Dermatologic Applications of Rituximab

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Rituximab is a chimeric murine-human monoclonal antibody to CD20 that induces the depletion of B cells in vivo. Approved for the treatment of relapsed or refractory low-grade or follicular CD20$^+$ B-cell lymphoma, rituximab has been used with success for the treatment of several dermatologic disorders, including pemphigus vulgaris; atopic dermatitis; some immune-mediated vasculitides; epidermolysis bullosa acquisita; cryoglobulinemia; primary cutaneous B-cell lymphoma; dermatomyositis; and chronic graft versus host disease. The overall safety profile of rituximab has been favorable, with the most common adverse events related to infusion reaction associated with intravenous administration. Intralesional injection of rituximab has been evaluated with some success in a small number of patients with cutaneous B-cell lymphomas.

Rituximab is a chimeric murine-human monoclonal antibody to CD20 that induces the depletion of B cells in vivo.[1-4] In 1980, CD20 was identified as the first B lymphocyte–specific antigen that is initially expressed by pre–B lymphocytes and subsequently continues to be expressed by mature B lymphocytes as they develop.[5] In 1994, Reff et al[1] developed a chimeric anti-CD20 antibody produced by the fusions of the mouse variable region with the human immunoglobulin G_1 heavy chain and ê light chain. By 1997, rituximab was approved by the US Food and Drug Administration (FDA) as the first monoclonal antibody approved for the treatment of relapsed or refractory low-grade or follicular CD20$^+$ B-cell lymphoma.[1-6] Rituximab and its FDA-approved indications are familiar to most dermatologists, but a multitude of new, non–FDA-approved uses have been studied and other therapeutic applications continue to evolve.[2-5] The drug is a promising agent for the treatment of diseases associated with B cells and their associated antibodies.[7] A list of potential off-label indications of rituximab in dermatology is found in the Table.[2-5] This article reviews the mechanism of action, dosage, and adverse effects of rituximab in addition to serving as a review of the current literature on selected non–FDA-approved dermatologic applications of rituximab.

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The authors report no conflicts of interest in relation to this article.

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MECHANISM OF ACTION

The CD20 receptor is the target of the mechanism of action of rituximab.[1-5] CD20 is a B-cell–specific antigen expressed on the surface of B lymphocytes throughout their differentiation from the pre–B-cell to the mature B-cell stage. This antigen is not found on the surface of plasma cells or stem cells.[1-3] From a clinical perspective, this sparing of the plasma cells and hematopoietic precursor cells results in a nondramatic reduction of immunoglobulin levels and the return of B cells into the circulation within 6 months of therapy.[2-4,8,9] Regarding chemical structure, rituximab is composed of a murine variable region (Fab fragment) that is fused to a human constant region (Fc fragment). The Fab fragment binds specifically to the CD20 antigen. Following this binding, the Fc fragment facilitates the recruitment of immune cells to aid in the lysis of the CD20$^+$

Potential Dermatologic Indications for Rituximab [2-5]

Acute GVH disease
Angioedema
Atopic eczema
Bullous pemphigoid
Chronic GVH disease
Cryoglobulinemia
Dermatomyositis
Epidermolysis bullosa acquisita
Immunobullous disease
Mucous membrane pemphigoid
Paraneoplastic pemphigus
Pemphigus foliaceus
Pemphigus vulgaris
Primary cutaneous B-cell lymphoma
Schnitzler syndrome
Scleroderma
Systemic lupus erythematosus
Vasculitis
Vitiligo
Waldenström macroglobulinemia

Abbreviation: GVH, graft versus host.

