Novel applications of Rituximab in dermatological disorders

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ABSTRACT

Rituximab is a monoclonal therapeutic anti-CD20 antibody that has been approved for use in lymphoma and rheumatoid arthritis. Over the past decade several reports based on case series and observational studies have recorded the benefits of rituximab in particular groups of dermatological patients. Off-label use of rituximab in many dermatological indications is not uncommon in many countries in the world. This article reviews the available data that may be of use to the practicing dermatologist. Because of its potential complications, paucity of clinical data, and cost considerations, rituximab is favoured only when standard systemic therapies fail or corticosteroids are absolutely contraindicated. Further research is required in this field.

Key words: Anti-CD20 antibody, dermatology, rituximab

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.137766

Quick Response Code:

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INTRODUCTION

The basic understanding of inflammatory dermatoses and autoimmune-mediated skin disorders has significantly progressed and widened our understanding of fundamental immune mechanisms that shape the intricate system of chronic inflammation and autoimmunity.[1] Current studies have shown that B cells play a serious role in autoimmunity and disease expression through several functions. These include autoantibody production, cytokine secretion, antigen presentation, and co-stimulatory effect. Thus, therapies targeting B cells could be utilized for treating connective tissue disorders.[2,3]

Two-way interactions between B and T cells could be crucial to understanding autoimmunity: B cells signal and stimulate T cells through antigen presentation as well as through additional ligand interactions. T cells signal and trigger B cells through cytokines and cell-surface ligands. These interactions are hypothesized to generate a positive feedback loop leading to autoimmunity and chronic inflammation. B-cell production of proinflammatory cytokines such as TNFα and IL-6 is supposed to play a role in pathology of autoimmune disorders. Additionally, the autoimmune response is exacerbated through autoantibody production by plasma cells and B cells. Targets for therapy include mechanisms for B-cell survival and maturation as well as cell-surface ligands. Two such B-cell-specific cell-surface markers are CD20 and CD22. These are targets for therapeutic monoclonal antibodies (mAbs), the effect of which is to deplete B cells at specific stages in their development.[4-6]

Rituximab was introduced into clinical practice as a medication with substantial potential. Its use in patients with B-cell lymphoma and rheumatoid arthritis (refractory to disease-modifying antirheumatic drugs (DMARD) and/or anti-tumor necrosis factor therapy (TNF)) since 2006 revealed several indications in autoimmune diseases, many of which include the skin, accordingly necessitating dermatologists to develop familiarity with both the characteristics of anti-CD20 antibodies and the role of B cells in multiple skin diseases. Recognizing these developments, dermatologists should be able to use rituximab more regularly and suitably in patients besides drawing up consensus guidelines grounded on the large case series. In other words, establishing the indications for rituximab will make it possible to shorten disease course and reduce morbidity due to more specific drugs.[7,8] B cells played a significant role in the pathophysiology of rheumatoid arthritis (RA) and numerous clinical trials attested that B-cell depletion therapy significantly assisted patients who had hitherto failed other remedies.[9-13] As more is understood about rituximab and its potential as a targeted biologic treatment in

various autoimmune and immune-mediated diseases, clinicians are paving the way for the expanding use of this medication in the field of dermatology.

MECHANISM OF ACTON

Rituximab is an immunoglobulin G1 (IgG1) kappa monoclonal antibody composed of a murine variable region (Fab portion) that is fused onto a human constant region (Fc portion) [Figure 1]. The Fab portion binds specifically to the CD20 antigen, located exclusively on the surface of pre-B and mature B lymphocytes [Figure 2]. Once bound, the Fc portion of rituximab recruits immune effector cells to help mediate cell lysis of the CD20+ B lymphocytes via three possible mechanisms [Figure 3]:

- complement-dependent cytotoxicity (CDC)
- antibody-dependent cell-mediated cytotoxicity (ADCC)
- apoptosis.

CD20 is expressed only on pre-B and mature B lymphocytes; thus, treatment with rituximab spares hematopoietic stem cells and plasma cells because they lack CD20 antigen. This selectivity allows for B-cell regeneration from unaffected hematopoietic precursors as well as the continued production of immunoglobulins from plasma cells. B-cell regeneration into peripheral circulation has been shown to occur at approximately 6 to 12 months following therapy, and serum immunoglobulins have not been shown to decrease significantly.[14-19]

Rituximab therapy may be used to secondarily reduce the production of T-cell modulating cytokines, interfere with the presentation and processing of autoantigens, besides decreased activation of autoreactive T cells. The success of rituximab in T-cell-mediated autoimmune diseases, such as RA, and in conditions not directly linked to autoantibody production, such as atopic dermatitis (AD) supports the possible use of rituximab for the benefit of these alternative mechanisms. However, the exact contribution of each mechanism to the various proposed diagnoses remain unclear at this time.[20-23]

