



Rituximab:

An Autoimmune Disease Therapy

Autoimmune disease patients who do not respond to standard therapies are increasingly being treated with rituximab with safe and effective results.

By Amy Ehlers, BS, PharmD, BCPS

Rituximab (Rituxan) is a monoclonal antibody that was first approved in 1997 for the treatment of B-cell lymphoma. It was considered a breakthrough treatment for B-cell lymphoma due to its lower side-effect profile when compared with traditional chemotherapy treatments alone. Antibody therapies are different from chemotherapies because they target malignant cells while sparing healthy cells. Typically, chemotherapies kill any cell, good or bad, that is rapidly dividing, which is what leads to the well-known chemotherapy side effects of hair loss, bone marrow suppression and inflammation of

gastrointestinal membranes (mucositis). Antibody therapies, on the other hand, kill only those cells identified by the immune system and are known as immunomodulatory agents. Because rituximab is an immunomodulatory agent, doctors have recently begun prescribing it for the treatment of several autoimmune disorders.

How Rituximab Works

Understanding how rituximab works requires a brief overview of the B cells (also known as B lymphocytes) and their role in the immune system. Lymphocytes are white blood cells that are responsible for the activity of the immune system. They are initially formed in the bone marrow and either migrate to the thymus gland and develop into T cells (also known as T lymphocytes) or remain and develop into B cells. T cells are the main regulators of immune function. Specific subsets of T cells provide signals to stimulate B cells. The B cells are responsible for producing antibodies to the antigens. Some of the activated B cells will form memory B cells that allow for a quicker response to the antigens upon further exposure.

Rituximab works by specifically targeting the CD20 protein on B cells. When rituximab attaches to the CD20 protein, the B cells may be further attacked by complement proteins, which result in their destruction. The B cells coated with rituximab may be removed from the circulation by a particular part of the immune system known as the RES (reticulo-endothelial system), or in some instances, the B cells merely internalize the CD20 protein with the rituximab antibody attached. Because the CD20 protein is found on mature B cells, it does not affect the formation of future B cells, thereby avoiding ongoing or continuous suppression of the immune system.

The side effects of rituximab include infusion reactions such as fever, headache, chills and nausea. More serious adverse events include hepatitis B reactivation, cardiac arrhythmias, renal toxicity, tumor lysis syndrome (TLS) and progressive multifocal leukoencephalopathy (PML). However, these events rarely occur, and they may be due to some other factor than rituximab.

Rituximab as an Autoimmune Therapy

As rituximab's successful use began to increase, interest grew in its use as a treatment for autoimmune diseases due to its action as an immunomodulating agent. In 2006, rituximab received its FDA-approved indication for moderate to severe rheumatoid arthritis in combination with methotrexate in patients who have had an inadequate

response to TNF (tumor necrosis factor) antagonist therapies.

Since then, there have been hundreds of small studies and case reports involving the use of rituximab in many autoimmune disorders with varying degrees of success. This use of rituximab is considered by the FDA as off-label, but it may be considered when other traditional first-line therapies have failed for autoimmune diseases such as pemphigus, Guillain-Barré syndrome, polymyositis/dermatomyositis and myasthenia gravis.

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Pemphigus is an autoimmune disorder in which there is significant blistering of the skin and mucous membranes due to antibody formation against the proteins that join skin cells together. Blisters may form anywhere on the body, including the mouth and throat. Standard treatment for pemphigus includes high-dose oral steroids (prednisone) and/or an immunosuppressant such as azathioprine (Imuran). In cases that are refractory to these, intravenous immune globulin (IVIG) is used. However, if patients are not candidates for IVIG, there are nearly no viable options, which led to the trialing of rituximab in these patients. In a retrospective study on 47 patients with pemphigus who were treated with biweekly rituximab infusions, the results showed a remission rate of 76 percent after the first cycle of two infusions of rituximab at days one and 15, and the remission rate reached 91 percent after additional rituximab cycles.¹

There also have been some successful reports of using rituximab in patients with Guillain-Barré syndrome (GBS) who had other comorbid conditions. In a case study of a patient with acute lymphoblastic leukemia in remission who underwent allogeneic peripheral blood stem transplantation and developed GBS, the patient was treated

with rituximab once a week for four weeks, which depleted the B lymphocyte targets of the Epstein-Barr virus and improved muscle strength.² Therefore, while the No. 1 treatment for GBS is plasma exchange and, in many instances IVIG, rituximab may be another possibility.

Polymyositis and dermatomyositis are autoimmune diseases in which there is inflammation of the muscles (polymyositis) or the skin, joints, esophagus or lungs (dermatomyositis) accompanied by weakness in the affected areas. As with pemphigus, standard treatments include corticosteroids or immunosuppressant drugs with IVIG use in patients unresponsive to these therapies. In one study of 13 patients with refractory myopathies who were treated with rituximab twice within a two-week interval, positive results were sustained for an average of 27 months in the primary outcomes of disease activity as measured by creatine phosphokinase, lactate dehydrogenase and muscle strength.³ In yet another pilot trial of seven patients receiving rituximab infusions once weekly for four weeks, patients were followed up after one year without additional rituximab infusions, and all evaluable patients exhibited significant clinical improvement in muscle strength. However, return of symptoms varied among patients.⁴

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Rituximab also appears to be effective in treating myasthenia gravis, an autoimmune neuromuscular disease leading to fluctuating muscle weakness and fatigability. In a case report of a 9-year-old girl diagnosed with myasthenia gravis who responded to initial standard treatments but then reported increased fatigue, weakness and decreased physical ability, she was treated with rituximab

once a week for four weeks along with 6-mercaptopurine (6-MP) and monthly IVIG infusions. Within one month of initiation of rituximab, gradual but significant clinical improvement was noted. Eighteen weeks after rituximab, 6-MP and monthly IVIG therapy, the patient was tapered off corticosteroids, and over the next year, the patient's physical activities resumed without weakness.⁵

Expanding Its Use

As more autoimmune diseases are diagnosed, the future use of rituximab will be expanded. There is already interest in using it for systemic lupus erythematosus, idiopathic thrombocytopenia purpura and Sjogren's syndrome. Most autoimmune disease treatments include corticosteroids and/or immunosuppressants. But, if these therapies are unable to control or minimize the disease process, or if patients develop intolerable, unwanted or unmanageable side effects, patients have few options. IVIG may be an alternate therapy, but due to some patients' comorbid health conditions and insurance coverage concerns, it may not be appropriate for all. In these patients, rituximab has the potential to be part of their medication regimen. To date, however, very few controlled clinical trials for the use of rituximab in autoimmune diseases have been conducted, and much of what is known about the drug's potential is based upon case reports. But, these reports have shown rituximab to be safe and tolerable for most patients with most side effects being infusion-related, allowing physicians and patients the option to try rituximab when other choices have failed. ■

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