B lymphocytes.[4] This process is multifactorial and includes the following mechanisms: complement-dependent cytotoxicity; antibody-dependent cell-mediated cytotoxicity; direct disruption of cellular signaling pathways; and triggering of apoptosis. The exact contributory role of each of the above mechanisms is not clear, and different mechanisms may dominate in the treatment of specific disease states.[1-5,10]

DOSING

Rituximab is typically administered as 4 weekly intravenous infusions of 375 mg/m^2. This dose is predicated on results from 2 studies. Dose-related toxicity of rituximab has been examined, and in doses up to 500 mg/m^2 no limitation was observed.[2-5,8,9] Moreover, Leandro et al[11] examined rituximab for the treatment of rheumatoid arthritis and documented doses of up to 600 mg/m^2, which proved to be effective, while maintaining a favorable safety profile with minimal adverse effects observed.[5] Currently, no consensus exists regarding the most efficacious dose or optimal dosing regimen.[2,3]

The most frequent side effects associated with the administration of rituximab are related to infusion reactions.[2-4] Prior to the administration of rituximab, premedication with an antihistamine (diphenhydramine) and an antipyretic (acetaminophen) is commonly recommended to reduce the incidence and intensity of infusion reactions. Methylprednisone has also been used in the prevention of adverse effects associated with infusion reactions from rituximab.[2-4]

ADVERSE EFFECTS

Rituximab is generally well tolerated, and the incidence of serious adverse effects is low. Mild to moderate infusion-related reactions are the most common side effects and typically are observed with the first administered dose.[2-5] The most common side effects in order of frequency are fever (48%); chills (32%); weakness (18%); nausea (17%); pruritus (12%); and rash (11%). These symptoms usually diminish or disappear with subsequent infusions and are reversible by temporarily discontinuing the infusion. As mentioned previously, premedication with an antihistamine and an antipyretic has been shown to help reduce the incidence of infusion-related adverse effects.[2-5,12]

Although rare, severe and potentially fatal adverse effects have been reported with rituximab therapy. These include severe infusion-related reactions; anaphylaxis; severe transient neutropenia; tumor lysis syndrome; reactivation of hepatitis B virus with fulminant hepatitis; interstitial pneumonitis; Stevens-Johnson syndrome; Kaposi sarcoma; and progressive multifocal leukoencephalopathy.[2-5,13-19]

PEMPHIGUS VULGARIS AND PARANEOPLASTIC PEMPHIGUS

Numerous case reports have described the utility of rituximab in the treatment of pemphigus vulgaris. The largest of these case series, published by Ahmed et al,[20] examined 11 patients. Of the 11 patients studied, 9 achieved complete remission. The other 2 patients had partial remission with subsequent relapses that were successfully treated with rituximab. Notably, the patients in these studies were started on rituximab after they had been deemed unresponsive to other more conventional treatment modalities. Other studies yielded similar results in which a majority of patients showed a favorable response categorized as either complete or partial remission.[2-5,7,20-27] This phenomenon is most likely related to the fact that pemphigus vulgaris is an antibody-mediated disease, and the mechanism of action of rituximab curtails the activity of B cells and the subsequent production of antibodies. Furthermore, a correlation has appeared that associates a decrease in pemphigus vulgaris autoantibody

levels with clinical improvement based on symptomatology. There are also documented studies illustrating the efficacy of rituximab in severe, recalcitrant pemphigus vulgaris. Given the success of rituximab in the setting of pemphigus vulgaris,[2-5,7,20-27] controlled trials on the use of this therapy in pemphigus would be both beneficial and warranted.

Rituximab has also been shown to result in the remission of paraneoplastic pemphigus. Paraneoplastic pemphigus is a disease caused by an autoimmune mechanism in patients with various malignancies, including non-Hodgkin lymphoma and chronic lymphocytic leukemia. The cutaneous manifestations of the disease are typically a polymorphous eruption in addition to an ulcerating stomatitis.[2-5] The works of Heizmann et al,[28] Borradori et al,[29] and Rossum et al[30] describe cases in which rituximab therapy has yielded the successful treatment of follicular non-Hodgkin lymphoma with refractory paraneoplastic pemphigus. The mechanism has yet to be fully delineated as it is unclear whether rituximab, in this setting, treats either the underlying malignancy, an autoimmune process associated with the malignancy, or both.[5,28-30] Although clinical trials aimed to describe the efficacy of rituximab in paraneoplastic pemphigus would be contributory, they are most likely difficult to carry out, secondary to the very low incidence of this particular disease state.