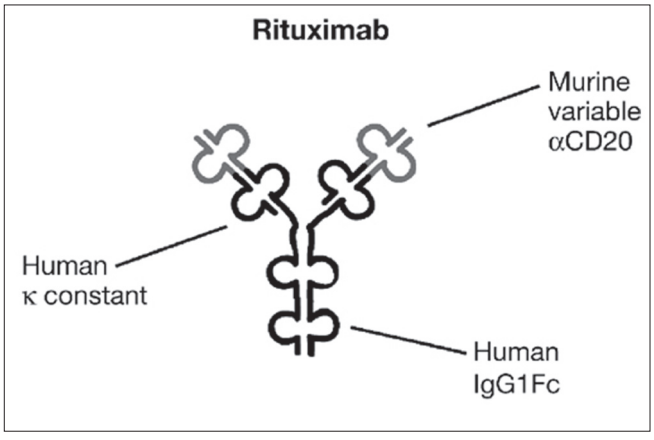

Figure 1: Structure of rituximab

DOSAGE AND ADMINISTRATION

Rituximab 375 mg/m^2 administered as an IV infusion, once a week either singly or combined with other chemotherapy regimens, is the dosage recommended for one of the two US FDA approved indications, that is, NHL.[24] For the other USFDA-approved indication, that is, RA, the recommended dosage guidelines is 1000 mg given at the interval of 2 weeks apart (day 1 and day 15).[25-27]

Although these protocols are the standard approved and most common, there is no official consensus on the most efficacious and safest dosing of rituximab in off-label applications. Regimens using rituximab concurrently with other medications (such as immunosuppressants and/or immuno-modulators) have also been reported in the literature. Specifically, high-dose intravenous immunoglobulin (IVIG) has proven beneficial for several autoimmune diseases and has therefore been investigated for its use in combination with rituximab.[7,28] Ahmed *et al.*,[28] reported clinical remission and a reduction of autoantibodies in several pemphigus vulgaris (PV) patients treated with the combination of rituximab (375 mg/m^2) and IVIG (2 g/kg). In autoimmune blistering disorders, the most commonly reported dosing schedule is 375 mg/m^2 administered as an IV infusion weekly for four consecutive weeks, as used in NHL.

APPLICATIONS OF RITUXIMAB

1. PRIMARY CUTANEOUS B-CELL LYMPHOMAS

B-cell lymphoproliferative disorders are a continuum from benign cutaneous lymphoid hyperplasia (CLH) or 'pseudolymphoma' to primary cutaneous B-cell lymphoma (PCBCL). PCBCLs are cutaneous non-Hodgkin lymphomas and can be classified clinically and by prognosis. A combination of antibiotics, topical or

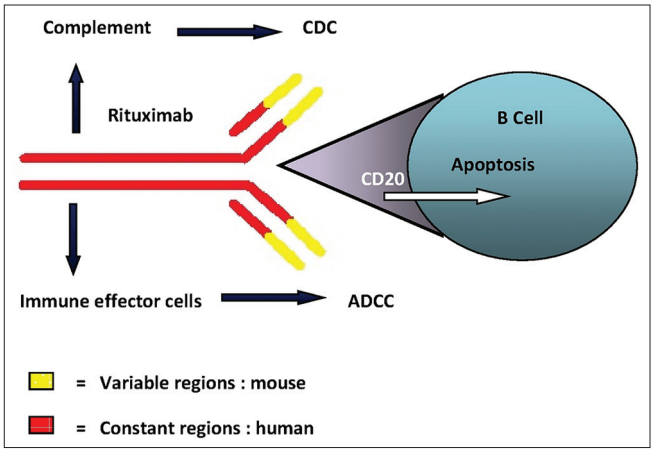

Figure 2: Rituximab binding to CD20 protein

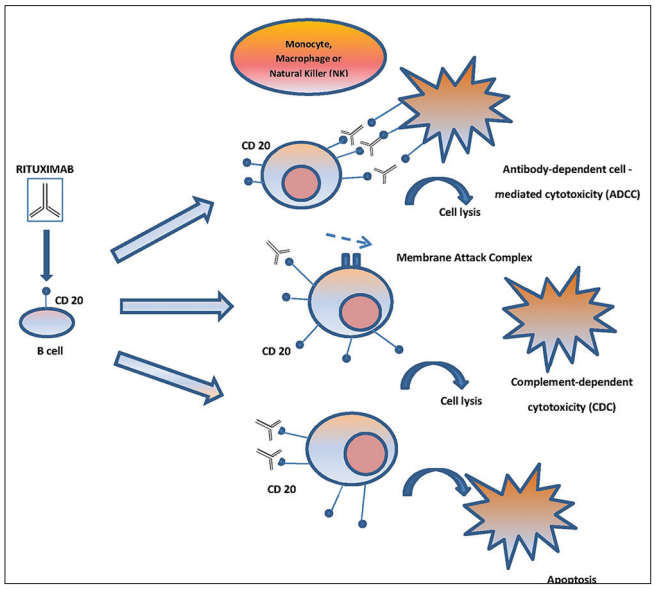

Figure 3: Mechanism of rituximab

intralesional corticosteroids, and/or localized radiotherapy was the conventional mode of treatment.[29] Systemic or intralesional interferon (IFN)-alpha could be an alternative in PCBCL with diffuse cutaneous lesions. In aggressive forms with poor prognosis, polychemotherapy is the first line of treatment although rituximab and radioimmunotherapy are evolving therapeutic options. In the majority of cases, the treatment of CBCL is straightforward. In aggressive forms, new therapies and biologic therapies may be of real interest.[30]

