REVIEW

Rituximab therapy in pemphigus and other autoantibody-mediated diseases [version 1; peer review: 3 approved]

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Abstract

Rituximab, a monoclonal antibody targeting the B cell marker CD20, was initially approved in 1997 by the United States Food and Drug Administration (FDA) for the treatment of non-Hodgkin lymphoma. Since that time, rituximab has been FDA-approved for rheumatoid arthritis and vasculitides such as granulomatosis with polyangiitis and microscopic polyangiitis. Additionally, rituximab has been used off-label in the treatment of numerous other autoimmune diseases, with notable success in pemphigus, an autoantibody-mediated skin blistering disease. The efficacy of rituximab therapy in pemphigus has spurred interest in its potential to treat other autoantibody-mediated diseases. This review summarizes the efficacy of rituximab in pemphigus and examines its off-label use in other select autoantibody-mediated diseases.

Keywords

Pemphigus , desmoglein , rituximab , autoantibody-mediated diseases ,

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Introduction

Autoimmunity occurs when the body's immune system mistakenly attacks self rather than foreign pathogens, leading to end-organ damage. B cells play a role in autoimmunity through several potential mechanisms, including antigen presentation, regulation of inflammation, and production of autoantibodies. These autoantibodies directly cause disease in several disorders, including pemphigus.

The critical role of B cells in autoimmune disorders has prompted interest in the use of B-cell-depleting therapies such as rituximab, a chimeric monoclonal antibody against the B cell surface antigen CD20. Of note, rituximab has striking efficacy in pemphigus, a finding mostly attributed to the central role of autoreactive B cells and autoantibodies in this disease. Rituximab has also been shown to downregulate autoreactive T helper cells in pemphigus patients, either by reducing B-cell-mediated antigen presentation or through direct depletion of CD20⁺ T cells; the latter has been identified at similar rare frequencies in patients with multiple sclerosis and rheumatoid arthritis and in healthy individuals although their pathophysiological significance to disease onset and remission after rituximab remains unclear^{1–3}. Nevertheless, the success of rituximab in pemphigus invites a reappraisal of its therapeutic efficacy in other autoantibody-mediated diseases. This review uses pemphigus as a paradigm to discuss the pathophysiology of select autoantibody-mediated diseases and to evaluate the role of rituximab in their treatment.

Pemphigus: a paradigm for autoantibody-mediated diseases

In pemphigus, autoantibodies to desmoglein (Dsg) skin cell adhesion proteins cause potentially severe epithelial blistering^{4,5}, which can lead to death from malnutrition, dehydration, and infection. There are two major subtypes of pemphigus: pemphigus vulgaris (PV), which is characterized by autoantibodies to Dsg3, and pemphigus foliaceus (PF), characterized by autoantibodies to Dsg1.

Laboratory studies and clinical observations have established that the anti-Dsg antibodies in pemphigus sera are by themselves the disease-causing agents. Dsg1 and Dsg3 ELISAs have high sensitivity and specificity (98–100%) for disease, indicating that pemphigus does not occur in the absence of anti-Dsg antibodies and, furthermore, disease activity correlates with serum autoantibody titer^{6–8}. Direct evidence for the pathogenicity of anti-Dsg antibodies comes from early observations that transplacental transfer of autoantibodies from mothers with PV leads to neonatal pemphigus^{9–12}. Definitive evidence derives from experiments showing that affinity purified anti-Dsg antibodies as well as recombinant monoclonal anti-Dsg antibodies cause characteristic pemphigus skin blisters^{13–18} and conversely that removal of anti-Dsg antibodies from pemphigus serum abolishes its pathogenicity^{19,20}. Moreover, anti-Dsg autoantibodies cause blister formation in human skin and animal models even as monovalent antibody fragments^{15,17,21,22}, indicating that antigen cross-linking or Fc-mediated functions are not required for pathogenicity, even though such mechanisms can contribute to blister formation²³. Autoimmunity against other antigens in pemphigus has also been

described^{24–28}. Regardless, these data collectively and definitively establish pemphigus as an autoantibody-mediated, not just an autoantibody-associated, disease. This conclusion spurs the rationale for evaluating the efficacy of B-cell-depleting agents in pemphigus.

Efficacy of rituximab in pemphigus

Rituximab has emerged as an effective therapeutic option for pemphigus patients. Nearly all patients (95–100%) experience initial disease control^{29,30}. A recent meta-analysis of 578 cases showed a complete remission (CR) rate of 76% after rituximab³¹, which included patients remaining on systemic immunosuppressive therapies; CR rates of 100% and 59% were reported in prospective studies, with the latter using a more stringent definition of CR^{30,32}. The rate of relapse generally increases with length of clinical follow-up, ranging from 40–81%, with long-term rates of CR off therapy observed in 39–45% of patients^{31,32}. One prospective study of rituximab and intravenous immunoglobulin (IVIg) in 11 patients reported 100% of patients achieving CR off therapy after long-term follow up³³.

The optimal dosing for rituximab in pemphigus has not been established. Because rituximab was initially approved for lymphoma, early pemphigus treatment protocols more often used the lymphoma dosing regimen (375 mg/m² weekly for four weeks). However, because the B cell burden in autoimmune disease is much lower than that in lymphoma, several studies have evaluated the RA regimen (two 1,000 mg doses given two weeks apart). A meta-analysis found no significant difference in CR rates between the two treatment regimens, although higher-dose protocols were associated with a significantly longer duration of disease remission³¹. Additionally, relapse after rituximab has been shown to be associated with the same anti-Dsg B cells observed during active disease³⁴, indicating that relapse is due to incomplete B cell depletion; thus, higher-dose regimens that are more likely to achieve complete B cell depletion should offer the highest chance for long-term CR off therapy.

Several findings suggest the use of rituximab as a component of first-line therapy for disease. These include an association between disease duration prior to rituximab and rate of CR³⁵, as well as a 100% rate of long-term CR off therapy in five patients who received rituximab as first-line therapy³². A randomized, open-label trial comparing rituximab and moderate-dose corticosteroids to high-dose corticosteroids as first-line therapy has recently completed, with study results pending publication (ClinicalTrials.gov ID: NCT00784589).

Other autoantibody-mediated diseases and the pemphigus paradigm

Several other autoantibody-mediated diseases occur in humans. However, they may vary from the pemphigus paradigm in the diversity of autoantigens, the sensitivity and specificity of the autoantibodies, and the downstream effects of antibody binding. Nevertheless, an increasing number of studies have shown similarly promising results for the use of rituximab in many of these diseases, in particular neuromyelitis optica (NMO), thrombotic thrombocytopenic purpura (TTP), and myasthenia gravis (MG).

The published literature includes a few hundred patients for each of these three diseases and has found notable improvements in remission and relapse rates. While randomized controlled trials are needed to confirm these initial findings, these three diseases represent areas of particular potential for B cell depletion strategies.

Neuromyelitis optica

NMO is characterized by inflammation, demyelination, and axonal injury to the spinal cord and optic nerve. The discovery that patients have antibodies against the astrocyte water channel aquaporin-4 (AQP4) helped distinguish NMO patients from those with multiple sclerosis^{36–38}, and these antibodies are now a central part of NMO diagnosis³⁹. While the antibodies are nearly 100% specific, their sensitivity varies by assay and study (48–87%)^{40,41}. Data have not consistently shown a correlation between antibody levels and disease activity or risk of relapse^{42,43}. However, the findings of select studies suggest that anti-AQP4 antibodies may have prognostic value: antibody titers correlate with extent of transverse myelitis, antibody levels increase sharply before relapse in some patients, and positive titers during the initial episode of transverse myelitis may predict recurrent attacks^{44–46}.

Strong support for the pathogenicity of anti-AQP4 antibodies comes from studies using monoclonal recombinant antibodies, purified antibodies, or patient serum^{47–50}. Passive transfer of antibodies into mouse and rat experimental autoimmune encephalomyelitis (EAE) models exacerbates EAE symptoms and causes characteristic NMO lesions, including demyelination and/or loss of astrocytes with a decrease in astrocyte surface AQP4 expression in areas adjacent to astrocyte depletion. Removal of anti-AQP4 antibodies from patient sera markedly reduced the pathology⁴⁹. In addition, plasma exchange has been used with success in steroid-refractory NMO patients^{51–53} and as first-line therapy⁵⁴. Still, several aspects of NMO pathogenesis require clarification, including whether anti-AQP4 antibodies are present in the central nervous system at the onset of disease. In addition, the observation that anti-AQP4 antibodies have produced pathology only in EAE models with prior T-cell-mediated inflammation has sparked interest in how the cellular immune response mediates disease^{47,49}. A recent study found that transfer of anti-AQP4 reactive T cells into mice led to inflammatory infiltrate and demyelination, without the loss of astrocytes and AQP4 observed with antibody transfer⁵⁵; thus, the authors postulate that T cells may initiate and localize the autoimmune response as well as regulate downstream immune mediators including antibodies. Collectively, these data indicate that NMO antibodies are necessary for specific aspects of disease pathology, but the data supporting their sufficiency for disease induction have not been as clearly established.

