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Rituximab Treatment in Dermatology

Muazzez Çiğdem Oba,[*1] MD, Özge Aşkın, [1] MD, Burhan Engin,[1] MD, Zekayi Kutlubay,[1] MD, Server Serdaroğlu,[1] MD

Address: [*]Department of Dermatology and Venereology. Istanbul University, Cerrahpaşa Medical Faculty
E-mail: muazzez.oba@istanbul.edu.tr
Corresponding Author: Dr. Muazzez Çiğdem Oba, Department of Dermatology and Venereology Istanbul University, Cerrahpaşa Medical Faculty,İstanbul Turkey

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Abstract

Background: Rituximab is a chimeric monoclonal antibody targeting CD-20, which is a B cell surface antigen. Autoimmune vesiculobullous diseases, connective tissue diseases, graft-versus-host disease and vasculitis are the main categories of dermatoses for which rituximab has shown successful clinical applications. Infusion reactions and infections are the most common adverse-effects. This review summarizes the pharmacology, mechanism of action, clinical uses and adverse effects of this promising agent.

Introduction

Rituximab is a monoclonal antibody targeting CD-20, which is a B cell surface antigen. As a B cell depleting agent, first FDA-approved indication of rituximab was the B-cell non-Hodgkin's lymphoma. In the following years, the drug obtained approval for the treatment of rheumatoid arthritis, chronic lymphocytic leukemia granulomatosis with polyangiitis, microscopic polyangiitis and lastly pemphigus vulgaris. Currently there is growing evidence for the use of rituximab in the treatment of various autoimmune and dermatologic diseases. This review summarizes the pharmacology, mechanism of action, clinical uses and adverse effects of this promising agent.

Pharmacology

Rituximab has an approximate molecular weight of 145 kDa. It is genetically engineered chimeric monoclonal IgG1 kappa antibody. It consists of murine light and heavy chain variable region sequences and human constant region sequences [1]. Variable region of the antibody binds to CD20 antigen.

Rituximab half-life is estimated to be 3 weeks [2]. Clearance pathways are not well-known, but thought to be through phagocytosis by the reticuloendothelial system [3].

Mechanism of Action

Rituximab exerts its effects mainly by decreasing number of CD 20+ B cells. As known, B cells are the mediators of autoimmunity. Among others, they play role in autoantibody production, cytokine release, antigen presentation and costimulation [4]. Upon binding of rituximab to CD20 antigen, B cell depletion occurs through three main mechanisms: Antibody-dependent cellular cytotoxicity, complement-mediated cytolysis, triggering of apoptosis [5]. Besides its effects on B cells, rituximab treatment also leads to secondary

immunomodulatory changes in T cell population such as decreased numbers of memory T cells and increased numbers of regulatory T cells [**6,7**].

The transmembrane glycoprotein CD20 antigen is expressed on pre-B cells and preplasma cells. Hematopoietic stem cells, pro-B cells and plasma cells are spared of the effects of rituximab as these cells are devoid of CD20 antigen [**8**]. Following rituximab infusion, CD20+B cell count in peripheral blood decrease approximately by 90% in 3 days. B cell depletion is sustained during 6-9 mon ths. In addition, as B cells cannot transform into plasmablasts and plasma cells, new autoantibody production stops [**9**]. Of note, with prolonged disease continuous autoantigen stimulation triggers the formation of long-lived plasma cells. These long-lived plasma cells continue autoantibody production despite rituximab treatment. This is why rituximab therapy is more effective when administered at early phases of the disease [**10**].

Clinical Uses

Clinical applications of rituximab may be grouped under six headings (**Table 1**).

Rituximab 375 mg/m2 administered as iv infusion once a week for 4 weeks is the FDA approved dosage for lymphoma. For rheumatoid artritis (autoimmune protocol) 1000 mg iv infusion is given 2 weeks apart (day 0 and day 15) [**4**].