The effectiveness, tolerance, and adverse effects of intralesional rituximab (ILR) in 18 patients with follicle centre (FCL) and 17 patients with marginal zone (MZL) PCBL were evaluated. In 71% and 23% of patients, respectively, complete response (CR) and partial response was achieved. Eight weeks was the mean time to CR in patients who received 10 mg of ILR per lesion. Similar response rates were observed in MZL and FCL. Median disease-free survival was 114.1 weeks. The median follow up was for a period of 21 months. Thus, it should be considered a useful alternative in patients with recurrent lesions and in whom the sequelae of radiotherapy or surgery would be significant.[31]

Additionally, the therapeutic value of the anti-CD20 antibody rituximab was evaluated by a retrospective analysis in 16 consecutive patients with primary cutaneous CD20+ B-cell lymphomas by Valencak *et al*. Systemic therapy with rituximab 375 mg/m^2 once a week for four or six consecutive weeks was administered to the 16 patients enrolled. Eleven patients had primary cutaneous follicle center cell lymphoma and five patients had a primary cutaneous marginal zone B-cell lymphoma. Fourteen patients (87.5%) achieved complete remission (CR) of the sixteen patients with PCBCL. However, 5 to 14 (35%) patients with CR relapsed, in an interval between 6 and 37 months. There were no severe side effects. Thus, single-agent treatment with i.v. rituximab appears to be feasible and safe resulting in a high rate of durable remissions. In lieu of the promising results, rituximab could prove to be a potential treatment option and should be directly compared with local radiotherapy.[32]

Preference for the leg (72%), a high proportion of Bcl-2 expression (85%), an advanced age at onset (mean age, 76 years), frequent relapses and extracutaneous dissemination are certain characteristics of primary cutaneous diffuse large B-cell lymphoma, leg type. The overall 5-year disease-specific survival rate was 41%. Location on the leg and multiple skin lesions were predictive of death, based upon a multivariate analysis. Particularly in patients with multiple tumors on the legs, primary cutaneous diffuse large B-cell lymphoma, leg type is a distinct entity with a poor prognosis. Notwithstanding the advanced age of many patients a combination of anthracycline-containing chemotherapies and rituximab could improve prognosis.[33]

2. MELANOMAS

Melanomas constitute a distinct cell subpopulation. Numerous of these subpopulations, as well as one expressing CD20, might harbour stem cell-like or tumor-initiating characteristics. Pinc *et al*. hypothesized that adjuvant anti-CD20 therapy might assist patients at high risk of disease recurrence. Consequently, they began a small pilot trial to study the effect of the anti-CD20 antibody rituximab in a group of melanoma patients with stage IV metastatic disease who were considered disease-free by way of surgery, chemotherapy and/or radiation therapy. Safety was the primary objective, whereas description of recurrence-free intervals (RFI) and overall survival (OS) were the secondary objectives. Rituximab 375 mg/m^2 once a week for 4 weeks followed by a maintenance therapy every 8 weeks was administered to nine patients. The treatment was withdrawn after 2 years or with disease recurrence. Treatment was well tolerated. The median neither of RFI nor of OS has been reached after a median observation of 42 months. Six out of nine patients are still alive and five of them are recurrence-free in spite of the therapy that ended after 2 years. However, the patient number is too small for definitive conclusions. This data may characterize a first instance of the prospective therapeutic value of targeting CD20 (+) cell populations-at least for a subset of patients.[34]

Based on the preclinical data, it is stated that melanoma, once established, is sustained by a minor, non-random subset of cancer cells that are characterized by CD20 expression. Notwithstanding this fact, current therapeutic schedules endeavour to eradicate all malignant cells of a melanoma lesion. Schlaak *et al.* also tried to eliminate those cells in a progressing chemotherapy-refractory metastatic melanoma patient by lesional injections of the anti-CD20 therapeutic antibody rituximab and simultaneous low-dose systemic dacarbazine therapy. Although

the frequencies of CD20+ melanoma cells within the tumor lesions were initially about 2% and the bulk of tumor cells did not express CD20. Long-lasting remission of treated tumor lesions was produced by rituximab therapy. Additionally, rituximab decreased the melanoma serum marker S-100 to physiological levels. Rituximab also induced a switch of serum cytokines from a T helper-2 to a pro-inflammatory T helper-1 cell profile. No grade 3/4 toxicity related to treatment was observed besides B cell elimination and decline in gamma globulin levels. Thus, targeting the minor subset of CD20+ 'melanoma sustaining cells' induces regression of chemotherapy-refractory melanoma and highlights the potency of selective cancer cell targeting in the treatment of melanoma.[35]