ATOPIC ECZEMA

In atopic eczema, a disease that has been shown to be orchestrated by T cells, B cells are also components in the pathogenesis as they are found among the dermal infiltrating cells.[31] With this in mind, the first report on the use of rituximab in the treatment of atopic eczema was published in 2008 by Simon et al.[32] Their research showed the ability of rituximab to reduce B-cell counts in the skin lesions of patients with atopic eczema by 50%. Although the B-cell numbers were not entirely depleted, their quantitative reduction yielded an improvement in atopic eczema symptoms, reduced skin inflammation, and resulted in a concurrent normalization of the skin's architecture. Their work supported the notion that depletion of B cells can improve the clinical signs and symptoms of atopic eczema. It also demonstrated that rituximab appears to be a promising therapy for patients with severe atopic eczema refractory to topical corticosteroids, topical calcineurin inhibitor therapy, or both. The authors further support the view that clinical trials are necessary to define the safety and efficacy of rituximab in patients with atopic eczema.[32]

EPIDERMOLYSIS BULLOSA ACQUISITA

The works of Crichlow et al,[33] Wallet-Faber et al,[34] and Schmidt et al[35] collectively describe cases in which patients with refractory epidermolysis bullosa acquisita achieved remission with rituximab therapy within a range of 11 to 20 weeks. Crichlow et al[33] studied a patient who received rituximab as an addition to mycophenolate mofetil. Wallet-Faber et al[34] commenced rituximab therapy in a patient whom they examined after he had exhibited resistance to high-dose systemic corticosteroid therapy and other immunosuppressive medications.[34] The case presented by Schmidt et al[35] described a patient in whom rituximab was given prior to a treatment regimen composed of additional immunomodulators, including azathioprine, prednisolone, and colchicine.[35] The mechanism of action of rituximab in these patients is likely similar to that found in other diseases in which a disruption of antibody-dependent activities of B cells occurs. In the setting of epidermolysis bullosa acquisita and other B-cell–mediated diseases, these activities include the presentation of autoantigens, the co-stimulation of T cells, and the regulation of leukocytes and dendritic cells.[2,3] Case reports on the application of rituximab in epidermolysis bullosa acquisita are few, and no formal clinical trials have been documented thus far. Further research in this facet of rituximab therapy would be pertinent.

VASCULITIS

Immune-mediated vasculitides are a hypersensitivity reaction pattern mediated by immune complexes composed of antibody-antigen formations. The fact that rituximab decreases antibody production enables it to serve as a useful treatment for the autoimmune subsets of vasculitis.[7] Multiple open-label trials and case reports have been published documenting the successful use of rituximab in antineutrophil cytoplasmic antibody-associated vasculitis and cutaneous small-vessel vasculitis.[36-43] A majority of the patients studied showed complete remission with rituximab therapy. The minority comprised patients with partial remission and no response to treatment. In one of the larger published studies, Keogh et al[39] observed the successful induction of remission in 11 patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. Overall, treatment with rituximab was well tolerated, with few instances of serious adverse effects. The works of Sneller[40] and Wong[43] discussed the ability of rituximab to decrease the production of antineutrophilic cytoplasmic antibodies, which are key players in the pathogenesis of antibody-associated vasculitis. This effect is founded on the ability of rituximab to reduce the population of B cells in the circulation.