Rituximab is commonly used to prevent relapse in NMO. Following a seminal study in eight patients⁵⁶, promising results have led to larger studies that have included more AQP4 IgG seropositive patients using a regimen of rituximab induction (either lymphoma or RA protocol) followed by maintenance infusions. The optimal rituximab maintenance strategy has not been established. Some studies used a fixed schedule (e.g. re-treatment every

6–9 months)^{57,58} and chose to re-treat sooner if CD19⁺ B cell count rose⁵⁹, while others re-treated based solely on memory B cell repletion⁶⁰. Studies with patients previously on other therapies found a 50–70% rate of relapse-free disease and a decrease in annualized relapse rate (ARR) of up to 96%^{57,59–61}. Rituximab has also been effective as initial therapy (84% rate of relapse-free disease; 97% reduction in ARR)⁵⁸, and the European Federation of Neurological Societies has recommended rituximab as first-line treatment for NMO⁶².

Thrombotic thrombocytopenic purpura

TTP is a life-threatening thrombotic microangiopathy that arises when the metalloprotease ADAMTS13 does not cleave von Willebrand factor (vWF); this leads to the persistence of ultra-large vWF multimers that promote platelet aggregation and vessel occlusion. Acquired idiopathic TTP stems from autoantibodies against ADAMTS13. Inhibitory antibodies can prevent proteolysis by binding to the domain of ADAMTS13 that interacts with vWF^{63,64}. More rarely, non-inhibitory antibodies that have no *in vitro* neutralization effect can still interfere with ADAMTS13 activity *in vivo* by promoting its clearance or preventing its binding to factors such as endothelial cells⁶⁵. Anti-ADAMTS13 antibodies have been detected in >95% of patients with severely deficient ADAMTS13 levels (i.e. <10% normal)^{66,67}. However, the antibodies are less specific, as they have also been found in patients with systemic lupus erythematosus and anti-phospholipid antibody syndrome, as well as in healthy individuals^{66,68}. Conflicting data exist regarding an association between antibody titer and disease course^{69–71}.

Antibody pathogenicity was demonstrated by mouse monoclonal antibodies against ADAMTS13 that triggered TTP in baboons⁷². New data also show that expression of inhibitory human single chain variable fragment (scFv) antibodies in mice results in features of TTP, further suggesting that antibody effect does not necessarily require Fc-mediated mechanisms⁷³. Additional support comes from the successful use of plasmapheresis to remove inhibitors and replace functional ADAMTS13, which is associated with an 80–90% survival rate and is used as standard first-line therapy^{74–76}.

Rituximab has been used in roughly 250 TTP patients in the literature, either in refractory patients, as initial treatment, or during remission to prevent relapse⁷⁷. In a prospective study of 22 TTP patients with refractory disease, rituximab led to faster achievement of remission and higher rates of remission at 35 days (100%) compared to historic controls (78%)⁷⁸. While rituximab led to lower relapse rates at one year (0%) compared to controls (9%), the long-term relapse rate did not differ between the groups. When used in the initial treatment of acute TTP, rituximab led to lower relapse rates at one year compared to historic controls (0% vs. 16%), as well as during follow-up (11% vs. 55%), although the follow-up duration was longer in the control group⁷⁹. Lastly, studies have used rituximab maintenance dosing during remission to prevent relapse in patients with severe ADAMTS13 deficiency. In a recent cross-sectional study, those on rituximab had lower rates of relapse during the follow-up period (10%) compared to historic controls (39%), although follow-up for the controls was again longer. In general, rituximab is associated with an increase in ADAMTS13

activity and a decrease in inhibitor levels. Currently, rituximab is recommended for use in patients refractory to plasmapheresis and steroids and as initial treatment in severe forms of acute TTP⁸⁰.

Myasthenia gravis

MG was the first autoantibody-mediated neurologic disease to be discovered⁸¹, and the disease has two main autoantigenic targets. Roughly 80–90% of patients have antibodies against the nicotinic acetylcholine receptor (AChR); these cause complement-mediated destruction^{82–85}, crosslinking-induced activation and downregulation⁸⁶, or direct interference with ACh binding of the AChR⁸⁷, resulting in muscle fatigue and weakness. While autoantibody titers are not predictive of disease course⁸⁸, the causal role of autoantibodies has long been established: transplacental transfer of antibodies from mothers with myasthenia to the neonate can cause transient muscle weakness, and passive transfer of patient serum to mice leads to smaller miniature endplate potentials (MEPPs) and reduced AChR density^{81,89}.

MG can also be caused by antibodies against muscle-specific receptor tyrosine kinase (MuSK), a transmembrane protein found on the post-synaptic membrane. Anti-MuSK antibodies are found in 40–70% of myasthenia patients lacking anti-AChR antibodies, although a lower prevalence has been observed in a few studies, particularly those in Asian ethnic groups^{90–92}. As the antibodies are mostly IgG4 and do not fix complement, immune complexes are not found in the synapse^{93,94}. Growing evidence has supported, though not firmly established, their pathogenic role. While muscle biopsies from MuSK-Ab-positive patients had smaller MEPPs, they did not show the reduction in AChR density or the striking synaptic structural changes observed in AChR-Ab-positive patients^{94,95}. However, mice injected with purified anti-MuSK antibodies exhibit changes in synapse morphology (including reduced AChR density) and muscle weakness⁹⁶. In addition, the high success rate of plasma exchange in MuSK-Ab-positive patients supports a pathogenic role of the antibody⁹⁷.

Rituximab has been used in MG patients refractory to conventional immunosuppressive therapy. Roughly 200 MG patients have received rituximab in the literature, which predominantly consists of case reports and case series. Compared to AChR-Ab-positive patients, those with anti-MuSK antibodies have a higher response rate as well as more marked and sustained improvement^{98,99}, leading investigators to propose that rituximab may have benefit earlier in the treatment of these patients⁹⁹. A recent meta-analysis showed an overall response rate of 84% and found non-significant differences in the response rates among anti-MuSK-positive patients (89%), anti-AChR-positive patients (80%), and double seronegative patients (86%)¹⁰⁰. The first double-blind randomized controlled trial of rituximab in anti-AChR-positive MG patients is ongoing (ClinicalTrials.gov ID: NCT02110706), and a second trial in patients with new onset, generalized MG is currently recruiting (ClinicalTrials.gov ID: NCT02950155).

Graves' disease

Thyrotropin receptor autoantibodies (TRAb), or thyroid stimulating hormone receptor (TSHR) autoantibodies, play a critical role in autoimmune thyroid disease and are classified as stimulating,

blocking, or neutral (although the latter has been shown to modulate downstream TSHR signaling). The hyperthyroidism characteristic of Graves' disease is caused by stimulatory TRAb, which are observed in nearly all patients¹⁰¹. While antibody levels decline with therapy, and while antibody persistence has been linked to a higher risk of relapse, TRAb level is not considered a reliable predictor of treatment response¹⁰². The pathogenicity of TRAb has long been established by passive transfer experiments with patient serum, and by the ability of maternal autoantibodies to cause transient hyperthyroidism in the neonate^{103,104}. Additional support comes from the recent isolation of two stimulatory human monoclonal TRAbs – M22 and K1-18. These have similar TSHR binding affinity as antibodies from patient sera, with thousands-fold greater potency. The Fab fragment of M22, but not of K1-18, has similar characteristics to the intact autoantibody^{105–107}.

Case series and open-label studies of rituximab in Graves' orbitopathy (GO) have shown a >90% rate of disease inactivation¹⁰⁸. Two double-blind randomized controlled trials have been published to date, both in euthyroid patients with active, moderate-to-severe GO. The first study in 25 patients found no difference in clinical improvement between rituximab and placebo¹⁰⁹, while the second trial in 31 patients found greater clinical improvements with rituximab versus methylprednisolone¹¹⁰. The authors of the second trial note that the discrepancy could be due to differences in the study populations, including number of patients, duration of disease, and prior steroid use. Still, in light of this inconsistency as well as previous data, rituximab is recommended as a second-line option for patients who are unresponsive to corticosteroids¹¹¹.

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) results from autoantibodies against multiple platelet surface proteins, including glycoproteins (GP)Ib/IX and GPIIa/IIIb, leading to platelet destruction^{112,113}. Unlike pemphigus, anti-platelet antibodies have low sensitivity for the disease, with detection in roughly half of patients^{114–116}. *In vitro* studies have shown that these antibodies bind complement, inhibit megakaryocytopoiesis, and hinder proplatelet formation^{117,118}. Evidence of their pathogenicity stems from seminal studies in the 1950s and 1960s showing that transfer of plasma from ITP patients induced thrombocytopenia in human recipients without the disease^{112,119}.