3. AUTOIMMUNE VESICULOBULLOUS DISORDERS

Autoimmune bullous diseases are a heterogeneous group of disorders that can be subdivided according to the level of split formation in the intraepidermal blistering diseases such as pemphigus vulgaris and subepidermal bullous disorders, the latter including pemphigoid diseases, and dermatitis herpetiformis. These characterize a diverse group of disorders of the skin and mucosa that are usually accompanied with IgG or IgA autoantibodies against discrete adhesion molecules of the skin. In pemphigus, antibodies are also directed against antigens (desmoglein 1 and 3) in the desmosomes linking keratinocytes and against acetylcholine receptors. The antibody-induced loss of adhesion between keratinocytes causes blister formation and widespread erosions. Systemic immunosuppressive drugs typically represent the foremost therapeutic regimen. Primarily, systemic corticosteroids are generally administered in combination with steroid-sparing, immunosuppressive agents. [36,37]

Trials with high-dose corticosteroids either as pulse therapy or in daily doses have shown that they are not superior to moderate daily doses and these could be accompanied by very serious adverse effects. However, a recent study demonstrated a significant reduction in corticosteroid requirements among patients receiving immunosuppressive agents. Newer therapies, such as biologic agents (in particular rituximab), calcineurin inhibitors, or immunoadsorption also appear promising.[38]

Eleven patients with extensive PV were treated with the anti-CD20 antibody, rituximab (375 mg/m^2 body surface area once a week for 4 weeks). Besides a peripheral B-cell depletion for 6–12 months, a significant reduction in the levels of serum autoantibodies and marked clinical improvement was observed in all PV patients treated with rituximab. There was a significant decrease in the frequencies of dsg3-specific CD4(+) Th1 and Th2 cells for 6 and 12 months, respectively. Additionally, the overall count of CD3(+) CD4(+) T lymphocytes and the frequency of tetanus toxoid-reactive CD4(+) Th cells remained unchanged. Thus, these findings suggest: (1) the depletion of autoreactive B cells and (2) presumably specific downregulation of dsg3-specific CD4 (+) Th cells, are the two mechanisms involved in the response to rituximab in PV.[39]

Newer therapeutic strategies such as immunoadsorption (IA) and the anti-CD20 antibody rituximab aim at directly interfering with pathogenic autoantibodies (auto-Abs) in refractory cases. To determine the long term efficacy of IA in conjunction with rituximab in patients with difficult-to-treat PV, Behzad *et al.* evaluated the clinical response to treatment by measuring the autoimmune bullous skin disorder intensity score, IgG auto-Abs against desmoglein 1 and 3 (Dsg1 and Dsg3) and the dose of systemic corticosteroids. Clinical and serological parameters of 10 patients with difficult-to-treat PV were also retrospectively analyzed. Therapy consisted of IA at 4-week intervals, followed by rituximab either twice at 1000 mg or four times at 375 mg/m^2. Corticosteroid was tapered according to the individual clinical status. Six months after the first IA treatment 8 of 10 patients demonstrated a complete remission on therapy while one patient showed a partial response and one patient was unresponsive to the treatment. At 12 months, six of eight patients were in complete remission on therapy; one patient showed stable disease and one patient had relapsed. Overall, anti-Dsg3 IgG and anti-Dsg1 IgG auto-Abs correlated well with the clinical activity. These findings suggest that the combination of IA and rituximab induces rapid clinical remission and long term control in difficult-to-treat pemphigus.[40]

However, only a few larger case series are available on this subject and information on the efficacy of retreatment with rituximab during relapses is lacking. Hence, Kasperkiewicz *et al.* sought to determine efficacy and adverse effects of adjuvant rituximab. Seventeen patients with refractory autoimmune blistering dermatoses were treated four times with rituximab at an individual dose of 375 mg/m^2 in weekly intervals or twice with 1000 mg 2 weeks apart. Six of eight patients with a relapse after this regimen received rituximab again twice with 1000 mg in a 2-week interval. All lesions cleared in 14 patients whereas partial healing was found in three others. Relapses occurred in eight patients (five pemphigus vulgaris (PV), two pemphigus foliaceus (PF), one bullous pemphigoid (BP)). Retreatment with rituximab again resulted in complete (two PV, one PF, one BP) or partial (two PV) remission. No serious side effects associated were observed with Rituximab therapy. Adjuvant rituximab is effective and well tolerated not only in patients with pemphigus but also with pemphigoid. Efficacy and safety of rituximab are maintained when it is re-administered during relapses.[41]

Craythorne *et al.,* report six cases of patients with oral and skin PV with recalcitrant or rapidly progressive disease treated with a novel dosing regimen of rituximab as a single agent. All patients achieved a complete response to a maximum follow-up of 34 months.[42]

Kim *et al.* conducted a retrospective analysis of 199 patients diagnosed with pemphigus vulgaris (PV) and pemphigus foliaceus (PF) between 1993 and 2008 in Korea. Based upon the definitions proposed by the International Pemphigus Committee, complete and partial remissions were evaluated. Complete and partial remission rate for PV was 77% at 5 years and 94% at 10 years after initial diagnosis. All the 16 patients who were recalcitrant to conventional therapy achieved overall remission and remarkable clinical improvement without adverse effects because of rituximab therapy. Thus, the study suggests rituximab to be an effective and safe drug for patients who are resistant to conventional therapy.[43]

