Rituximab

Rituximab is a monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells. Rituximab destroys B cells and is therefore used to treat diseases which are characterized by overactive, dysfunctional, or excessive numbers of B cells. This includes many lymphomas, leukemias, transplant rejection, and autoimmune disorders. Rituximab is a chimeric molecule.

The drug is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[2] It has a wholesale price of USD$159–$2,480 per vial as of 2014.[3]

1 Medical uses

Rituximab destroys both normal and malignant B cells that have CD20 on their surfaces and is therefore used to treat diseases which are characterized by having too many B cells, overactive B cells, or dysfunctional B cells.

1.1 Hematological cancers

Rituximab is used to treat cancers of the white blood system such as leukemias and lymphomas, including non-Hodgkin's lymphoma and lymphocyte predominant subtype of Hodgkin's Lymphoma.[4]

1.2 Autoimmune diseases

Rituximab has been shown to be an effective rheumatoid arthritis treatment in three randomised controlled trials and is now licensed for use in refractory rheumatoid disease.[5] In the United States, it has been FDA-approved for use in combination with methotrexate (MTX) for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more anti-TNF-alpha therapy. In Europe, the license is slightly more restrictive: it is licensed for use in combination with MTX in patients with severe active RA who have had an inadequate response to one or more anti-TNF therapy.[6]

There is some evidence for efficacy, but not necessarily safety, in a range of other autoimmune diseases, and rituximab is widely used off-label to treat difficult cases of multiple sclerosis,[7] systemic lupus erythematosus, chronic inflammatory demyelinating polyneuropathy and autoimmune anemias.[8] The most dangerous, although among the most rare, side effect is progressive multifocal leukoencephalopathy (PML) infection, which is usually fatal; however only a very small number of cases have been recorded occurring in autoimmune diseases.[8][9]

Other autoimmune diseases that have been treated with rituximab include autoimmune hemolytic anemia, pure red cell aplasia, thrombotic thrombocytopenic purpura (TTP),[10] idiopathic thrombocytopenic purpura (ITP),[11][12] Evans syndrome,[13] vasculitis (for example granulomatosis with polyangiitis, formerly Wegener's), bullous skin disorders (for example pemphigus, pemphigoid—with very encouraging results of approximately 85% rapid recovery in pemphigus, according to a 2006 study),[14] type 1 diabetes mellitus, Sjogren's syndrome, anti-NMDA receptor encephalitis and Devic's disease,[15] Graves' ophthalmopathy,[16] autoimmune pancreatitis,[17] Opsoclonus myoclonus syndrome (OMS),[18] and IgG4-related disease.[19] There is some evidence that it is ineffective in treating IgA-mediated autoimmune diseases.[20]

In October 2011, a double-blind controlled study was published in PLOS ONE which suggests that rituximab can help patients with chronic fatigue syndrome, leading to a proposed theory relating chronic fatigue syndrome to other autoimmune conditions, however more research is required to verify if such a link exists.[21] A new multicentre double-blinded trial with 152 patients began in October 2014,[22] after a follow-up open study published in July 2015 suggested a longer acting effect when four maintenance doses were added to the dosing schedule.[23] Two-thirds of the patients responded favorably to the drug, in accordance with previous findings.[24][25][26]

1.3 Organ transplants

Rituximab is being used off-label in the management of kidney transplant recipients. This drug may have some utility in transplants involving incompatible blood groups. It is also used as induction therapy in highly sensitized patients going for kidney transplantation. The use of rituximab has not been proven to be efficacious in this setting and like all depleting agents, carries with it the risk of infection.

2 Adverse events

Serious adverse events, which can cause death and disability, include:[27]

- Severe infusion reaction.
- Cardiac arrest
- Cytokine release syndrome
- Tumor lysis syndrome, causing acute renal failure
- Infections
  - Hepatitis B reactivation
  - Other viral infections
  - Progressive multifocal leukoencephalopathy (PML)
- Immune toxicity, with depletion of B cells in 70% to 80% of lymphoma patients
- Pulmonary toxicity[28]
- Bowel obstruction and perforation[29]

Two patients with systemic lupus erythematosus died of progressive multifocal leukoencephalopathy (PML) after being treated with rituximab. PML is caused by activation of JC virus, a common virus in the brain which is usually latent. Reactivation of the JC virus usually results in death or severe brain damage.[30]

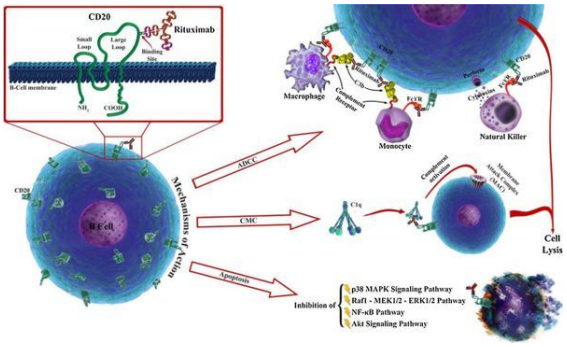
At least one patient with rheumatoid arthritis developed PML after treatment with rituximab.[31]

Rituximab has been reported as a possible cofactor in a chronic Hepatitis E infection in a person with lymphoma. Hepatitis E infection is normally an acute infection, suggesting the drug in combination with lymphoma may have weakened the body's immune response to the virus.[32]