Following the first prospective study of rituximab in ITP in 2001¹²⁰, subsequent studies have indicated a complete response rate of 44% and an overall response rate of 63% (defined as platelet count >150 and >50 × 10⁹ cells/L, respectively)¹²¹; however, only 21–23% of patients have responses lasting five years^{122,123}. One large randomized controlled trial in steroid-refractory patients compared rituximab to placebo with or without corticosteroids and found no difference in preventing the need for splenectomy¹²⁴. Similarly, a smaller pilot study examined rituximab versus placebo as adjuvants to standard care and found no difference in the composite endpoint of platelet count <50 × 10⁹/L, significant bleeding, or need for rescue treatment¹²⁵. Recent efforts to improve therapeutic efficacy have included combining rituximab with other approved ITP therapies. Three randomized controlled trials show higher rates

of sustained response with combined rituximab and steroids versus steroid therapy alone, suggesting an early role for rituximab in treatment^{126–128}. A single-arm pilot study also investigated the addition of cyclosporine to this combination, which led to a response rate of 60% with remission persisting for longer than seven months¹²⁹. Alternative options such as adding recombinant human thrombopoietin to rituximab have also indicated potential benefit¹³⁰.

Autoimmune hemolytic anemia

In autoimmune hemolytic anemia (AIHA), the binding of antibodies to different antigens on the red blood cell (RBC) surface leads to RBC agglutination and lysis. Antibodies in warm AIHA are predominantly IgG, act at body temperature, and lead to both complement-mediated and Fc-dependent RBC destruction. In contrast, cold agglutinin disease (CAD) involves mainly IgM that bind at low temperature and result in complement-mediated RBC removal¹³¹. The antibodies are highly sensitive and are required for disease diagnosis. Early demonstration of their pathogenicity came from studies on human erythrocytes sensitized with patient IgG or IgM and reintroduced into normal volunteers^{132,133}. The role of plasma exchange in warm AIHA has not yet been established¹³⁴. In CAD, plasma exchange is considered a reasonable second-line option and is used in situations of elevated risk, including perioperatively and in cases of severe hemolysis^{134–136}.

The literature in AIHA has, until recently, been limited to case reports and small prospective studies, with significant heterogeneity. A recent meta-analysis found an overall response rate of 73% and a complete response rate of 37%, though definitions of response differed by study¹³⁷. The overall and complete response rates were notably higher among warm AIHA patients (79% and 42%, respectively) compared to those with CAD (57% and 21%, respectively). Similar to studies in ITP, one open-label randomized controlled trial in warm AIHA showed that the combination of rituximab and prednisone led to a higher complete response rate at 12 months (75%) versus prednisone alone (36%), as well as a higher rate of relapse-free survival at 36 months¹³⁸.

Anti-glomerular basement membrane disease

In anti-glomerular basement membrane (GBM) disease, antibodies to the alpha 3 chain of collagen IV – $\alpha 3(\text{IV})$ – cause rapidly progressing glomerulonephritis and pulmonary hemorrhage (Goodpasture's syndrome), glomerulonephritis alone, or, more rarely, isolated pulmonary hemorrhage^{139,140}. These antibodies bind rapidly and tightly to the basement membrane with slow dissociation¹⁴¹. Newer immunoassays have shown a sensitivity of 95–100% and specificity of 90–100%¹⁴². Of note, anti- $\alpha 3(\text{IV})$ IgG are also found in healthy individuals, although these have lower titers, reduced affinity, and different IgG subclass composition compared to those isolated from patients¹⁴³. Given this finding, renal biopsy in addition to antibody screening is recommended to confirm diagnosis.

The pathogenicity of anti- $\alpha 3(\text{IV})$ antibodies was established by the demonstration that antibodies from patient serum and from

nephritic kidneys induce rapid glomerulonephritis in squirrel monkeys¹⁴⁴. Currently, standard treatment involves the expedient use of plasmapheresis combined with cyclophosphamide and corticosteroids. The addition of plasmapheresis to initial therapy has led to striking improvements in survival (from <20% to 65–100%), though response depends heavily on renal function at the initiation of therapy^{145,146}.

Very few studies have been conducted on rituximab in anti-GBM disease. The largest case series included eight patients with severe and/or refractory disease¹⁴⁷. Seven patients achieved CR with no relapses, and rituximab was associated with a patient survival of 100%, a renal survival of 75%, and a disappearance of serum anti-GBM antibodies.

Lambert-Eaton myasthenic syndrome

In Lambert-Eaton myasthenic syndrome (LEMS), antibodies to voltage-gated calcium channels (VGCCs) on the presynaptic terminal reduce ACh release, leading to muscle weakness and autonomic symptoms. Antibodies to the P/Q-type of VGCC are found in 85–95% of patients; they have also been observed at a lower frequency in people with malignancy, amyotrophic lateral sclerosis, and other diseases^{148–150}. Thus, the diagnosis of LEMS requires the consideration of electrophysiologic and clinical findings along with antibody presence. Passive transfer of purified anti-VGCC antibodies into mice reproduces the electrophysiological and morphologic changes found at the neuromuscular junction in LEMS patients^{151–153}; moreover, decreased ACh release was observed in complement-deficient mice¹⁵⁴. The autoimmune origin of LEMS has prompted the sporadic use of plasmapheresis with immunosuppression, with varying responses^{155–158}.

Data on rituximab in LEMS come from a very small number of case reports and case series^{159,160}. Key findings were shown in a case series that included two patients with refractory disease, both with anti-VGCC antibodies¹⁶⁰. Both patients experienced improvement but not CR.

Epidermolysis bullosa acquisita and bullous pemphigoid

Epidermolysis bullosa acquisita (EBA) and bullous pemphigoid (BP) are subepithelial blistering diseases characterized by antibodies against different epithelial basement membrane zone antigens; specifically, EBA results from antibodies against type VII collagen (COL7), while BP arises from antibodies against BP antigen 180 (BP180, or COL17) or against BP230¹⁶¹. For EBA, the COL7 ELISA is highly sensitive and specific (>94%) in patients whose sera test positive with indirect immunofluorescence (IIF) to the dermal side of salt-split skin^{162–164}. In patients with negative IIF on salt-split skin, the COL7 ELISA has high specificity (98%) but poor sensitivity (23%), leading the authors to recommend serration pattern analysis for this patient population¹⁶⁵. For BP, results of the BP180 and BP230 ELISA assays vary: most studies indicate a sensitivity and specificity of 70–98% and 90–100%, respectively, for the BP180 ELISA and 59–77% and 62–100%, respectively, for the BP230 ELISA^{166–171}. Studies that compared the use of both the BP180 and the BP230 serologic assays to either assay alone found

that the combined approach generally demonstrated improved sensitivity (87–100%) and similar specificity (88–90%) for disease diagnosis^{166,170–172}.

In both diseases, antibody titers correlate with disease activity^{163,173}, and their pathogenicity is established. For EBA, rabbit IgG against murine COL7 recapitulate the EBA phenotype in mice, as do antibodies purified from patient sera. Of note, no blisters were observed with (Fab')₂ fragments from these same antibodies or in complement-deficient mice, indicating a critical role for Fc-mediated processes^{174,175}. Similarly, purified human anti-BP180 antibodies and recombinant human IgG1 anti-BP180 monoclonal antibodies lead to BP-like blisters in humanized BP180 mice^{176,177}. Fab fragments not only fail to produce this phenotype but also protect mice against autoantibody-mediated blistering¹⁷⁸. Further support for the pathogenic role of antibodies in disease comes from the use of immunoadsorption to induce remission in recalcitrant EBA and BP^{179–182}.

Small case series in BP patients have shown favorable results with rituximab in recalcitrant disease^{183–185}, including a study of 12 patients receiving rituximab and IVIg who all achieved both clinical and serological remission¹⁸⁶. In addition, a study of 13 BP patients found a significantly higher rate of remission with the first-line use of rituximab and corticosteroids compared to steroids alone¹⁸⁷. Larger prospective studies are needed to confirm these early results.

Data on rituximab in EBA derive mainly from case reports, making estimates of treatment response challenging. Still, rituximab has shown promising results in a few patients with refractory disease^{188–193}, either alone or in combination with immunoadsorption^{179,194}.

Summary

In conclusion, the use of rituximab has led to promising results in several autoantibody-mediated diseases. Larger studies including randomized controlled trials are needed to further evaluate its effectiveness, dosing, and placement in therapeutic algorithms. Looking forward, autoantibody-mediated diseases represent an area of great potential for rituximab and other B-cell-depleting therapies.