In addition to the 2 subsets of vasculitis mentioned, rituximab has been shown to be efficacious in the treatment of vasculitis associated with Churg-Strauss syndrome and of giant cell arteritis.[2,3,44-46]

CRYOGLOBULINEMIA

Rituximab has also been shown to be an effective treatment modality for cryoglobulinemia.[47-51] Cryoglobulinemia is a systemic vasculitis linked to immune complex deposition in several organs. The mechanism of action of rituximab in this setting is similar to that found in the treatment of vasculitis described above with the end point being reduced B-cell antibody production. Following rituximab therapy, decreased levels of cryoglobulins and increased levels of complement were both associated with clinical improvement. Furthermore, rituximab proved to be an effective treatment for the dermatologic manifestations of cryoglobulinemia. These lesions include ulcers, purpura, and urticaria.[7] The research of Zaja et al[51] concluded that rituximab may further serve as a safe and effective alternative to the standard immunosuppressive drug regimen in the treatment of mixed cryoglobulinemia.[7] Based on the utility of rituximab in this disease process, a multicenter, controlled, randomized, clinical trial is currently being conducted to compare rituximab with the currently available treatments in severe mixed cryoglobulinemia.[52]

PRIMARY CUTANEOUS B-CELL LYMPHOMA

Multiple publications document the success of rituximab therapy in the treatment of primary cutaneous B-cell lymphoma and most describe a complete response. The efficacy of rituximab in this setting has also been reported in patients who have initially relapsed or failed other treatment modalities. Nearly 60 individual cases have been reported and these cases comprise a variety of subtypes, including diffuse large B-cell lymphoma; follicular center cell lymphoma; large B-cell lymphoma of the leg; mantle cell lymphoma; and marginal zone lymphoma.[2-7,53-70] The high efficacy and success of rituximab in the treatment of this group of diseases is not surprising given that B cells are the substrate of the inhibitory action of rituximab. The 2 largest series each comprised 10 patients.[53,67] In the series presented by Heinzerling et al,[53] 10 patients were treated with intravenous rituximab monotherapy at a dose of 375 mg/m^2 on a weekly basis. Eight patients received 4 infusions, 1 patient received 2 infusions, and 1 patient received only a single infusion. The overall response rate was 70%, with a complete response rate of 20% and a partial response rate of 50%. Gellrich et al[67] presented 10 patients who received 8 weekly infusions of 375 mg/m^2 of rituximab as monotherapy. The documented response rate in this study was 90%, with a complete response rate of 70% and a partial response rate of 20%.

The efficacy of intralesional rituximab administration has been studied in published reports.[2,4,64,68,71-73] These reports collectively included 18 patients. Fifteen patients exhibited complete remission of all of their lesions, whereas the other 3 patients showed a variable response consisting of remission of some lesions and a reduction in the size of other lesions. In conclusion, intralesional injection of rituximab was shown to allow for smaller dosages than those used with intravenous administration. However, relapse rates appear to be higher with intralesional therapy than with the conventional route of intravenous infusion. Intralesional rituximab would be very applicable in dermatology as long as efficacy and safety are substantiated in a larger group of patients. Further study is needed in this area.

DERMATOMYOSITIS

A few publications have documented the efficacy of rituximab in the treatment of dermatomyositis.[2-5,74-77] An open-label pilot study published by Levine[74] has reported the successful use of rituximab in the treatment of dermatomyositis refractory to standard therapeutic approaches in a population of 7 patients. Using dynamometry, an increase in muscle strength ranging from a 36% to a 113% increase as compared with baseline, was noted in all patients. Furthermore, 5 of the 7 patients had skin eruptions and the other 2 patients had alopecia. Those patients presenting with skin eruptions reported improvement, and the 2 individuals with alopecia reported a regrowth of hair. Regarding the dosage, all patients were treated with 4 weekly intravenous infusions of rituximab. Of note, 3 patients received infusions of 100 mg/m^2 as opposed to the standard dose of 375 mg/m^2. This lower dose did not appear to reduce the efficacy of rituximab therapy as compared with other patients in this study who were treated with a higher dose.

The work of Dinh et al[77] reported marked clinical improvement in the dermatologic manifestations in 3 patients with dermatomyositis who were treated with rituximab.[77] In this small cohort, the heliotrope rash and the violaceous poikiloderma were the cutaneous manifestation subsets that were most responsive to treatment with rituximab.