Autoimmune Vesiculobullous Diseases

Rituximab has been used with success in treatment-resistant pemphigus, relapsing pemphigus and in patients with contraindications to systemic corticosteroids. Both the lymphoma dosage and autoimmune dosage was used in case series in the literature. In recent studies patients were mostly treated using the autoimmune protocol [**9**]. Recently first-line use of rituximab in the treatment of pemphigus was evaluated in a randomized clinical trial. In this study, the combination therapy of rituximab with short-term steroids was found to be superior to conventional high-dose steroid therapy in terms of both efficacy and safety. 46 patients were treated with rituximab in autoimmune protocol combined with low-dose prednisone (0.5-1 mg / kg / day) tapered rapidly in 3-6 months; followed by rituximab in the 12th and 18th months. 41 patients were treated with high dose steroids (1-1.5 mg / kg / day) tapered in 12-18 months. Complete remission rates in the second year after treatment were 34% in the group receiving conventional treatment and 89% in the rituximab group. The relapse rates with rituximab were less than the conventional treatment (23% vs 46%). Cumulative steroid dose and treatment side effects were 3 times and 2 times less, respectively, in the group receiving rituximab [**11**].

So far, rituximab is mostly used as a combination therapy for the treatment of pemphigus. In a recent review evaluating data of 283 pemphigus patients; 52% of the patients were using corticosteroids and immunosuppressives, 29% of the patients were using corticosteroids along with rituximab. In only 19% of the cases, rituximab was administered as monotherapy. In general, complete remission rates were reported to be over 80%. In most series, rituximab was associated with decreased need for corticosteroids [9]. Rituximab infusions were also used in combination with IvIg. Induction treatment was performed with 2 cycles of weekly 375mg / m2 rituximab applied for 3 weeks and 2mg / kg IVIG applied at 4th week. Then, monthly rituximab and IvIg were applied for 4 months (3rd, 4th, 5th, 6th months). All patients received complete response after 7 to 10 rituximab infusions. The mean duration of clinical remission was reported as 31 months [**12**].

The use of rituximab in the maintenance of pemphigus has also been discussed. In a single-center study, patients who had partial remission at 6th month were treated with an additional rituximab infusion but those in complete remission 6th month were not given rituximab. The authors observed that relapses were less common (33% vs. 50%) in rituximab treated group. However, there is no definitive information about the duration of infusion, infusion number and infusion doses in maintenance treatment of rituximab [**9,13**].

Paradoxical exacerbation of pemphigus has been reported with rituximab therapy. It is thought that rituximab in pemphigus may cause the worsening of the disease by disrupting the balance between the regulatory cells

Table 1. Clinical Uses of Rituxima

1. Autoimmune vesiculobullous diseases
Pemphigus vulgaris, pemphigus foliaseus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, bullous pemphigoid, mucous membrane pemphigoid, dermatitis herpetiformis
2. Autoimmune connective tissue diseases
Dermatomyositis, cutaneous lupus erythematosus
3. Graft-versus-host disease (GVHD)
4. Vasculitis
Wegener's granulomatosis (WG), microscopic polyangiitis, cryoglobulinemic vasculitis, Churg–Strauss syndrome, and Henoch–Schönlein purpura.
5. Cutaneous B-cell lymphoma
6. Others
Melanoma, atopic dermatitis, chronic spontaneous urticaria

and pathogenic B cells. Combining rituximab therapy with steroids is thought to be useful in reducing paradoxical reactions [**14**].

Rituximab may be considered for the treatment of bullous pemphigoid and mucous membrane pemphigoid unresponsive to conventional agents. Rituximab may prevent the scar formation in unaffected eye in patients with mucous membrane pemphigoid. Treatment-related infective and cardiac complications must be kept in mind in elderly patients [**15**].

Immunosuppressives may be used in patients with dermatitis herpetiformis who are resistant to gluten-free diet and dapsone therapy. In the literature, clinical and serologic response was obtained with rituximab in a treatment-resistant patient [**16**].

Autoimmune Connective Tissue Diseases

ISuccessful results with rituximab have been reported in cutaneous lupus erythematosus, especially in subacute cutaneous lupus, in patients resistant to classical therapies. As in pemphigus, rituximab reduces the dose of systemic steroids in lupus patients [**17**].

Rituximab therapy improves both the skin and mucscle symptoms in dermatomyositis patients whose disease is refractory to steroids [**18, 19**].

Graft-versus-host disease (GVHD)

Good responses were reported with rituximab in skin and mucosal findings of corticosteroid-resistant chronic GVHD [**20**].