Competing interests

Aimee Payne has served as a consultant for Syntimmune and TG Therapeutics.

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References

1. Eming R, Nagel A, Wolff-Franke S, *et al.*: **Rituximab exerts a dual effect in pemphigus vulgaris.** *J Invest Dermatol.* 2008; **128**(12): 2850–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
2. Palanichamy A, Jahn S, Nickles D, *et al.*: **Rituximab efficiently depletes increased CD20-expressing T cells in multiple sclerosis patients.** *J Immunol.* 2014; **193**(2): 580–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
3. Wilk E, Witte T, Marquardt N, *et al.*: **Depletion of functionally active CD20+ T cells by rituximab treatment.** *Arthritis Rheum.* 2009; **60**(12): 3563–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Eyre RW, Stanley JR: **Human autoantibodies against a desmosomal protein complex with a calcium-sensitive epitope are characteristic of pemphigus foliaceus patients.** *J Exp Med.* 1987; **165**(6): 1719–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Amagai M, Klaus-Kovtun V, Stanley JR: **Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion.** *Cell.* 1991; **67**(5): 869–77.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Amagai M, Komai A, Hashimoto T, *et al.*: **Usefulness of enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3 for serodiagnosis of pemphigus.** *Br J Dermatol.* 1999; **140**(6): 351–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Cheng SW, Kobayashi M, Kinoshita-Kuroda K, *et al.*: **Monitoring disease activity in pemphigus with enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3.** *Br J Dermatol.* 2002; **147**(2): 261–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Schmidt E, Dahnrich C, Rosemann A, *et al.*: **Novel ELISA systems for antibodies to desmoglein 1 and 3: correlation of disease activity with serum autoantibody levels in individual pemphigus patients.** *Exp Dermatol.* 2010; **19**(5): 458–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Green D, Maize JC: **Maternal pemphigus vulgaris with *in vivo* bound antibodies in the stillborn fetus.** *J Am Acad Dermatol.* 1982; **7**(3): 388–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Moncada B, Kettelsen S, Hernández-Moctezuma JL, *et al.*: **Neonatal pemphigus vulgaris: role of passively transferred pemphigus antibodies.** *Br J Dermatol.* 1982; **106**(4): 465–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Wasserstrum N, Laros RK Jr: **Transplacental transmission of pemphigus.** *JAMA.* 1983; **249**(11): 1480–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
12. Hup JM, Bruinsma RA, Boersma ER, *et al.*: **Neonatal pemphigus vulgaris: transplacental transmission of antibodies.** *Pediatr Dermatol.* 1986; **3**(6): 468–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Amagai M, Karpati S, Prussick R, *et al.*: **Autoantibodies against the amino-terminal cadherin-like binding domain of pemphigus vulgaris antigen are pathogenic.** *J Clin Invest.* 1992; **90**(3): 919–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. Ding X, Diaz LA, Fairley JA, *et al.*: **The anti-desmoglein 1 autoantibodies in pemphigus vulgaris sera are pathogenic.** *J Invest Dermatol.* 1999; **112**(5): 739–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Payne AS, Ishii K, Kacir S, *et al.*: **Genetic and functional characterization of human pemphigus vulgaris monoclonal autoantibodies isolated by phage display.** *J Clin Invest.* 2005; **115**(4): 888–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Di Zenzo G, Di Lullo G, Corti D, *et al.*: **Pemphigus autoantibodies generated through somatic mutations target the desmoglein-3 cis-interface.** *J Clin Invest.* 2012; **122**(10): 3781–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
17. Ishii K, Lin C, Siegel DL, *et al.*: **Isolation of pathogenic monoclonal anti-desmoglein 1 human antibodies by phage display of pemphigus foliaceus autoantibodies.** *J Invest Dermatol.* 2008; **128**(4): 939–48.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
18. Yeh SW, Cavacini LA, Bhol KC, *et al.*: **Pathogenic human monoclonal antibody against desmoglein 3.** *Clin Immunol.* 2006; **120**(1): 68–75.
[PubMed Abstract](#) | [Publisher Full Text](#)