Kanwar *et al.* studied the efficacy of rituximab in the treatment of resistant or severe pemphigus in Indian patients. Patients with pemphigus were treated with intravenous rituximab 1000 mg in adults or 375 mg/m^2 body surface area in children by two doses, 15 days apart in this open labeled pilot study. A total of 9 (90%) of ten patients responded to the treatment. Three (30%) had complete remission of disease and were off all treatment. Four (40%) patients had CR and were on low dose oral prednisolone. Two (20%) patients had partial remission and were on low dose prednisolone. One patient died of sepsis. The mean time to disease control was 8 weeks. Response to treatment showed good correlation with index values of anti-Dsg1 antibody. Additionally, patients were followed-up for 12-18 months and no relapses were seen. Rituximab is effective in treating resistant and severe pemphigus in Indian patients. Acute complications can occur during rituximab infusion and require close monitoring.[44]

Although the mainstay of therapy for childhood pemphigus vulgaris (CPV) is steroids, adjuvant immunosuppressive drugs are often needed to control the disease. Thus, an important part of CPV morbidity can be related to treatment. The introduction of this drug led to a dramatic clinical response and a long term clinical remission. Based on the experience and the data reported in the literature, it is believed that rituximab may be a safe and efficacious agent for the treatment of severe CPV.[45]

Horváth *et al.* investigated whether a lower dose of rituximab is also effective for pemphigus. Patients with pemphigus were treated with a single course of two infusions of rituximab (500 mg each) at an interval of 2 weeks. Fifteen patients were enrolled in the study: Three with pemphigus foliaceus (PF) and 12 with pemphigus vulgaris (PV). All 15 patients responded to therapy. Eight patients achieved complete remission in a median period of 5 weeks and seven patients achieved partial remission in a median period of 34.5 weeks. Relapses (40%) were seen between 53 and 103 weeks after start of therapy. B-cell numbers dropped to <1% after first infusion, and remained undetectable in patients with sustained remission. The follow-up was 32–152 weeks (median 94). The antidesmoglein 1 index correlated well with the clinical severity in PF, but this was less obvious in PV. Thus, this study demonstrates that a low dose of rituximab is an effective and safe treatment for pemphigus. Relapses may occur, mostly at the end of the second year. A long follow-up is required to determine the proper dosage of this expensive drug in pemphigus.[46]

Mucous membrane pemphigoid (MMP) still is a potentially life- and sight-threatening disease. In a subpopulation of patients with severe MMP, traditional immunosuppressants are not effective or contraindicated. Twenty-five patients with severe refractory MMP, including five with mucous membrane-dominant epidermolysis bullosa acquisita, received one or two cycles of rituximab (375 mg/m^2 weekly for 4 weeks). Concomitant therapy with dapsone and/or sulfasalazine therapy was maintained during rituximab cycles in 21 patients. By a median time of 12 weeks after the first cycle, complete responses in all affected sites (ocular and/or extraocular) were obtained in 17 patients (68%). Five additional patients responded completely after a second cycle, yielding an 88% complete response rate. Rituximab appears to have rapid and dramatic efficacy in patients with severe, refractory MMP. The occurrence of severe infections in patients receiving concomitant conventional immunosuppressants supports using rituximab without other immunosuppressants. Controlled prospective studies are warranted to define an optimal treatment protocol.[47]

Controlling conjunctival inflammation by means of systemic immunosuppression is the main aim in the treatment of MMP. Topical conservative or surgical measures are required to prevent the cicatricial progression and management of the resulting ocular surface disease. The efficacy of dapsone in mild to moderate disease and cyclophosphamide in severe disease has been established in two randomized trials. Small uncontrolled studies have demonstrated the efficacy of other agents such as methotrexate, azathioprine, mycophenolate mofetil, or monoclonal antibodies including daclizumab or rituximab. For eyelid problems such as entropion and trichiasis, surgery is the primary option. Surgical treatment may also be warranted for ocular surface disease and secondary complications, for example, cataract formation and glaucoma. Any surgery is associated with the risk of a relapse of inflammation and should be postponed until inflammation is controlled by systemic therapy. Close collaboration of a specialized ophthalmologist with specialists from dermatology and internal medicine is mandatory for the management of MMP.[48]

4. ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by eczematous skin lesions, pruritus, and typical histopathological features. T cells are thought to play a key role, but B cells might also participate in the pathogenesis of AD. Simon *et al.* investigated whether depletion of B cells by monoclonal anti-CD20 antibody therapy (rituximab) would improve severe forms of disease. Two intravenous

applications of rituximab, each 1000 mg, 2 weeks apart were administered to six patients with severe manifestations. Clinical parameters (eczema area and severity index, pruritus), total and allergen-specific IgE levels, skin histology, and inflammatory cells, and cytokine expression in the skin and peripheral blood before and after therapy were monitored to evaluate the efficacy of rituximab. Within 4 to 8 weeks all patients showed an improvement of their skin symptoms. A significant decrease was seen in the eczema area and severity index. A dramatic improvement was observed in histologic alterations such as spongiosis, acanthosis, and dermal infiltrate, including T and B cell numbers. Blood B cells were below detectable levels as a consequence of rituximab administration, skin B cells were reduced by approximately 50% only. Expression of IL-5 and IL-13 was reduced after therapy. Though allergen-specific IgE levels were not altered, a slight reduction in total IgE concentrations in blood was observed. B cells play a major role in AE (atopic eczema) pathogenesis. Treatment with an anti-CD20 antibody leads to an impressive improvement of AD in patients with severe disease.[22,49]

5. CONNECTIVE TISSUE DISORDERS

Dermatomyositis

Juvenile dermatomyositis (JDM) is an autoimmune disease of the skin and muscle that affects children. The etiology is poorly understood, but genetic susceptibility, environmental triggers, and abnormal immune responses are each thought to play a part. T cells have traditionally been implicated in the immunopathogenesis of JDM, but dendritic cells, B cells, and microchimerism are increasingly associated. Additionally, myositis-specific autoantibodies (MSA) can be present in the sera of affected patients and may correlate with distinct clinical phenotypes. Given the role of humoral immunity and MSA, there has been recent interest in the use of rituximab to treat JDM.[50]

Using quantitative scales, Chung *et al.*, sought to evaluate the effects of rituximab therapy on muscle strength and skin disease in patients with dermatomyositis. An open-label trial of rituximab therapy was conducted in eight adult patients with dermatomyositis. Patients received two infusions of rituximab (1 g each) 2 weeks apart without peri-infusional steroids. Depletion of peripheral B cells had modest effects on muscle disease and limited effects on skin disease in the cohort of patients with dermatomyositis. It is hoped that a prospective clinical trial with more patients will shed light on the issue in the near future.[51,74]

Cutaneous lupus erythematosus

Treatments for cutaneous LE initially include preventive (e.g. photoprotective) strategies and topical therapies (corticosteroids and topical calcineurin inhibitors). For skin disease not controlled with these interventions, oral antimalarial agents (most commonly hydroxychloroquine) are often beneficial. Additional systemic therapies may be subdivided into conventional treatments (including corticosteroids, methotrexate, thalidomide, retinoids, dapsone, and azathioprine) and newer immunomodulatory therapies (including efalizumab, antitumor necrosis factor agents, intravenous immunoglobulin, and rituximab).[52] Rituximab, has been used to treat systemic lupus erythematosus; however, in cutaneous lupus erythematosus (CLE), most biologics have only been applied in single cases. Thus, many treatment options exist for CLE, but not many are supported by evidence from randomized controlled trials. The complexity of the therapeutic approach in systemic lupus erythematosus (SLE) is increased by the large number of patients who do not respond to the first-line therapies and by relapses after initial clinical remission. In these patients, second-line drugs are often prescribed according to individual clinical decisions. The emergence of biological therapies has increased the therapeutic armamentarium available in these complex situations, but their use is limited by the lack of licensing. Available data on the use of rituximab in SLE rely on a large number of case reports and some observational studies. Current evidence on the therapeutic use of rituximab in adult SLE patients was analyzed by Ramos-Casals *et al.,* by a systematic review of reports included in the PubMed database between 2002 and 2007. A total of 188 SLE patients treated with rituximab were identified; considerable improvement in one or more of the systemic SLE manifestations was observed in 171 (91%) patients. A 91% therapeutic response was seen in 103 patients with renal involvement (lupus nephritis). Forty-four (23%) patients developed adverse events; the most frequent being infections (19%). Based on the available data, its use as a first-line therapy or in patients with a predominantly mild form of the disease is not advised. The global analysis of all cases reported to date support the off-label use of rituximab in severe, refractory SLE cases. However, it is not yet possible to make any definite recommendations.[55]

Vasculitis

In most instances, cutaneous vasculitis represents a self-limited condition and will be relieved by leg elevation, avoidance of standing, and therapy with NSAIDs. A combination of corticosteroids and cyclophosphamide is required therapy for systemic vasculitis, which is associated with a high risk of permanent organ damage or death. In cases of refractory vasculitis, plasmapheresis and intravenous immunoglobulin are viable considerations. The new biologic therapies that act via cytokine blockade or lymphocyte depletion, such as the tumor necrosis factor-alpha inhibitor infliximab and the anti-B-cell antibody rituximab, respectively, are showing benefit in certain settings such as connective tissue disease and antineutrophil cytoplasmic antibody (ANCA)-associated primary vasculitis syndromes (Wegener granulomatosis, Churg–Strauss syndrome, and microscopic polyangiitis).[53]

Systemic sclerosis

Several recent lines of evidence indicate a potential role for B cells in the development of SSc. Remarkably, CD19 loss or B-cell depletion using antimouse CD20 antibody suppresses the development of skin hyperplasia and autoimmunity in tight-skin mice. Additionally, a recent study revealed a possible beneficial effect of antihuman CD20 antibody (rituximab) therapy for SSc patients.[54]

