Rituximab (Rituxan)


*AJNR Am J Neuroradiol* 2010, 31 (7) 1178-1180
doi: [https://doi.org/10.3174/ajnr.A2142](https://doi.org/10.3174/ajnr.A2142)
http://www.ajnr.org/content/31/7/1178

This information is current as of October 22, 2023.
**PHARMACOLOGY VIGNETTE**

**Rituximab (Rituxan)**

**SUMMARY:** Rituximab is a monoclonal antibody that was first approved by the FDA as an antineoplastic agent designed to treat B-cell malignancies. This article will review the mechanism of action and clinical role of this anti-B-cell agent.

**ABBREVIATIONS:** FDA = US Food and Drug Administration; FSE = fast spin-echo

Rituximab is a monoclonal antibody that targets CD20, a specific B-cell surface antigen. Rituximab (Rituxan; Biogen-IDEC/Genentech, South San Francisco, California) was the first monoclonal antibody approved for the treatment of non-Hodgkin lymphoma. In 1997, the FDA approved rituximab for the treatment of refractory low-grade lymphoma. This medication has since been used for the treatment of a number of CD20-positive B-cell malignancies. The selectivity of the drug for B-cells led to further investigations involving autoimmune B-cell-driven diseases, including rheumatoid arthritis. Rituximab has since been approved for the treatment of rheumatoid arthritis by the FDA.

**Mechanism of Action**

Rituximab is a chimeric murine/human monoclonal immunoglobulin G1 antibody that targets CD20, which is a B-cell differentiation marker. CD20 is a cell-surface marker specifically found on pre-B and mature B lymphocytes and is not found on other cell types or free in circulation. The only binding site for rituximab is CD20 on B-cells. The binding of rituximab to cell surface CD20 located on the B lymphocytes results in destruction of the lymphocyte by 3 potential mechanisms, including complement-dependent cytotoxicity, stimulation of apoptosis, or antibody-dependent cytotoxicity (Fig 1). Complement-mediated cytotoxicity most likely is the dominant mechanism in vivo.

**Clinical Indications**

Rituximab has been approved by the FDA for various B-cell non-Hodgkin lymphomas (clinical case: Figs 2 and 3) and rheumatoid arthritis. There are multiple off-label uses, including chronic lymphocytic leukemia, systemic lupus erythematosus, multiple sclerosis, autoimmune hemolytic anemia, posttransplant lymphoproliferative disorder, graft-versus-host disease, pemphigus vulgaris, chronic immune-mediated thrombocytopenia, and Evans Syndrome.

**Administration**

Rituximab is a prescription drug administered intravenously. The half-life is relative to the dose and number of doses administered but ranges between 1.6 and 20 days. The medication remains detectable in the serum for ≤6 months after a single infusion. B lymphocyte depletion typically occurs by 2 weeks and recovery begins at 6 months and continues until 12 months. Patients may continue to have subtle abnormalities in B lymphocyte populations for several years following treatment.

**Side Effects**

There are several specific US boxed warnings on the package insert:

- **Transfusion Reaction.** Severe transfusion reactions resulting in anaphylaxis characterized by fever, hypotension, bronchospasm, urticaria, and angioedema. Eighty percent of cases are seen with the first infusion.
- **Progressive Multifocal Leukoencephalopathy.** Progressive multifocal leukoencephalopathy is a serious central nervous system infection due to the JC virus, which typically occurs within 12 months of the first infusion. Diagnosis requires MR imaging and spinal tap.
- **Skin.** Severe mucocutaneous reactions resembling Stevens-Johnson reactions or toxic epidermal necrolysis.
- **Tumor Lysis Syndrome.** Tumor lysis syndrome is caused by tumor cell death typified by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. It may be complicated by acute renal failure.
- **Infections.** Patients are susceptible to opportunistic infections, including pneumocystis pneumonia. Patients are also prone to severe viral infections with parvovirus B19, varicella, cytomegalovirus, or herpes simplex virus.
- **Hepatitis.** Reactivation of hepatitis B has been reported, resulting in fulminant hepatitis and hepatic failure. Screen high-risk patients before the initiation of therapy.

**Economic Issues**

Rituximab costs approximately $630 for a 10-mg vial. Typical dosing regimens range from 375 to 500 mg/m² for 1–4 doses, depending on the indication but can be as high as 1000 mg for rheumatoid arthritis.

**Clinical Issues**

Patients require periodic laboratory follow-up with complete blood count, comprehensive metabolic panel, immunoglobulin levels, and lymphocyte counts/subpopulations. This is dependent on dose, indication, and duration of therapy. Any new neurologic or skin changes need to be evaluated by a physician.

Received March 10, 2010; accepted March 12.

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DOI 10.3174/ajnr.A2142
A 68-year-old woman presented with clumsiness, dropping things from her right hand, difficulty speaking, and right facial droop. A, T2-weighted axial FSE image of the brain shows patchy areas of increased T2-signal-intensity edema surrounding a low T2-signal-intensity lesion at the left temporal and frontal parietal lobes. B, T1-weighted postcontrast axial spin-echo image of the brain shows irregular and patchy enhancement of the lesion. Surrounding edema is seen as a low T1 signal intensity. A biopsy of the mass was performed, and CD20-positive B-cell lymphoma was diagnosed.

The patient was admitted and received chemotherapy with methotrexate, vincristine, and rituximab. Follow-up MR imaging was performed 2 cycles into her chemotherapy. A, T2-weighted axial FSE image shows only residual edema as high T2 signal intensity in the deep white matter of the left frontal parietal lobes. B, Enhanced T1-weighted axial spin-echo image shows resolution of the enhancing mass.

Fig 1. Schematic illustration of the mechanism of action of rituximab. The antibody labels B lymphocytes, which have the CD20 cell marker. These cells are then killed by 1 of 3 mechanisms: antibody-dependent cytotoxicity, complement-dependent cytotoxicity, or stimulation of apoptosis. Illustration by Priya A. Rajdev.
References