drugs can enhance RTX efficacy. Abraham, et al. presented the case of a 59-year-old woman with CLL who was treated with RTX and fresh frozen plasma as a source of complement after she was found to be refractory to R-CHOP [19]. The patient displayed a noticeable response to the treatment. An abnormality in the patient's complement system was the likely cause for the resistance. In addition, it was found that most CLL patients have low complement levels [19]. This study demonstrated a crucial point that may explain the reduced RTX efficacy in patients with CLL. Unfortunately, the death of the patient from sepsis caused by E. coli did not allow measurement of the complement levels after treatment [19]. However, the toxicity of the treatment, which might have been responsible for sepsis and death, was marginalized. Further studies are strongly recommended to discover the cause of resistance and the toxicity of the treatment in order to provide effective and safe treatment to CLL patients.

A study by Smolewski, et al. illustrated the effectiveness of bortezomib in the treatment of multiple myeloma and mantle cell lymphoma; plus RTX was found to kill B-CLL cells *in vitro* [39]. Seventy-three random samples collected from patients with B-CLL suggested beneficial effects of the combination treatment in eliminating the malignant cells. The combination treatment was compared with previous studies where RTX or bortezomib was used alone [39]. The combined therapy demonstrated a high potential to kill B-CLL cells even at low doses, considering that high doses of bortezomib or RTX would be required when used alone. This study was the first research examining this type of treatment [39]. Nonetheless, the *in vitro* responses to treatment are not the same as the *in vivo* responses as the *in vitro*

environment differs greatly from that *in vivo*. Therefore, more *in vivo* research focusing on this therapy is suggested in order to demonstrate the advantages and adverse effects of this combination treatment.

Klepfish, et al. studied a 70-year-old woman diagnosed with B-CLL, with a WBC count of 45 × 103 and severe lymphocytosis [19]. She was treated with RTX plus methotrexate and dexamethazone, an anti-metabolite, and an anti-folate, respectively. Unexpectedly, she responded to the treatment and her WBC count returned to a normal range at 5.1 × 103, although she exhibited poor prognostic factors. Klepfish, et al. recommended further studies to identify the correlation between prognostic factors and favorable response to RTX in order to better our understanding of this therapy [19].

RTX in Autoimmune Disorders

B cells play an essential role in the immune system by binding to non-self-antigens. In autoimmune disorders, B cells bind to self-antigens due to various abnormalities. Recently, RTX has been used for the treatment of several autoimmune disorders [6]. Studies on rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and incompatible ABO transplantation are reviewed below.

Rheumatoid arthritis: In 2006, RTX was approved by the FDA for the treatment of patients with rheumatoid arthritis (RA) [6,22]. RA is an inflammatory autoimmune disease that mainly affects the synovial membranes of joints [6,20]. As B cells were responsible for the pathophysiology of the disease, RTX was an effective therapy [6,20-23,40].

Gurcan, et al. and Caporali, et al. reviewed two studies [6,22]. One study included 161 RA patients treated with either RTX and MX or RTX and CYP. Their responses were measured according to the American College of Rheumatology 20% response scores (ACR20), wherein 73% response was observed. In the second study of 520 patients given either RTX or a placebo (311 RTX and 209 placebo), the patients treated with RTX fared significantly better [6,22]. Despite the efficacy of RTX, the safety of this treatment should be further examined.

Fleischmann, et al., Caporali, et al. and Sibilia, et al. reviewed numerous articles that demonstrated the efficacy and safety of RTX in RA cases [20,22,23]. They found the most common side effects to be acute infusion reactions, including headache, nausea, pruritus, urticaria, and hypertension. However, these symptoms can be controlled by corticosteroids or antihistamines [20,22,23]. In addition, most adverse side effects were proven to be mild-to-moderate but were rarely severe [20,22]. Furthermore, the incidence of side effects in the second course was lower than that in the first course; infection rates increased among patients as a consequence of the immunity suppression from reduced B cell counts [20]. Nevertheless, the rates were within the acceptable ranges. The most common infections in patients were upper respiratory tract infections and urinary tract infections [20,22,23].