19. Amagai M, Hashimoto T, Shimizu N, *et al.*: Absorption of pathogenic autoantibodies by the extracellular domain of pemphigus vulgaris antigen (Dsg3) produced by baculovirus. *J Clin Invest.* 1994; 94(1): 59–67. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Amagai M, Hashimoto T, Green KJ, *et al.*: Antigen-specific immunoadsorption of pathogenic autoantibodies in pemphigus foliaceus. *J Invest Dermatol.* 1995; 104(6): 895–901. [PubMed Abstract](#) | [Publisher Full Text](#)
21. Mascaró JM Jr, España A, Liu Z, *et al.*: Mechanisms of acantholysis in pemphigus vulgaris: role of IgG valence. *Clin Immunol Immunopathol.* 1997; 85(1): 90–6. [PubMed Abstract](#) | [Publisher Full Text](#)
22. Rock B, Labib RS, Diaz LA: Monovalent Fab' immunoglobulin fragments from endemic pemphigus foliaceus autoantibodies reproduce the human disease in neonatal Balb/c mice. *J Clin Invest.* 1990; 85(1): 296–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. **F** Saito M, Stahley SN, Caughman CY, *et al.*: Signaling dependent and independent mechanisms in pemphigus vulgaris blister formation. *PLoS One.* 2012; 7(12): e50696. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
24. **F** Mao X, Nagler AR, Farber SA, *et al.*: Autoimmunity to desmocollin 3 in pemphigus vulgaris. *Am J Pathol.* 2010; 177(6): 2724–30. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
25. **F** Rafei D, Müller R, Ishii N, *et al.*: IgG autoantibodies against desmocollin 3 in pemphigus sera induce loss of keratinocyte adhesion. *Am J Pathol.* 2011; 178(2): 718–23. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
26. Nguyen VT, Ndoye A, Grando SA: Pemphigus vulgaris antibody identifies pemphaxin. A novel keratinocyte annexin-like molecule binding acetylcholine. *J Biol Chem.* 2000; 275(38): 29466–76. [PubMed Abstract](#) | [Publisher Full Text](#)
27. Nguyen VT, Ndoye A, Grando SA: Novel human alpha9 acetylcholine receptor regulating keratinocyte adhesion is targeted by Pemphigus vulgaris autoimmunity. *Am J Pathol.* 2000; 157(4): 1377–91. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Chen Y, Chernyavsky A, Webber RJ, *et al.*: Critical Role of the Neonatal Fc Receptor (FcRn) in the Pathogenic Action of Antimitochondrial Autoantibodies Synergizing with Anti-desmoglein Autoantibodies in Pemphigus Vulgaris. *J Biol Chem.* 2015; 290(39): 23826–37. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. **F** Joly P, Mouquet H, Roujeau JC, *et al.*: A single cycle of rituximab for the treatment of severe pemphigus. *N Engl J Med.* 2007; 357(6): 545–52. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
30. **F** Ahmed AR, Spigelman Z, Cavacini LA, *et al.*: Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med.* 2006; 355(17): 1772–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
31. **F** Wang HH, Liu CW, Li YC, *et al.*: Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. *Acta Derm Venereol.* 2015; 95(8): 928–32. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
32. **F** Colliou N, Picard D, Caillot F, *et al.*: Long-term remissions of severe pemphigus after rituximab therapy are associated with prolonged failure of desmoglein B cell response. *Sci Transl Med.* 2013; 5(175): 175ra30. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
33. Ahmed AR, Kaveri S, Spigelman Z: Long-Term Remissions in Recalcitrant Pemphigus Vulgaris. *N Engl J Med.* 2015; 373(27): 2693–4. [PubMed Abstract](#) | [Publisher Full Text](#)
34. Hammers CM, Chen J, Lin C, *et al.*: Persistence of anti-desmoglein 3 IgG⁺ B-cell clones in pemphigus patients over years. *J Invest Dermatol.* 2015; 135(3): 742–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. **F** Lunardon L, Tsai KJ, Proppert KJ, *et al.*: Adjuvant rituximab therapy of pemphigus: a single-center experience with 31 patients. *Arch Dermatol.* 2012; 148(9): 1031–6. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
36. **F** Lennon VA, Kryzer TJ, Pittock SJ, *et al.*: IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med.* 2005; 202(4): 473–7. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
37. Lennon VA, Wingerchuk DM, Kryzer TJ, *et al.*: A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet.* 2004; 364(9451): 2106–12. [PubMed Abstract](#) | [Publisher Full Text](#)
38. **F** Roemer SF, Parisi JE, Lennon VA, *et al.*: Pattern-specific loss of aquaporin-4 immunoreactivity distinguishes neuromyelitis optica from multiple sclerosis. *Brain.* 2007; 130(Pt 5): 1194–205. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
39. **F** Wingerchuk DM, Banwell B, Bennett JL, *et al.*: International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015; 85(2): 177–89. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
40. Waters PJ, McKeon A, Leite MI, *et al.*: Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. *Neurology.* 2012; 78(9): 665–71; discussion 669. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Jiao Y, Fryer JP, Lennon VA, *et al.*: Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. *Neurology.* 2013; 81(14): 1197–204. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Isobe N, Yonekawa T, Matsushita T, *et al.*: Quantitative assays for anti-aquaporin-4 antibody with subclass analysis in neuromyelitis optica. *Mult Scler.* 2012; 18(11): 1541–51. [PubMed Abstract](#) | [Publisher Full Text](#)
43. Isobe N, Yonekawa T, Matsushita T, *et al.*: Clinical relevance of serum aquaporin-4 antibody levels in neuromyelitis optica. *Neurochem Res.* 2013; 38(5): 997–1001. [PubMed Abstract](#) | [Publisher Full Text](#)
44. Weinshenker BG, Wingerchuk DM, Vukusic S, *et al.*: Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol.* 2006; 59(3): 566–9. [PubMed Abstract](#) | [Publisher Full Text](#)
45. Takahashi T, Fujihara K, Nakashima I, *et al.*: Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. *Brain.* 2007; 130(Pt 5): 1235–43. [PubMed Abstract](#) | [Publisher Full Text](#)
46. Jarius S, Aboul-Enein F, Waters P, *et al.*: Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. *Brain.* 2008; 131(Pt 11): 3072–80. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
47. Saini H, Rifkin R, Gorelik M, *et al.*: Passively transferred human NMO-IgG exacerbates demyelination in mouse experimental autoimmune encephalomyelitis. *BMC Neurol.* 2013; 13: 104. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Bennett JL, Lam C, Kalluri SR, *et al.*: Intrathecal pathogenic anti-aquaporin-4 antibodies in early neuromyelitis optica. *Ann Neurol.* 2009; 66(5): 617–29. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
49. Bradl M, Misu T, Takahashi T, *et al.*: Neuromyelitis optica: pathogenicity of patient immunoglobulin in vivo. *Ann Neurol.* 2009; 66(5): 630–43. [PubMed Abstract](#) | [Publisher Full Text](#)
50. Kinoshita M, Nakatsuji Y, Kimura T, *et al.*: Neuromyelitis optica: Passive transfer to rats by human immunoglobulin. *Biochem Biophys Res Commun.* 2009; 386(4): 623–7. [PubMed Abstract](#) | [Publisher Full Text](#)
51. **F** Abboud H, Petrak A, Mealy M, *et al.*: Treatment of acute relapses in neuromyelitis optica: Steroids alone versus steroids plus plasma exchange. *Mult Scler.* 2016; 22(2): 185–92. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. Watanabe S, Nakashima I, Misu T, *et al.*: Therapeutic efficacy of plasma exchange in NMO-IgG-positive patients with neuromyelitis optica. *Mult Scler.* 2007; 13(1): 128–32. [PubMed Abstract](#) | [Publisher Full Text](#)
53. Bonnan M, Valentino R, Olindo S, *et al.*: Plasma exchange in severe spinal attacks associated with neuromyelitis optica spectrum disorder. *Mult Scler.* 2009; 15(4): 487–92. [PubMed Abstract](#) | [Publisher Full Text](#)
54. **F** Kleiter I, Gahlen A, Borisow N, *et al.*: Neuromyelitis optica: Evaluation of 871 attacks and 1,153 treatment courses. *Ann Neurol.* 2016; 79(2): 206–16. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
55. **F** Jones MV, Huang H, Calabresi PA, *et al.*: Pathogenic aquaporin-4 reactive T cells are sufficient to induce mouse model of neuromyelitis optica. *Acta Neuropathol Commun.* 2015; 3: 28. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. Cree BA, Lamb S, Morgan K, *et al.*: An open label study of the effects of rituximab in neuromyelitis optica. *Neurology.* 2005; 64(7): 1270–2. [PubMed Abstract](#) | [Publisher Full Text](#)
57. **F** Collongues N, Brassat D, Maillart E, *et al.*: Efficacy of rituximab in refractory neuromyelitis optica. *Mult Scler.* 2016; 22(7): 955–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
58. **F** Zéphir H, Bernard-Valnet R, Lebrun C, *et al.*: Rituximab as first-line therapy in neuromyelitis optica: efficiency and tolerability. *J Neurol.* 2015; 262(10): 2329–35. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
59. **F** Mealy MA, Wingerchuk DM, Palace J, *et al.*: Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. *JAMA Neurol.* 2014; 71(3): 324–30. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
60. **F** Kim S, Jeong IH, Hyun JW, *et al.*: Treatment Outcomes With Rituximab in 100 Patients With Neuromyelitis Optica: Influence of FCGR3A Polymorphisms on the Therapeutic Response to Rituximab. *JAMA Neurol.* 2015; 72(9): 989–95. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
61. **F** Radaelli M, Moiola L, Sangalli F, *et al.*: Neuromyelitis optica spectrum