In the setting of dermatomyositis, the exact mechanism of rituximab is not known. The currently accepted mechanism for the pathogenesis of dermatomyositis is initiated by autoantibodies leading to the formation of a membrane attack complex via binding to an antigen on the endothelial cell wall surface of endomysial capillaries. From a clinical perspective, this process results in swelling, necrosis, inflammation, and muscle ischemia. It is postulated that rituximab may act in this setting by decreasing the B-cell production of one of the defined autoantibodies, or an undefined autoantibody, to an endothelial cell autoantigen, thus disrupting the initiation of the process described above.[2,3] Dermatomyositis

is another disease in which rituximab has been shown to be efficacious, and further research on this subject matter would be relevant as well.

CHRONIC GRAFT VERSUS HOST DISEASE

The efficacy of rituximab in the treatment of chronic graft versus host (GVH) disease has been reported in case series publications. Cutaneous findings of GVH disease most often include lichenoid and scleroderma skin changes. In 2000, Ratanatharathorn et al[78] documented the success of rituximab in the treatment of thrombocytopenia secondary to GVH disease in patients who were refractory to conventional immunosuppressive therapy. Interestingly, in addition to the resolution of the thrombocytopenia, a concurrent abatement of the cutaneous changes of GVH disease was also observed.[2,3,5,78-80] In 2003, Ratanatharathorn et al[79] published a study comprising 8 patients with chronic GVH disease refractory to other modalities of immunosuppressive therapy who were treated with 375-mg/m^2 intravenous infusions of rituximab weekly for 4 weeks. Half of the patients showed a successful response, whereas the other half were categorized as nonresponders. It is notable to mention that there was a greater interval from the time of transplantation to the institution of rituximab therapy in the 4 patients in whom a response to rituximab did not occur. Given the small number of publications on the use of rituximab in GVH disease, the relationship between the timing of treatment and patient response has not been fully elucidated and would provide appropriate grounds for further research.[5]

In 2006, Cutler et al[80] published the largest case series comprising 21 patients with corticosteroid-refractory chronic GVH disease who were treated with rituximab. The overall clinical response rate was 70%, and the data revealed that cutaneous and musculoskeletal manifestations of GVH disease were most responsive to treatment when compared to the mucous membrane and hepatic manifestations of the disease. These patients were treated with 1 to 3 cycles of 4 weekly intravenous infusions of rituximab at doses of 375 mg/m^2.

The full in vivo mechanism of action of rituximab in the treatment of chronic GVH disease has not yet been described. Given the reported success of rituximab in GVH disease and based on the mechanism of action being predicated on the activity of rituximab against B-cell antigens, it is theorized that B cells do indeed play a role in chronic GVH disease.[78-80] Further clinical data on the optimal use of rituximab in chronic GVH disease and a more developed understanding of its immunologic mechanism of action in the disease would be beneficial.

CONCLUSION

Although initially approved and used for the treatment of low-grade or follicular non-Hodgkin lymphoma, rituximab has exhibited great efficacy and promise in the treatment of dermatologic disorders that are autoimmune or immune mediated in nature.[4] Rituximab, in the realm of dermatologic application, has failed to demonstrate a serious side effect profile, with infusion reactions and treatable infectious complications comprising the most frequently encountered adverse effects. In most patients, the drug was safe and tolerable, with few discontinuations secondary to the inability of patients to withstand the adverse effects of the drug.[5] As discussed individually in the previous sections, clinical trials are certainly warranted to evaluate the efficacy, optimal dosing regimens, and safety of rituximab in the treatment of multiple dermatologic disease states. For instance, the use of intralesional rituximab in cutaneous B-cell lymphomas is of special significance to the dermatologist, especially if clinical trials confirm the lack of systemic adverse effects with a concurrently high success rate.[5] As further clinical data continues to emerge on the use of rituximab for dermatologic disorders, it is likely that the list of indications for this promising modality of therapy will expand.

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