Systemic lupus erythematosus (SLE): SLE is characterized by the development of anti-DNA autoantibodies and deposition of the immune complex within the body [6,24]. RTX was used in cases refractory to first-line therapy [6,24]. Sutter, et al. evaluated the effect of RTX on 12 patients with SLE who all responded successfully [24]; Gurcan, et al. presented two studies that examined RTX treatment in SLE patients [6]. In the first study, 208 patients were treated with RTX; 159 patients responded to the treatment. The second study examined pediatric patients; SLE is typically more severe in children as a result of their unique type of Fc receptor. The efficacy of RTX was shown to depend on the Fc receptor's structure. The study, designed to evaluate the effect of RTX on this group of patients, reported response in 84% of patients 6. Although RTX was more effective in children, the safety of the treatment was controversial [6]. Different opinions emerged probably owing to the limited research carried out in this area. Therefore, further studies are strongly suggested to illustrate the safety of RTX in adults and children with SLE.

Rituximab in incompatible ABO transplantation: ABO antigens are expressed on tissue cells [41]. In an incompatible ABO transplantation, the patients might already have antibodies against the transplanted grafts, thereby treating it as foreign. As a result, transplantation typically fails, and acute humoral rejection results [41,42]. Although splenectomy is usually performed to reduce the risk of allograft rejection, RTX was proven to be more effective than splenectomy in these cases [41,42].

In a study conducted in Korea by Kim et al., three patients who had ABO-incompatible liver transplantation were given 375 mg/m^2 RTX without any splenectomy procedure [41]. Antibody levels were evaluated 7 days before the transplantation and afterward. Antibody levels did not increase; likewise, the patients did not present any symptoms

of acute humoral rejection. However, three patients had bacterial infections, and one of these patients died as a consequence of *Pseudomonas* sepsis, despite having good hepatic function [41].

Chikaraishi, et al. presented a study in Japan that included 8 patients with ABO-incompatible kidney transplants 42 administered 200 mg/m^2 RTX without a splenectomy procedure. The therapy was successful in all patients without any reported side effects such as infection [42]. RTX was thus shown to be very effective in such transplantation cases. However, the dosage remains controversial. The adverse effects in the first study by Kim, et al. were probably caused by the high dose of 375 mg/m^2 given to the patients [41]. A dose of 200 mg/m^2 was demonstrated to be effective and safe in incompatible ABO transplantations. Further studies are recommended to illustrate the optimal dosage and to reveal the effects of the therapy on different age groups. Considering that both of these studies were conducted in Asia, more studies on varied ethnic groups are suggested.

CONCLUSION

The chimeric IgG1 monoclonal antibody, RTX, is one of the antibody-dependent therapies considered to significantly improve B cell-related disorders. The efficacy of RTX depends on several different factors, such as the expression of CD20 and CRP and the genetic structure of the binding site. CDC and ADCC are the main mechanisms of B cell elimination, although several points related to the mechanisms are either controversial or unknown. RTX was shown to be effective and generally safe for use in the treatment of some types of lymphomas, leukemias, and autoimmune diseases. RTX is the first treatment of choice in NHL. Most studies have corroborated the benefits of RTX in both DLBCL and FL cases. In addition, RTX is safe for use in pregnant patients and children with NHL. However, a few cases were reported to be refractory to RTX. Furthermore, RTX is a controversial treatment in B CLL cases; the reduced efficacy of the therapy in CLL in comparison with NHL is could be attributed to reduced CD20 expression on the B cells. The studies have reported some side effects, such as hypotension, granulocytopenia, and chills. Similarly, mild-to-severe infections can occur and appear to be mainly dose-related. Despite these adverse effects, RTX plus chemotherapy is effective in a considerable number of CLL cases, and it was shown that adding a complement source to RTX treatment increases the overall efficacy. Recently, RTX has demonstrated favorable results in numerous autoimmune disorder cases. The FDA approved RTX as a treatment for RA in 2006; the treatment causes mild-to-moderate infections, but these are not severe or fatal. The most common adverse effect is an acute infusion reaction, which can be controlled by corticosteroids and antihistamines. In SLE patients, RTX was found to be effective but is not considered safe for children. RTX has been suggested for incompatible ABO transplantation in place of splenectomy to avoid acute humoral rejection. Indeed, the therapy was very beneficial, but the dose remains controversial.

Further studies on the use of RTX in the treatment of B cell-related disorders would offer many advantages. First, studies could focus on the reasons underlying resistance to RTX, which are currently unknown or unconfirmed presumptions. Second, a study of the mechanisms by which RTX kills B cells would lead to a better understanding of these mechanisms, and this would increase our understanding of the disease pathophysiology and its contributing factors. Third, more research on the proper doses under different conditions, disorders, and ages will certainly lead to better and safer use of the treatment, which in turn, will reduce toxicity and severe side effects. Lastly, further studies that include different ethnic groups are expected to demonstrate variability in responses owing to genetic differences.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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