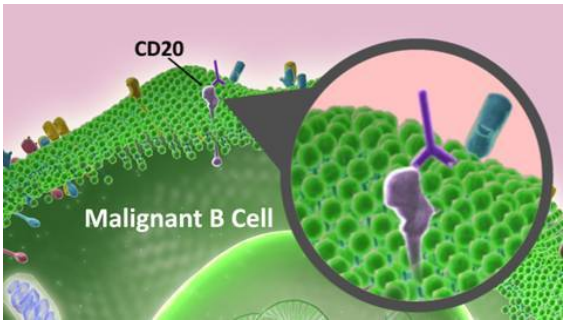
3 Mechanisms of action

The antibody binds to CD20. CD20 is widely expressed on B cells, from early pre-B cells to later in differentiation, but it is absent on terminally differentiated plasma cells. CD20 does not shed, modulate or internalise. Although the function of CD20 is unknown, it may play a role in Ca^{2+} influx across plasma membranes, maintaining intracellular Ca^{2+} concentration and allowing activation of B cells.

Rituximab tends to stick to one side of B cells, where CD20 is, forming a cap and drawing proteins over to that side. The presence of the cap changed the effectiveness of natural killer (NK) cells in destroying these B cells. When an NK cell latched onto the cap, it had an 80% success rate at killing the cell. In contrast, when the B cell lacked



Rituximab mechanisms of action; the three major independent mechanisms are (1) antibody dependent cellular cytotoxicity (ADCC), (2) complement mediated cytotoxicity (CMC), and (3) apoptosis; subset panel illustrates a schematic view of CD20 structure and rituximab.[33]



Rituximab binding to CD20. The CD20 proteins are sticking out of the cell membrane, and rituximab, the Y-shaped antibody, is binding to the CD20 proteins.

this asymmetric protein cluster, it was killed only 40% of the time.[34][35]

The following effects have been found:[36]

- The Fc portion of rituximab mediates antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).
- Rituximab has a general regulatory effect on the cell cycle.
- It increases MHC II and adhesion molecules LFA-1 and LFA-3 (lymphocyte function-associated antigen).
- It elicits shedding of CD23.
- It downregulates the B cell receptor.
- It induces apoptosis of CD20+ cells.

The combined effect results in the elimination of B cells (including the cancerous ones) from the body, allowing a new population of healthy B cells to develop from lymphoid stem cells.

Rituximab binds to amino acids 170-173 and 182-185 on CD20, which are physically close to each other as a result of a disulfide bond between amino acids 167 and 183.[37]

4 History

Rituximab was developed by researcher Nabil Hanna and coworkers at IDEC Pharmaceuticals under the name **IDEC-C2B8**.[38] The U.S. patent for the drug was issued in 1998 and expired in 2015.[39]

Based on its safety and effectiveness in clinical trials,[40] rituximab was approved by the U.S. Food and Drug Administration in 1997 to treat B-cell non-Hodgkin lymphomas resistant to other chemotherapy regimens.[41] Rituximab, in combination with CHOP chemotherapy, is superior to CHOP alone in the treatment of diffuse large B-cell lymphoma and many other B-cell lymphomas.[42] In 2010 it was approved by the European Commission for maintenance treatment after initial treatment of follicular lymphoma.[43]

Rituximab is currently co-marketed by Biogen Idec and Genentech in the U.S., by Hoffmann–La Roche in Canada and the European Union, Chugai Pharmaceuticals, Zenyaku Kogyo in Japan and AryoGen in Iran.

It is on the World Health Organization's List of Essential Medicines, a list of the most important medications needed in a basic health system.[44]

Originally available for intravenous injection (e.g. over 2.5 hrs), in 2016 it gained EU approval in a formulation for subcutaneous injection for CLL.[45]

5 Specialty drug

In 2014 Genentech reclassified Avastin, Herceptin and Rituxan as specialty drugs which are only available through specialty pharmacies from October 2014.[46] Because discounts no longer apply, hospitals will pay more. "Specialty drugs usually fall under the FDA's Risk Evaluation and Mitigation Strategy (REMS) program, established for compounds like the testosterone drug AndroGel that may have unusual side effects; or for drugs that are unusually expensive."[46]

6 Other anti-CD20 monoclonals

The efficacy and success of Rituximab has led to some other anti-CD20 monoclonal antibodies being developed:

- ocrelizumab, humanized (90%−95% human) B cell-depleting agent.
- ofatumumab (HuMax-CD20) a fully human B cell-depleting agent.[47]
- Third-generation anti-CD20s such as obinutuzumab have a glycoengineered Fc fragment (Fc)[48] with enhanced binding to Fc gamma receptors, which increase ADCC (antibody-dependent cellular cytotoxicity).[49] This strategy for enhancing a monoclonal antibody's ability to induce ADCC takes advantage of the fact that the displayed Fc glycan controls the antibody's affinity for Fc receptors.[50]

The added value of a humanized molecule in oncology, compared to the original design, has not been demonstrated to this date.

Another approach to B cell diseases is to block the interaction of B cell survival or growth factors with their receptors on B cells. The monoclonal antibody Belimumab and atacicept are examples of such an approach.

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8 External links

- Rituximab Information from the US Food and Drug Administration
- U.S. National Library of Medicine: Drug Information Portal - Rituximab

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