6. GRAFT VERSUS HOST DISEASE

Following allogeneic hematopoietic stem cell transplantation (HSCT) GVHD is the leading cause of procedural-related morbidity and mortality. Evaluating anti-B cell therapy with rituximab in patients undergoing allogeneic hematopoietic cell transplantation has emerged following the understanding of the significant part of B lymphocytes in alloreactivity. Evidence restricted to nonrandomized studies from single institutions using higher than conventional doses of rituximab suggest a favorable decrease in incidence and severity of acute graft-versus-host disease (GVHD). Seventy percent of individuals undergoing HSCT develop chronic GVHD (cGVHD), and about 40% of those patients are refractory to conventional T-lymphocyte-directed therapies. In individuals with steroid-refractory cGVHD limited treatments options are available. In retrospective and prospective studies rituximab therapy has established clinical efficacy with controllable toxicities in individuals with extensive cGVHD.[56] Primarily in cases of dermatologic and mucosal involvement, rituximab is used as an effective treatment of corticosteroid-refractory chronic GVHD with good responses. Few studies have demonstrated that posttransplant administration of rituximab appears to reduce the rate of chronic GVHD.[57]

Following allogeneic hematopoietic stem cell transplantation Teshima *et al.,* prospectively evaluated the safety and efficacy of the anti-CD20 chimeric monoclonal antibody rituximab for the treatment of corticosteroid-refractory chronic graft-versus-host disease (GVHD). Seven patients were treated with 375 mg/m^2 rituximab weekly for four consecutive weeks. A decrease in the dose of steroids in four patients was possible due to rituximab administration. One year of rituximab therapy led to a partial response in three patients, where three had stable disease, and one had progressive disease. Responsive manifestations included mild to moderate skin and oral lesions, and immune hemolytic anemia, and thrombocytopenia. Rituximab was not beneficial in patients with severe manifestations involving the skin, fascia, and eye. No severe toxicity was observed during rituximab treatment. These observations suggest that rituximab therapy may be effective for select patients with corticosteroid-refractory chronic GVHD that is not advanced.[57]

Additionally, literature was accessed through MEDLINE and International Pharmaceutical Abstracts (form 1990 to 2008), both indexed and non-indexed citations, using the terms rituximab, graft-versus-host disease, monoclonal antibodies, and CD20. Furthermore, reference citations from the publications identified were reviewed. All articles discussing rituximab as a therapeutic option in the treatment of GVHD that were published in English and enrolled human study participants were evaluated.[56] For patients with extensive steroid-refractory cGVHD, rituximab is a treatment option as per available data. For individuals with steroid-refractory cGVHD manifesting as thrombocytopenia or with sclerodermatous, cutaneous, and rheumatologic involvement rituximab may be particularly effective.[58]

7. MISCELLANEOUS

Kimura disease (KD) is a rare condition that predominantly affects young middle-aged Asian men. Tumors in the head and neck region with associated eosinophilia and elevated serum immunoglobulin E levels are certain of its classical features. However, the exact pathogenesis of this condition remains unknown. Although some regard it as a reactive condition, others believe that it is a T-cell-mediated disease. Due to the presence of lymphoid follicles and the persistent high serum immunoglobulin E levels, Ghosn *et al.* elected to attempt treatment with rituximab. Although the KD lesions persisted, they became softer and less nodular.[59]

Chronic urticaria, osteosclerotic bone lesions, and monoclonal IgM gammopathy are some of the features associated with the rare Schnitzler syndrome. It can herald the onset of a true lymphoproliferative disorder including Waldenström macroglobulinemia and seldom, systemic marginal zone B-cell lymphoma. The skin symptoms were reduced by the combined treatment of rituximab and radiotherapy.[60]

Intravascular large B-cell lymphoma (IVBCL) is a rare malignant neoplasm characterized by the proliferation of large B cells within the blood vessels. The disease can be limited to the skin, but involvement of other organs is common. A case of cutaneous IVBCL in a 62-year-old man with minimal histological changes in contrast to prominent skin lesions was successfully treated with rituximab in combination with Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisolone (CHOP) chemotherapy.[61]

Various open-label uncontrolled studies have suggested that rituximab could benefit patients with autoimmune diseases who are refractory to standard of care. Studies have evaluated the safety and clinical outcomes of rituximab in several standard-of-care-refractory autoimmune diseases (within rheumatology, nephrology, dermatology, and neurology) other than rheumatoid arthritis or non-Hodgkin's lymphoma in a real-life clinical setting. As part of the German Registry of Autoimmune Diseases, patients who received rituximab having shown an inadequate response to standard-of-care, had their safety and clinical

outcomes data retrospectively analyzed.[62] The main outcome measures were safety and clinical response, as judged at the discretion of the investigators. The following was their observation:

- A total of 370 patients with various autoimmune diseases (23.0% with systemic lupus erythematosus, 15.7% antineutrophil cytoplasmic antibody-associated granulomatous vasculitides, 15.1% multiple sclerosis and 10.0% pemphigus) from 42 centers received a mean dose of 2,440 mg of rituximab over a median (range) of 194 (180 to 1,407) days
- The overall rate of serious infections was 5.3 per 100 patient-years during rituximab therapy
- Opportunistic infections were infrequent across the whole study population, and mostly occurred in patients with systemic lupus erythematosus
- There were 11 deaths (3.0% of patients) after rituximab treatment (mean 11.6 months after first infusion, range 0.8 to 31.3 months), with most of the deaths caused by infections
- Overall (*n* = 293), 13.3% of patients showed no response, 45.1% showed a partial response and 41.6% showed a complete response
- Responses were also reflected by reduced use of glucocorticoids and various immunosuppressives during rituximab therapy and follow-up compared with before rituximab
- Rituximab generally had a positive effect on patient well-being (physician's visual analogue scale; mean improvement from baseline of 12.1 mm).

Data from this registry indicates that rituximab is a commonly employed, well-tolerated therapy with potential beneficial effects in standard of care-refractory autoimmune diseases, and support the results from other open-label, uncontrolled studies.[62]

ADVERSE EFFECTS

Dermatological adverse effects

Frequent but not so serious cutaneous side effects are observed following rituximab therapy. Forty four percent suffered some side effect involving the skin and appendages. Specifically, 15% of patients complained of night sweats, 15% developed 'skin rash', 14% had pruritus, and 8% developed urticarial.[63] Two bacterial infections, one patient with persistent pruritus were some of the observed side effects in a systemic eight-cycle rituximab therapy in primary cutaneous B-cell lymphomas.[64]

Serious cutaneous side effects were caused in 2% of patients. These include paraneoplastic pemphigus, Stevens–Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis as per the package insert.[65] The onset of the reactions varied from 1 to 13 weeks following rituximab exposure. Numerous reports note that rituximab can cause serum sickness and vasculitis.[66,67] Lowndes reported a case of Stevens-Johnson syndrome after treatment with rituximab.[68] Buda-Okreglak described a novel, delayed, proinflammatory syndrome that occurred at or near completion of a 4-week dose-intense course with rituximab.[69] It is possible that, as an immunosuppressant, rituximab may increase the likelihood for development of cancer. There is one report of Merkel cell carcinoma (MCC) occurring in Chronic Lymphocytic Leukemia (CLL) patients soon after treatment with 2-CdA (Cladribine) and/or rituximab, suggesting that this complication rarely observed in CLL patients may have a link with strongly immunosuppressive therapy with 2-CdA and rituximab.[70]

Nondermatological adverse effects Black box warnings include the following:[24]

- Fatal infusion reactions: Deaths within 24 h of rituximab infusion have been reported
- Tumor Lysis syndrome (TLS)
- Severe mucocutaneous reactions
- Hepatitis B reactivation with related fulminant hepatitis.
- Hypersensitivity reactions
- Serious or life-threatening cardiac arrhythmias (hypotension can occur as well)
- Severe renal toxicity, including acute renal failure requiring dialysis and, in some cases, a fatal outcome.

Precautions:[24]

- Since rituximab targets all CD20-positive B lymphocytes, malignant and nonmalignant, complete blood counts (CBC) and platelet counts ought to be obtained at steady intervals
- Renal toxicity was seen with this drug in combination with cisplatin in clinical trials
- Rituximab can increase the risk of infection
- Immune/autoimmune events have been reported[24]
- Rixuximab has a multiplicity of hematologic side effects including cytopenias.

Approximately 80% of fatal infusion reactions occur with the first infusion. Temporarily stopping or slowing the IV infusion often reverses or relieves symptoms, and premedication with analgesics (acetaminophen), antihistamines (diphenhydramine), and glucocorticoids (methylprednisolone) can control such events. After the first infusion, infusion-related reactions are much less common.[71-73]

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system that has been reported as rare adverse drug reaction (ADR) of immunosuppressive drugs.[75] Although this is a rare adverse event associated with rituximab therapy, the devastating nature of PML mandates continued vigilance, particularly in patients with current or prior exposure to an alkylating agent.[76]

CONCLUSION

Rituximab is a promising agent for the treatment of B-cell related diseases. It has many side effects, some common and some not common. While presently only approved for use in the treatment of NHL and RA, rituximab has revealed therapeutic worth in diverse autoimmune and immune-mediated dermatological conditions in which traditional therapy has failed or produced substantial intolerance. Pending additional controlled clinical studies to corroborate the safety and efficacy of rituximab therapy in dermatological disorders, evidence concerning the off-label usage of this medication will come from anecdotal case reports and cohort studies. With only mild, infusion-related, and infectious complications occurring in the majority of patients, rituximab is safe and tolerable. However, stringent caution and supervision should be monitored with each patient treated since the long term efficacy, tolerability, and dosing in dermatological conditions has not been firmly established.

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Cite this article as: Bhandari PR, Pai VV. Novel applications of Rituximab in dermatological disorders. Indian Dermatol Online J 2014;5:250-9.
Source of Support: Nil, **Conflict of Interest:** None declared.