Targeted Biologic Therapy for B-cell-driven Autoimmune Diseases

Targeted, biologic therapies have proven to be effective options for the management of several autoimmune diseases. Perhaps the best known are the tumor necrosis factor alpha inhibitors (e.g., adalimumab, infliximab), which are being used for the treatment of rheumatoid arthritis, psoriasis and inflammatory bowel disease.

One of the other types of therapy that has been well studied and has also demonstrated efficacy and safety across a number of autoimmune diseases is B-cell depletion, with rituximab being the best studied of the compounds targeting this pathway.

This brief review will examine the role of B-cell abnormalities in the pathophysiology of autoimmune diseases and summarize the most important clinical trial evidence that has led to the use of rituximab for the treatment of these diseases.

The Role of B Cells in Autoimmune Diseases

B cells have several important functions in the pathophysiology of autoimmune disease, including autoantibody production, cytokine release, antigen presentation and T cell activation.1 A review by Hogan et al (2010) describes these B-cell related functions in detail.1 The following provides a brief summary of this review.

Rituximab: Mechanism of Action

Rituximab is an intravenously administered biological therapy currently indicated in Canada for the treatment of RA, granulomatosis with polyangiitis (GPA, also known as Wegener’s Granulomatosis), microscopic polyangiitis (MPA), non-Hodgkin’s lymphoma and chronic lymphocytic leukemia.2

The mechanism of action of rituximab is selective depletion of B cells. Rituximab selectively binds to the CD20 antigen on the surface of B cells, which activates cellular mechanisms to initiate B cell depletion. Importantly, CD20 is expressed only at certain stages of B-cell development, which excludes expression on stem cells and fully mature plasma cells. As stem cells are not affected by anti-CD20 antibodies, levels of B cells eventually recover. Moreover, because existing plasma cells are also unaffected by treatment with anti-CD20 antibodies, the levels of protective antibodies remain relatively normal.3-5

Rituximab: Clinical Trial Evidence

Efficacy and safety of rituximab has been studied in a number of autoimmune diseases:

- **Rheumatoid arthritis**
- **ANCA-associated vasculitis**
- **Cryoglobunemia**
- **Myositis**
- **Lupus**
- **Pemphigus**
- **Sjögren’s syndrome**

Conclusions

The theoretical benefit of B-cell depletion in the treatment of auto-immune diseases has been borne out by a number of clinical trials in several different disease states. The data for rheumatoid arthritis and vasculitis, explored in some detail above, is quite compelling, and has led to the approval of rituximab, a B-cell depleting agent, for the treatment of these diseases.

In addition, research with rituximab into other autoimmune disorders has demonstrated a potential role beyond the agent’s current indications. The results of ongoing trials in these other diseases will provide evidence-based guidance in establishing the appropriate role of rituximab in the respective treatment paradigms.