- disorders: long-term safety and efficacy of rituximab in Caucasian patients. *Mult Scler*. 2016; 22(4): 511–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
62. Sellner J, Boggild M, Clanet M, *et al.*: EFNS guidelines on diagnosis and management of neuromyelitis optica. *Eur J Neurol*. 2010; 17(8): 1019–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
 63. Soejima K, Matsumoto M, Kokame K, *et al.*: ADAMTS-13 cysteine-rich/spacer domains are functionally essential for von Willebrand factor cleavage. *Blood*. 2003; 102(9): 3232–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 64. Tsai HM, Lian EC: Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med*. 1998; 339(22): 1585–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 65. Scheifflinger F, Knöbl P, Trattner B, *et al.*: Nonneutralizing IgM and IgG antibodies to von Willebrand factor-cleaving protease (ADAMTS-13) in a patient with thrombotic thrombocytopenic purpura. *Blood*. 2003; 102(9): 3241–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 66. Rieger M, Mannucci PM, Kremer Hovinga JA, *et al.*: ADAMTS13 autoantibodies in patients with thrombotic microangiopathies and other immunomediated diseases. *Blood*. 2005; 106(4): 1262–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 67. Scully M, Yarranton H, Liesner R, *et al.*: Regional UK TTP registry: correlation with laboratory ADAMTS 13 analysis and clinical features. *Br J Haematol*. 2008; 142(5): 819–26.
[PubMed Abstract](#) | [Publisher Full Text](#)
 68. Grillberger R, Casina VC, Turecek PL, *et al.*: Anti-ADAMTS13 IgG autoantibodies present in healthy individuals share linear epitopes with those in patients with thrombotic thrombocytopenic purpura. *Haematologica*. 2014; 99(4): e58–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 69. Zheng XL, Kaufman RM, Goodnough LT, *et al.*: Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and nonidiopathic thrombotic thrombocytopenic purpura. *Blood*. 2004; 103(11): 4043–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 70. Böhm M, Betz C, Miesbach W, *et al.*: The course of ADAMTS-13 activity and inhibitor titre in the treatment of thrombotic thrombocytopenic purpura with plasma exchange and vincristine. *Br J Haematol*. 2005; 129(5): 644–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
 71. Vesely SK, George JN, Lämmle B, *et al.*: ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood*. 2003; 102(1): 60–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 72. Feys HB, Roodt J, Vandeputte N, *et al.*: Thrombotic thrombocytopenic purpura directly linked with ADAMTS13 inhibition in the baboon (*Papio ursinus*). *Blood*. 2010; 116(12): 2005–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
 73. **F** Ostertag EM, Bdeir K, Kacir S, *et al.*: ADAMTS13 autoantibodies cloned from patients with acquired thrombotic thrombocytopenic purpura: 2. Pathogenicity in an animal model. *Transfusion*. 2016; 56(7): 1775–85.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 74. Bell WR, Braine HG, Ness PM, *et al.*: Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. *N Engl J Med*. 1991; 325(6): 398–403.
[PubMed Abstract](#) | [Publisher Full Text](#)
 75. Rock GA, Shumak KH, Buskard NA, *et al.*: Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med*. 1991; 325(6): 393–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 76. von Baeyer H: Plasmapheresis in thrombotic microangiopathy-associated syndromes: review of outcome data derived from clinical trials and open studies. *Ther Apher*. 2002; 6(4): 320–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 77. Lim W, Vesely SK, George JN: The role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura. *Blood*. 2015; 125(10): 1526–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 78. Froissart A, Buffet M, Veyradier A, *et al.*: Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. *Crit Care Med*. 2012; 40(1): 104–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
 79. Scully M, McDonald V, Cavenagh J, *et al.*: A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood*. 2011; 118(7): 1746–53.
[PubMed Abstract](#) | [Publisher Full Text](#)
 80. Scully M, Hunt BJ, Benjamin S, *et al.*: Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. 2012; 158(3): 323–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
 81. Simpson JA: 'Myasthenia Gravis: A New Hypothesis'. *Scott Med J*. 1960; 5(10): 419–436.
[Publisher Full Text](#)
 82. Lennon VA, Seybold ME, Lindstrom JM, *et al.*: Role of complement in the pathogenesis of experimental autoimmune myasthenia gravis. *J Exp Med*. 1978; 147(4): 973–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 83. Biesecker G, Gomez CM: Inhibition of acute passive transfer experimental autoimmune myasthenia gravis with Fab antibody to complement C6. *J Immunol*. 1989; 142(8): 2654–9.
[PubMed Abstract](#)
 84. Piddlesden SJ, Jiang S, Levin JL, *et al.*: Soluble complement receptor 1 (sCR1) protects against experimental autoimmune myasthenia gravis. *J Neuroimmunol*. 1996; 71(1–2): 173–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 85. Lin F, Kaminski HJ, Conti-Fine BM, *et al.*: Markedly enhanced susceptibility to experimental autoimmune myasthenia gravis in the absence of decay-accelerating factor protection. *J Clin Invest*. 2002; 110(9): 1269–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 86. Drachman DB, Angus CW, Adams RN, *et al.*: Myasthenic antibodies cross-link acetylcholine receptors to accelerate degradation. *N Engl J Med*. 1978; 298(20): 1116–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
 87. Gomez CM, Richman DP: Anti-acetylcholine receptor antibodies directed against the alpha-bungarotoxin binding site induce a unique form of experimental myasthenia. *Proc Natl Acad Sci U S A*. 1983; 80(13): 4089–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 88. Sanders DB, Burns TM, Cutter GR, *et al.*: Does change in acetylcholine receptor antibody level correlate with clinical change in myasthenia gravis? *Muscle Nerve*. 2014; 49(4): 483–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 89. Toyka KV, Brachman DB, Pestronk A, *et al.*: Myasthenia gravis: passive transfer from man to mouse. *Science*. 1975; 190(4212): 397–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 90. Hoch W, McConville J, Helms S, *et al.*: Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med*. 2001; 7(3): 365–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 91. McConville J, Farrugia ME, Beeson D, *et al.*: Detection and characterization of MuSK antibodies in seronegative myasthenia gravis. *Ann Neurol*. 2004; 55(4): 580–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 92. Yeh JH, Chen WH, Chiu HC, *et al.*: Low frequency of MuSK antibody in generalized seronegative myasthenia gravis among Chinese. *Neurology*. 2004; 62(11): 2131–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
 93. Vincent A, Bowen J, Newsom-Davis J, *et al.*: Seronegative generalised myasthenia gravis: clinical features, antibodies, and their targets. *Lancet Neurol*. 2003; 2(2): 99–106.
[PubMed Abstract](#) | [Publisher Full Text](#)
 94. Shiraishi H, Motomura M, Yoshimura T, *et al.*: Acetylcholine receptors loss and postsynaptic damage in MuSK antibody-positive myasthenia gravis. *Ann Neurol*. 2005; 57(2): 289–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
 95. Selcen D, Fukuda T, Shen XM, *et al.*: Are MuSK antibodies the primary cause of myasthenic symptoms? *Neurology*. 2004; 62(11): 1945–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
 96. Cole RN, Reddel SW, Gervasio OL, *et al.*: Anti-MuSK patient antibodies disrupt the mouse neuromuscular junction. *Ann Neurol*. 2008; 63(6): 782–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 97. Gupta JT, Sanders DB, Evoli A: Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts. *Muscle Nerve*. 2011; 44(1): 36–40.
[PubMed Abstract](#) | [Publisher Full Text](#)
 98. **F** Sun F, Ladha SS, Yang L, *et al.*: Interleukin-10 producing-B cells and their association with responsiveness to rituximab in myasthenia gravis. *Muscle Nerve*. 2014; 49(4): 487–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 99. Díaz-Manera J, Martínez-Hernández E, Querol L, *et al.*: Long-lasting treatment effect of rituximab in MuSK myasthenia. *Neurology*. 2012; 78(3): 189–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
 100. **F** Iorio R, Damato V, Alboini PE, *et al.*: Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis. *J Neurol*. 2015; 262(5): 1115–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 101. Kamijo K, Murayama H, Uzu T, *et al.*: A novel bioreporter assay for thyrotropin receptor antibodies using a chimeric thyrotropin receptor (mc4) is more useful in differentiation of Graves' disease from painless thyroiditis than conventional thyrotropin-stimulating antibody assay using porcine thyroid cells. *Thyroid*. 2010; 20(8): 851–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 102. Michelangeli V, Poon C, Taft J, *et al.*: The prognostic value of thyrotropin receptor antibody measurement in the early stages of treatment of Graves' disease with antithyroid drugs. *Thyroid*. 1998; 8(2): 119–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
 103. Adams DD, Fastier FN, Howie JB, *et al.*: Stimulation of the human thyroid by