Vasculitis

Rituximab for anti-neutrophil cytoplasmic antibody-associated vasculitides (granulomatosis with polyangiitis and microscopic polyangiitis) has been reported to be successful in induction of remission [**21**]. Rituximab may also be effective in the treatment of cryoglobulinemic vasculitis, Churg–Strauss syndrome and Henoch–Schönlein purpura [**22, 23, 24**].

Cutaneous B-cell lymphoma

Primary cutaneous B-cell lymphomas are non-Hodgkin's lymphomas originating from the skin including primary cutaneous marginal zone lymphoma, primary cutaneous follicular lymphoma, primary cutaneous diffuse large B-cell lymphoma - leg type, and others. In these cases systemic treatment and in the presence of a few lesions, intralesional treatment with rituximab may be applied [**25, 26**]. Eighteen patients with follicular lymphoma and 17 patients with marginal zone lym phoma were treated with intralesional rituximab, most of them with 10mg/lesion rituximab 3 times a week at 1 month intervals. Complete and partial response rates were reported as 71% and 23% respectively [**27**]. In another study, complete remission was reported in 14 of 16 patients who received systemic treatment with the same diagnoses [**28**].

Others

In a series of 9 patients with stage IV metastatic melanoma without evident disease, rituximab was shown to reduce recurrence rates [**29**]. Successful results have also been reported in a recent series of 7 patients with advanced melanoma. Considering good safety profile of rituximab future studies may investigate the combined use of anti-PD-1 antibody therapy with rituximab [**30**].

Six patients with severe atopic dermatitis all showed an improvement in disease activity scores within 4 to 8 weeks following rituximab therapy [**31**]. Rituximab therapy is thought to act through blockage of T cell activation in patients with atopic dermatitis [**32**]. However, treatment failures and worsening of the disease have also been reported [**33, 34**].

The number of memory B cells responsible for autoantibody formation decreases with rituximab therapy. This mechanism has resulted in the use of rituximab in resistant chronic spontaneous urticaria. In the vast majority of case reports in the literature, rapid and long-term (over 8 months) response to rituximab was obtained in chronic spontaneous urticaria patients [**35**].

Adverse effects

Overall severe adverse effects are infrequent with rituximab therapy, as compared with corticosteroids and immunosuppressants. Most common adverse effects are infusion reactions and infections [**32, 36**].

The most commonly reported infusion reactions are tachycardia, rash, itching, chest pain and hypotension. These conditions are usually encountered in the first infusions. Most of the time, the symptoms resolve upon slowing the infusion rate. The risk of these reactions in subsequent infusions is significantly reduced. In the autoimmune protocol, 1000mg infusion administered at intervals of two weeks should be administered at approximately 5 hours. If the first infusion is well tolerated, other infusions can be administered in 3-4 hours. Premedication with paracetamol, diphenhydramine and met hylp rednisolone is effective in reducing infusion related reactions. Anaphylactic hypersensitivity reactions, which resemble infusion-related reactions, may also occur during the first few minutes of infusion due to sensitivity to murine proteins [**9, 32**].

Other side effects include infections, exacerbation of cardiovascular diseases, toxic epidermal necrolysis, leukoencephalopathy and viral reactivations. The rate of infections is 7% and rate of serious infections is between 1.3 and 1.9%. Two rare side effects of leukoencephalopathy and viral reactivations have not been reported with the use of rituximab in dermatological diseases. Worsening of cardiac conditions such as myocardial infarction, heart failure, pulmonary edema and atrial fibrillation have been reported. Cytopenias, especially neutropenia, can occur but usually show a mild and transient course [**32**].

Monitoring

Rituximab is contraindicated in patients with active infection. It is recommended that pretreatment vaccines be up-to-date. Live vaccines cannot be administered to patients receiving rituximab. Pregnancy and lactation are other contraindications to rituximab. Contraception is recommended for 12 months after the last rituximab application [**37**].

Basic investigations that must be performed in every patient is seen in (**Table 2**) [**38**]. Screening for HBV infection is of utmost importance as reactivation of HBV can lead to fulminant hepatitis and liver failure, which carry a high mortality rate [**39**]. After first infusion, complete blood count, renal function tests and liver function tests should be followed-up monthly.

Table 2. Basic Investigation Before Therapy

Complete blood count
Chest X-ray
Renal and liver function tests
Anti-HIV
HBsAG,
Anti HBC core total antibody
Anti HCV antibodies
Electrocardiogram (ECG)

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