Future therapies for pemphigus vulgaris: Rituximab and beyond

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The conventional treatment for patients with pemphigus vulgaris (PV) centers on global immunosuppression, such as the use of steroids and other immunosuppressive drugs, to decrease titers of antidesmoglein autoantibodies responsible for the acantholytic blisters. Global immunosuppressants, however, cause serious side effects. The emergence of anti-CD20 biologic medications, such as rituximab, as an adjunct to conventional therapy has shifted the focus to targeted destruction of autoimmune B cells. Next-generation biologic medications with improved modes of delivery, pharmacology, and side effect profiles are constantly being developed, adding to the diversity of options for PV treatment. We review promising monoclonal antibodies, including veltuzumab, obinutuzumab (GA-101), ofatumumab, ocaratuzumab (AME-133v), PRO131921, and belimumab. (J Am Acad Dermatol 2016;74:746-53.)

Key words: anti-CD20; autoimmune; biologics; blistering diseases; desmoglein; desmosomes; immunomodulators; immunosuppression; monoclonal antibodies; pemphigus vulgaris; rituximab.

INTRODUCTION

In the last decade, the success of anti—B cell monoclonal antibodies (mAbs) in the treatment of lymphoma and a variety of autoimmune diseases has shifted the therapeutic paradigm for refractory pemphigus vulgaris (PV) from global immunosuppression to targeted destruction of pathogenic B cells. While anti-CD20 monoclonal antibodies are a useful adjunct, immunosuppressive drugs, such as prednisone, azathioprine, and mycophenolate mofetil, remain first-line therapies for patients with PV.

The off-label use of rituximab—an anti-CD20 chimeric mAb approved by the US Food and Drug Administration for the treatment of non-Hodgkin lymphoma (NHL) and refractory rheumatoid arthritis (RA)—for the treatment of PV has shown success in many prospective and retrospective cohort studies.[1-5] Similar to conventional therapy, rituximab carries side effects of an increased risk of infections and can be costly to administer. While rituximab resistance is rarely encountered, relapse requiring retreatment at 6-month intervals is common. This article reviews the use of rituximab in patients with PV and suggests similar biologic options with therapeutic potential.

Abbreviations used:

ADCC:	antibody-dependent cell-mediated cytotoxicity
CDC:	complement-dependent cytotoxicity
CDR:	complementarity-determining region
CLL:	chronic lymphocytic leukemia
IV:	intravenous
mAbs:	monoclonal antibodies
NHL:	non-Hodgkin lymphoma
PV:	pemphigus vulgaris
RA:	rheumatoid arthritis
SLE:	systemic lupus erythematosus
TNF:	tumor necrosis factor

RITUXIMAB IN PEMPHIGUS VULGARIS

Rituximab is a human-to-mouse chimeric anti-CD20 mAb that targets the B cell—specific CD20 transmembrane glycoprotein to deplete normal and pathogenic B cells, while sparing terminally differentiated plasma cells. The mAb is neither internalized by the B cell nor shed from the

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Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication November 10, 2015.
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Published online January 11, 2016.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.11.008

plasma membrane, contributing to its persistence on the cell surface.[6] A variety of mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and direct triggering of apoptosis lead to death of the mAb-coated B cells and eventual shift to a normal B cell repertoire. Beyond its B cell–depleting function, rituximab has also been found to downregulate autoreactive $CD4^+$ T_H cells indirectly through deprivation of B cell antigen–presenting signals, leading to the development of anti–B cell-activating factor (BAFF) drugs, such as belimumab.[4]

Rituximab was first approved in 1997 for patients with refractory low-grade follicular B-cell lymphoma and in 2006 for patients with RA refractory to tumor necrosis factor (TNF) inhibitors.[6] Rituximab has become a welcome adjunct or alternative to long-term use of systemic steroids and immunosuppressive agents in patients with refractory PV, leading to complete, sustained remission in the majority of these patients, as shown in 5 independent, nonrandomized, prospective studies[1-4] and in 2 retrospective cohort studies.[7,8] A recent review by Ahmed and Shetty[9] analyzed the cumulative data on treatment of PV with rituximab and concomitant or subsequent conventional immunosuppressive therapies and found that clinical remission on rituximab therapy was seen in 90% to 95% of patients within <6 weeks. Complete resolution was observed within 3 to 4 months.[9] However, the incidence of relapse remained >50%, and serious adverse effects, including infection and septicemia, were seen in 4.8% and 2.1% of patients in the lymphoma and RA protocols, respectively. Nonetheless, rituximab has become an important treatment in patients with refractory PV.

CAPSULE SUMMARY

- Pemphigus vulgaris is currently treated with immunosuppressive therapies, which can cause serious side effects. Newer-generation anti-CD20 antibodies like rituximab are a safer alternative for treating patients with pemphigus vulgaris.
- This review introduces possibly safer alternatives to rituximab.
- This information can guide clinicians and researchers to developing and using these alternatives.

DISADVANTAGES OF RITUXIMAB

Adverse effects

Rituximab is generally well tolerated, and serious adverse events are rare. Infusion-related reactions include anaphylaxis, hypotension, fever, chills, headache, weakness, nausea, pruritus, and rash,[10] which can be ameliorated by slowing the intravenous (IV) infusion rate, temporarily stopping the infusion, or beginning treatment with analgesics, antihistamines, and glucocorticoids.[11] Grade 3 or 4 infusion reactions occur in 10% of patients treated with rituximab during the first infusion.[12] As with any immunosuppressive agent, rituximab increases the risk of infection. In an analysis of pooled data from 356 patients treated with rituximab monotherapy for lymphoma, 30% of patients had infectious events; 19% developed bacterial infections, 10% developed viral infections, and 1% developed fungal infections.[13] Adverse events noted in prospective and case studies of rituximab treatment for PV included hypotension during infusion,[14] sepsis,[10] herpes zoster,[14] and fatal pneumocystic carinii pneumonia in a patient undergoing therapy with rituximab combined with cyclophosphamide and prednisone.[15]

Cost and inconvenience

Varying drug costs and dosing regimens used in the off-label administration of rituximab are 2 reasons that there are currently no studies in the United States examining the cost–benefit analysis of the use of rituximab in patients with severe, refractory PV compared to conventional immunosuppressive therapy. The high cost of rituximab is also augmented by the need for slow IV infusion once a week. Under the lymphoma dosing regimen, a cycle of rituximab can cost approximately $88,000 for four 375-mg/$m^2$ doses weekly for 4 consecutive weeks.[16] The first infusion is administered slowly for approximately 8 hours, and subsequent infusions take approximately 3 hours. Despite this, the use of biologics like rituximab has been shown to be more cost effective than conventional therapies in the treatment of patients with RA and lymphoma.[17,18] Shifting the focus from rituximab to biologics that require fewer to no infusions would also drive costs down for patients with PV.

Relapse and resistance

Rituximab relapse and resistance have been well documented in studies of PV patients; in a study by Joly et al,[2] 9 of 21 patients relapsed, requiring retreatment. Postulated mechanisms of resistance have been numerous and varied, and include the following: (1) persisting memory and germinal B cells in spleen and lymph nodes; (2) the appearance of novel lineages of autoreactive