- infusions of plasma containing LATS protector. *J Clin Endocrinol Metab.* 1974; 39(5): 826–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
104. McKenzie JM, Zakarija M: Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. *Thyroid.* 1992; 2(2): 155–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 105. Evans M, Sanders J, Tagami T, *et al.*: Monoclonal autoantibodies to the TSH receptor, one with stimulating activity and one with blocking activity, obtained from the same blood sample. *Clin Endocrinol (Oxf).* 2010; 73(3): 404–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
 106. Sanders J, Evans M, Premawardhana LD, *et al.*: Human monoclonal thyroid stimulating autoantibody. *Lancet.* 2003; 362(9378): 126–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 107. Sanders J, Jeffreys J, Depraetere H, *et al.*: Characteristics of a human monoclonal autoantibody to the thyrotropin receptor: sequence structure and function. *Thyroid.* 2004; 14(8): 560–70.
[PubMed Abstract](#) | [Publisher Full Text](#)
 108. Salvi M, Vannucchi G, Beck-Peccoz P: Potential utility of rituximab for Graves' orbitopathy. *J Clin Endocrinol Metab.* 2013; 98(11): 4291–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 109. Stan MN, Garrity JA, Carranza Leon BG, *et al.*: Randomized controlled trial of rituximab in patients with Graves' orbitopathy. *J Clin Endocrinol Metab.* 2015; 100(2): 432–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 110. Salvi M, Vannucchi G, Currò N, *et al.*: Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. *J Clin Endocrinol Metab.* 2015; 100(2): 422–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 111. Bartalena L, Baldeschi L, Boboridis K, *et al.*: The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J.* 2016; 5(1): 9–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 112. Shulman NR, Marder VJ, Weinrach RS: Similarities between known antiplatelet antibodies and the factor responsible for thrombocytopenia in idiopathic purpura. Physiologic, serologic and isotopic studies. *Ann NY Acad Sci.* 1965; 124(2): 499–542.
[PubMed Abstract](#) | [Publisher Full Text](#)
 113. van Leeuwen EF, van der Ven JT, Engelfriet CP, *et al.*: Specificity of autoantibodies in autoimmune thrombocytopenia. *Blood.* 1982; 59(1): 23–6.
[PubMed Abstract](#)
 114. McMillan R, Wang L, Tani P: Prospective evaluation of the immunobead assay for the diagnosis of adult chronic immune thrombocytopenic purpura (ITP). *J Thromb Haemost.* 2003; 1(3): 485–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
 115. Warner MN, Moore JC, Warkentin TE, *et al.*: A prospective study of protein-specific assays used to investigate idiopathic thrombocytopenic purpura. *Br J Haematol.* 1999; 104(3): 442–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 116. Brighton TA, Evans S, Castaldi PA, *et al.*: Prospective evaluation of the clinical usefulness of an antigen-specific assay (MAIPA) in idiopathic thrombocytopenic purpura and other immune thrombocytopenias. *Blood.* 1996; 88(1): 194–201.
[PubMed Abstract](#)
 117. Tsubakio T, Tani P, Curd JG, *et al.*: Complement activation *in vitro* by antiplatelet antibodies in chronic immune thrombocytopenic purpura. *Br J Haematol.* 1986; 63(2): 293–300.
[PubMed Abstract](#) | [Publisher Full Text](#)
 118. Takahashi R, Sekine N, Nakatake T: Influence of monoclonal antiplatelet glycoprotein antibodies on *in vitro* human megakaryocyte colony formation and proplatelet formation. *Blood.* 1999; 93(6): 1951–8.
[PubMed Abstract](#)
 119. Harrington WJ, Sprague CC, Minnich V, *et al.*: Immunologic mechanisms in idiopathic and neonatal thrombocytopenic purpura. *Ann Intern Med.* 1953; 38(3): 433–69.
[PubMed Abstract](#) | [Publisher Full Text](#)
 120. Stasi R, Pagano A, Stipa E, *et al.*: Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. *Blood.* 2001; 98(4): 952–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 121. Arnold DM, Dentali F, Crowther MA, *et al.*: Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. *Ann Intern Med.* 2007; 146(1): 25–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
 122. Patel VL, Mahévas M, Lee SY, *et al.*: Outcomes 5 years after response to rituximab therapy in children and adults with immune thrombocytopenia. *Blood.* 2012; 119(25): 5989–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 123. Reboursiere E, Fouques H, Maigne G, *et al.*: Rituximab salvage therapy in adults with immune thrombocytopenia: retrospective study on efficacy and safety profiles. *Int J Hematol.* 2016; 104(1): 85–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 124. Ghanima W, Khelif A, Waage A, *et al.*: Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet.* 2015; 385(9978): 1653–61.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 125. Arnold DM, Heddle NM, Carruthers J, *et al.*: A pilot randomized trial of adjuvant rituximab or placebo for nonsplenectomized patients with immune thrombocytopenia. *Blood.* 2012; 119(6): 1356–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
 126. Li Z, Mou W, Lu G, *et al.*: Low-dose rituximab combined with short-term glucocorticoids up-regulates Treg cell levels in patients with immune thrombocytopenia. *Int J Hematol.* 2011; 93(1): 91–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 127. Gudbrandsdottir S, Birgens HS, Frederiksen H, *et al.*: Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia. *Blood.* 2013; 121(11): 1976–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 128. Zaja F, Baccarani M, Mazza P, *et al.*: Dexamethasone plus rituximab yields higher sustained response rates than dexamethasone monotherapy in adults with primary immune thrombocytopenia. *Blood.* 2010; 115(14): 2755–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 129. Choi PY, Roncolato F, Badoux X, *et al.*: A novel triple therapy for ITP using high-dose dexamethasone, low-dose rituximab, and cyclosporine (TT4). *Blood.* 2015; 126(4): 500–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 130. Zhou H, Xu M, Qin P, *et al.*: A multicenter randomized open-label study of rituximab plus rhTPO vs rituximab in corticosteroid-resistant or relapsed ITP. *Blood.* 2015; 125(10): 1541–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 131. Jaffe CJ, Atkinson JP, Frank MM: The role of complement in the clearance of cold agglutinin-sensitized erythrocytes in man. *J Clin Invest.* 1976; 58(4): 942–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 132. Jandl JH, Jones AR, Castle WB: The destruction of red cells by antibodies in man. I. Observations of the sequestration and lysis of red cells altered by immune mechanisms. *J Clin Invest.* 1957; 36(10): 1428–59.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 133. Atkinson JP, Frank MM: Studies on the *in vivo* effects of antibody. Interaction of IgM antibody and complement in the immune clearance and destruction of erythrocytes in man. *J Clin Invest.* 1974; 54(2): 339–48.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 134. Schwartz J, Padmanabhan A, Aquil N, *et al.*: Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. *J Clin Apher.* 2016; 31(3): 149–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 135. Geurs F, Ritter K, Mast A, *et al.*: Successful plasmapheresis in corticosteroid-resistant hemolysis in infectious mononucleosis: role of autoantibodies against triosephosphate isomerase. *Acta Haematol.* 1992; 88(2–3): 142–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 136. Zoppi M, Oppliger R, Althaus U, *et al.*: Reduction of plasma cold agglutinin titers by means of plasmapheresis to prepare a patient for coronary bypass surgery. *Infusionsther Transfusionsmed.* 1993; 20(1–2): 19–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
 137. Reynaud Q, Durieu I, Dutertre M, *et al.*: Efficacy and safety of rituximab in auto-immune hemolytic anemia: A meta-analysis of 21 studies. *Autoimmun Rev.* 2015; 14(4): 304–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 138. Birgens H, Frederiksen H, Hasselbalch HC, *et al.*: A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. *Br J Haematol.* 2013; 163(3): 393–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 139. Turner N, Mason PJ, Brown R, *et al.*: Molecular cloning of the human Goodpasture antigen demonstrates it to be the alpha 3 chain of type IV collagen. *J Clin Invest.* 1992; 89(2): 592–601.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 140. Kalluri R, Wilson CB, Weber M, *et al.*: Identification of the alpha 3 chain of type IV collagen as the common autoantigen in anti-basement membrane disease and Goodpasture syndrome. *J Am Soc Nephrol.* 1995; 6(4): 1178–85.
[PubMed Abstract](#)
 141. Rutgers A, Meyers KE, Canziani G, *et al.*: High affinity of anti-GBM antibodies from Goodpasture and transplanted Alport patients to alpha3(IV)NC1 collagen. *Kidney Int.* 2000; 58(1): 115–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
 142. Sinico RA, Radice A, Corace C, *et al.*: Anti-glomerular basement membrane antibodies in the diagnosis of Goodpasture syndrome: a comparison of different assays. *Nephrol Dial Transplant.* 2006; 21(2): 397–401.
[PubMed Abstract](#) | [Publisher Full Text](#)
 143. Cui Z, Wang H, Zhao MH: Natural autoantibodies against glomerular basement membrane exist in normal human sera. *Kidney Int.* 2006; 69(5): 894–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 144. Lerner RA, Glasscock RJ, Dixon FJ: The role of anti-glomerular basement

