



PERSPECTIVES

An antibody treats almost all refractory autoimmune diseases: Fact and beyond

An antiCD20 monoclonal antibody (rituximab) has been shown to rescue almost all refractory autoimmune diseases. The chimeric antiCD20 antibody is one of the world's most successfully therapeutic antibodies, with sales of approximately US\$5.6 billion in 2009.¹ Rituximab was first approved in 1997 by the US Food and Drug Administration (FDA) for treatment of B cell malignancies, and is now expanded to autoimmune indications, such as lupus nephritis, multiple sclerosis and vasculitis, particularly refractory autoimmune diseases that usually cause fatal outcomes.^{2–8} Autoimmunity is a complex process that involves the interaction of multiple immune cell types. B cells are thought to play a central role in the autoimmune disease serving as precursors to autoantibody-secreting plasma cells. In addition to producing antibodies, B cells are able to present antigen to T cells. Their depletion also results in the removal of antigen-presenting cells, reduced expression of molecules responsible for T cell costimulatory signals, and reduced levels of immune complexes formed between autoreactive antibodies and their antigen.

There are certain refractory autoimmune diseases successfully treated by rituximab including antiphospholipid syndrome (APS), thrombotic thrombocytopenic purpura (TTP), antineutrophil cytoplasmic antibody (ANCA) vasculitis, refractory rheumatoid arthritis, refractory juvenile dermatomyositis and refractory idiopathic thrombocytopenic purpura (ITP) (Table 1). In refractory APS, rituximab (100–375 mg/m²) decreased anticardiolipin antibody levels from 20.6 standardized IgG antiphospholipid units (GPLU) to undetectable levels in six of seven patients 6 to 9 months after treatment, and caused a high response rate—more than 90%—in another report.²

In refractory TTP, which usually causes a fatal outcome, rituximab achieved 92% complete response rate associated with the disappearance of ADAMTS-13 inhibitors and no subsequent relapses in a median follow-up of 24 months (range, 13–84 months).³ In refractory ANCA vasculitis, a retrospective study showed that complete remission occurred in 49 of the 65 patients (75%), partial remission in 15 (23%), and no response only in one (2%) in UK.⁴ In refractory rheumatoid arthritis (RA), rituximab was approved by the FDA

and European Medicine Agency for the treatment of RA after antiTNF α treatment failure.⁵ In refractory juvenile dermatomyositis, a case report showed that three of four patients showed clinical improvement.⁶ In refractory ITP, only two of the 18 patients treated with rituximab were classified as therapeutic failures (11%).⁷ In patients with refractory Sjögren's syndrome, the first double-blind study of rituximab showed a favorable result from a randomized trial to receive either two infusions of rituximab or placebo along with steroids.⁸

These promising results have shared a light to treat all autoimmune diseases by the antiCD20 strategy, particularly the most prevalent autoantibody disease, systemic lupus erythematosus (SLE). Unfortunately, the antiCD20 treatment added on the conventional treatment did not show a significant benefit over conventional treatments.² Moreover, not all refractory autoimmune diseases responded to the antiCD20 therapy. Some case reports showed that rituximab failed to rescue autoimmune associated macrophage activation syndrome (MAS), and caused a worsening psoriasis.⁹ In fact, psoriasis and MAS are known to be mediated by cell-mediated diseases, and patients with psoriasis responded to anticell immunity monoclonal antibody (Ustekinumab: antiIL12/23 monoclonal antibody). The antiB cell strategies may be suitable for autoantibody-mediated diseases but not cell-mediated diseases. Another strategy is to specifically target the receptors of autoantigen (self-deoxy nucleic acid, self-DNA), such as TLR7 and TLR9 which could initiate autoantibodies directed against self-DNA. Evidence has recently shown that abnormal recognition of TLR7 and TLR9 was involved in the pathogenesis of SLE, and inhibitors of TLR7 and TLR9 could improve lupus manifestations. Antagonists of TLR7 and/or TLR9 share the highlight for better specific target therapy of SLE and other autoimmune diseases.¹⁰

There are some other antiB cell monoclonal antibodies which have been developed, such as antiCD19 (Blinatumomab), antiCD22 (Epratuzumab), and antiCD52 (Alemtuzumab). The results of several large clinical trials using antiB cell surface markers to nonrenal or renal lupus patients has surprisingly not been successful.² Recently, another type of monoclonal antibody directed against soluble B cell

Table 1 Favorable and unfavorable benefits and side effects of rituximab treatment for autoimmune diseases.

Results	Autoimmune diseases	Response rates
Favorable results	Refractory APS ²	90% Remission
	Refractory TTP ³	92% Complete response
Unfavorable results	Refractory ANCA vasculitis ⁴	1% No response
	Refractory rheumatoid arthritis after failure of etanercept treatment ⁵	RTX+MTX vs. placebo + MTX: ACR20 (51% vs. 18%)
	Refractory juvenile dermatomyositis ⁶	75% (3 out of 4 cases)
	Refractory Sjögren's syndrome ⁷	Significant improvement in fatigue visual analog scale in the rituximab group ($p < 0.001$)
	Refractory ITP ⁸	11% therapeutic failure
	Add-on therapy for SLE with conventional treatment ²	No better than conventional therapy
Side effects	Macrophage Activation Syndrome	Refractory lupus-associated macrophage activation syndrome (two cases)
	Worsening psoriasis after Rituximab ⁹	Two case reports
	Common side effects: Infections, infusion hypersensitivity, hypogammaglobulinemia Rare side effects: reactivation of hepatitis B virus infection, tumor lysis syndrome, progressive multifocal leukoencephalopathy	

activation molecule, called antiBLyS/BAFF (Belimumab), which targets mature B cells but not precursor B cells, has shown promising clinical trials for SLE patients.²

Depletion of B cells by rituximab (chimeric monoclonal antibodies) causes a minimal-to-moderate decrease in total immunoglobulin levels during a few courses of treatment. Most of the common side effects of rituximab on the patients with autoimmune disease are minimal and tolerable, including drug-infusion reaction, infections and other rare side effects, such as reactivation of hepatitis B virus infection in patients with nonHodgkin lymphoma (NHL), tumor lysis syndrome in lymphoma patients, and rituximab-induced mucocutaneous reactions and progressive multifocal leukoencephalopathy. The next generation of antiB cell antibodies will be fully humanized monoclonal antibodies, which may induce less side effects and be suitable for making formulations for subcutaneous use instead of intravenous use. These trends will benefit autoimmune patients and increase the convenience of medication in the future.

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3 March 2011