- membrane antibody in the pathogenesis of human glomerulonephritis. *J Exp Med.* 1967; 126(6): 989–1004.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
145. Lockwood CM, Boulton-Jones JM, Lowenthal RM, *et al.*: Recovery from Goodpasture's syndrome after immunosuppressive treatment and plasmapheresis. *Br Med J.* 1975; 2(5965): 252–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 146. Levy JB, Turner AN, Rees AJ, *et al.*: Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. *Ann Intern Med.* 2001; 134(11): 1033–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
 147. **F** Touzot M, Poisson J, Faguer S, *et al.*: Rituximab in anti-GBM disease: A retrospective study of 8 patients. *J Autoimmun.* 2015; 60: 74–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 148. Motomura M, Johnston I, Lang B, *et al.*: An improved diagnostic assay for Lambert-Eaton myasthenic syndrome. *J Neurol Neurosurg Psychiatr.* 1995; 58(1): 85–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 149. Nakao YK, Motomura M, Fukudome T, *et al.*: Seronegative Lambert-Eaton myasthenic syndrome: study of 110 Japanese patients. *Neurology.* 2002; 59(11): 1773–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 150. Lennon VA, Kryzer TJ, Griesmann GE, *et al.*: Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. *N Engl J Med.* 1995; 332(22): 1467–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
 151. Lang B, Newsom-Davis J, Wray D, *et al.*: Autoimmune aetiology for myasthenic (Eaton-Lambert) syndrome. *Lancet.* 1981; 2(8240): 224–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 152. Lang B, Newsom-Davis J, Prior C, *et al.*: Antibodies to motor nerve terminals: an electrophysiological study of a human myasthenic syndrome transferred to mouse. *J Physiol.* 1983; 344: 335–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 153. Fukunaga H, Engel AG, Lang B, *et al.*: Passive transfer of Lambert-Eaton myasthenic syndrome with IgG from man to mouse depletes the presynaptic membrane active zones. *Proc Natl Acad Sci U S A.* 1983; 80(24): 7636–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 154. Lambert EH, Lennon VA: Selected IgG rapidly induces Lambert-Eaton myasthenic syndrome in mice: complement independence and EMG abnormalities. *Muscle Nerve.* 1988; 11(11): 1133–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
 155. Dau PC, Denys EH: Plasmapheresis and immunosuppressive drug therapy in the Eaton-Lambert syndrome. *Ann Neurol.* 1982; 11(6): 570–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 156. Newsom-Davis J, Murray NM: Plasma exchange and immunosuppressive drug treatment in the Lambert-Eaton myasthenic syndrome. *Neurology.* 1984; 34(4): 480–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 157. Motomura M, Hamasaki S, Nakane S, *et al.*: Apheresis treatment in Lambert-Eaton myasthenic syndrome. *Ther Apher.* 2000; 4(4): 287–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 158. Tim RW, Massey JM, Sanders DB: Lambert-Eaton myasthenic syndrome: electrodiagnostic findings and response to treatment. *Neurology.* 2000; 54(11): 2176–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 159. Pellkofer HL, Voltz R, Kuempfel T: Favorable response to rituximab in a patient with anti-VGCC-positive Lambert-Eaton myasthenic syndrome and cerebellar dysfunction. *Muscle Nerve.* 2009; 40(2): 305–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 160. Maddison P, McConville J, Farrugia ME, *et al.*: The use of rituximab in myasthenia gravis and Lambert-Eaton myasthenic syndrome. *J Neurol Neurosurg Psychiatry.* 2011; 82(6): 671–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 161. Woodley DT, Briggaman RA, O'Keefe EJ, *et al.*: Identification of the skin basement-membrane autoantigen in epidermolysis bullosa acquisita. *N Engl J Med.* 1984; 310(16): 1007–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
 162. **F** Saleh MA, Ishii K, Kim Y, *et al.*: Development of NC1 and NC2 domains of type VII collagen ELISA for the diagnosis and analysis of the time course of epidermolysis bullosa acquisita patients. *J Dermatol Sci.* 2011; 62(3): 169–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 163. Kim JH, Kim YH, Kim S, *et al.*: Serum levels of anti-type VII collagen antibodies detected by enzyme-linked immunosorbent assay in patients with epidermolysis bullosa acquisita are correlated with the severity of skin lesions. *J Eur Acad Dermatol Venereol.* 2013; 27(2): e224–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
 164. Komorowski L, Muller R, Vorobyev A, *et al.*: Sensitive and specific assays for routine serological diagnosis of epidermolysis bullosa acquisita. *J Am Acad Dermatol.* 2013; 68(3): e89–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
 165. Terra JB, Jonkman MF, Diercks GF, *et al.*: Low sensitivity of type VII collagen enzyme-linked immunosorbent assay in epidermolysis bullosa acquisita: serration pattern analysis on skin biopsy is required for diagnosis. *Br J Dermatol.* 2013; 169(1): 164–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 166. Lee EH, Kim YH, Kim S, *et al.*: Usefulness of Enzyme-linked Immunosorbent Assay Using Recombinant BP180 and BP230 for Serodiagnosis and Monitoring Disease Activity of Bullous Pemphigoid. *Ann Dermatol.* 2012; 24(1): 45–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 167. **F** Esmaili N, Mortazavi H, Kamyab-Hesari K, *et al.*: Diagnostic accuracy of BP180 NC16a and BP230-C3 ELISA in serum and saliva of patients with bullous pemphigoid. *Clin Exp Dermatol.* 2015; 40(3): 324–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 168. **F** Kobayashi M, Amagai M, Kuroda-Kinoshita K, *et al.*: BP180 ELISA using bacterial recombinant NC16a protein as a diagnostic and monitoring tool for bullous pemphigoid. *J Dermatol Sci.* 2002; 30(3): 224–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 169. Zillikens D, Mascaro JM, Rose PA, *et al.*: A highly sensitive enzyme-linked immunosorbent assay for the detection of circulating anti-BP180 autoantibodies in patients with bullous pemphigoid. *J Invest Dermatol.* 1997; 109(5): 679–83.
[PubMed Abstract](#) | [Publisher Full Text](#)
 170. Charneux J, Lorin J, Vitry F, *et al.*: Usefulness of BP230 and BP180-NC16a enzyme-linked immunosorbent assays in the initial diagnosis of bullous pemphigoid: a retrospective study of 138 patients. *Arch Dermatol.* 2011; 147(3): 286–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
 171. Roussel A, Benichou J, Randriamanantany ZA, *et al.*: Enzyme-linked immunosorbent assay for the combination of bullous pemphigoid antigens 1 and 2 in the diagnosis of bullous pemphigoid. *Arch Dermatol.* 2011; 147(3): 293–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 172. **F** van Beek N, Rentzsch K, Probst C, *et al.*: Serological diagnosis of autoimmune bullous skin diseases: prospective comparison of the BIOCHIP mosaic-based indirect immunofluorescence technique with the conventional multi-step single test strategy. *Orphanet J Rare Dis.* 2012; 7: 49.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 173. Schmidt E, Obe K, Brocker EB, *et al.*: Serum levels of autoantibodies to BP180 correlate with disease activity in patients with bullous pemphigoid. *Arch Dermatol.* 2000; 136(2): 174–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 174. Sitaru C, Mihai S, Otto C, *et al.*: Induction of dermal-epidermal separation in mice by passive transfer of antibodies specific to type VII collagen. *J Clin Invest.* 2005; 115(4): 870–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 175. **F** Woodley DT, Ram R, Doostan A, *et al.*: Induction of epidermolysis bullosa acquisita in mice by passive transfer of autoantibodies from patients. *J Invest Dermatol.* 2006; 126(6): 1323–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 176. **F** Li Q, Ujije H, Shibaki A, *et al.*: Human IgG1 monoclonal antibody against human collagen 17 noncollagenous 16A domain induces blisters via complement activation in experimental bullous pemphigoid model. *J Immunol.* 2010; 185(12): 7746–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 177. Liu Z, Sui W, Zhao M, *et al.*: Subepidermal blistering induced by human autoantibodies to BP180 requires innate immune players in a humanized bullous pemphigoid mouse model. *J Autoimmun.* 2008; 31(4): 331–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 178. **F** Wang G, Ujije H, Shibaki A, *et al.*: Blockade of autoantibody-initiated tissue damage by using recombinant fab antibody fragments against pathogenic autoantigen. *Am J Pathol.* 2010; 176(2): 914–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 179. Niedermeier A, Eming R, Pfütze M, *et al.*: Clinical response of severe mechanobullous epidermolysis bullosa acquisita to combined treatment with immunoadsorption and rituximab (anti-CD20 monoclonal antibodies). *Arch Dermatol.* 2007; 143(2): 192–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 180. Ino N, Kamata N, Matsuura C, *et al.*: Immunoadsorption for the treatment of bullous pemphigoid. *Ther Apher.* 1997; 1(4): 372–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 181. Herrero-González JE, Sitaru C, Klinker E, *et al.*: Successful adjuvant treatment of severe bullous pemphigoid by tryptophan immunoadsorption. *Clin Exp Dermatol.* 2005; 30(5): 519–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
 182. **F** Kasperkiewicz M, Schulze F, Meier M, *et al.*: Treatment of bullous pemphigoid with adjuvant immunoadsorption: a case series. *J Am Acad Dermatol.* 2014; 71(5): 1018–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 183. Lourari S, Herve C, Doffoel-Hantz V, *et al.*: Bullous and mucous membrane pemphigoid show a mixed response to rituximab: experience in seven patients. *J Eur Acad Dermatol Venereol.* 2011; 25(10): 1238–40.
[PubMed Abstract](#) | [Publisher Full Text](#)
 184. **F** Kasperkiewicz M, Shimanovich I, Ludwig RJ, *et al.*: Rituximab for treatment-

- refractory pemphigus and pemphigoid: a case series of 17 patients. *J Am Acad Dermatol.* 2011; **65**(3): 552–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
185. **F** Hall RP 3rd, Streilein RD, Hannah DL, *et al.*: Association of serum B-cell activating factor level and proportion of memory and transitional B cells with clinical response after rituximab treatment of bullous pemphigoid patients. *J Invest Dermatol.* 2013; **133**(12): 2786–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 186. Ahmed AR, Shetty S, Kaveri S, *et al.*: Treatment of recalcitrant bullous pemphigoid (BP) with a novel protocol: A retrospective study with a 6-year follow-up. *J Am Acad Dermatol.* 2016; **74**(4): 700–8.e3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 187. **F** Cho YT, Chu CY, Wang LF: First-line combination therapy with rituximab and corticosteroids provides a high complete remission rate in moderate-to-severe bullous pemphigoid. *Br J Dermatol.* 2015; **173**(1): 302–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 188. Schmidt E, Benoit S, Bröcker E, *et al.*: Successful adjuvant treatment of recalcitrant epidermolysis bullosa acquisita with anti-CD20 antibody rituximab. *Arch Dermatol.* 2006; **142**(2): 147–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
 189. Crichlow SM, Mortimer NJ, Harman KE: A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. *Br J Dermatol.* 2007; **156**(1): 194–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 190. Sadler E, Schaffleitner B, Lanschuetzer C, *et al.*: Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. *Br J Dermatol.* 2007; **157**(2): 417–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 191. Saha M, Cutler T, Bhogal B, *et al.*: Refractory epidermolysis bullosa acquisita: successful treatment with rituximab. *Clin Exp Dermatol.* 2009; **34**(8): e979–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
 192. Kim JH, Lee SE, Kim SC: Successful treatment of epidermolysis bullosa acquisita with rituximab therapy. *J Dermatol.* 2012; **39**(5): 477–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 193. **F** Iranzo P, Herrero-González JE, Mascaró-Galy JM, *et al.*: Epidermolysis bullosa acquisita: a retrospective analysis of 12 patients evaluated in four tertiary hospitals in Spain. *Br J Dermatol.* 2014; **171**(5): 1022–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 194. **F** Kolesnik M, Becker E, Reinhold D, *et al.*: Treatment of severe autoimmune blistering skin diseases with combination of protein A immunoadsorption and rituximab: a protocol without initial high dose or pulse steroid medication. *J Eur Acad Dermatol Venereol.* 2014; **28**(6): 771–80.
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