The first monoclonal antibodies were developed from mice, but these were short-lived and not very compatible with human immune systems. Monoclonal antibodies in use today are chimeric (a combination of mouse and human antibodies that is approximately 65% human), humanized (a combination that is 95% human), and fully human. All monoclonal antibody therapies are of the IgG type.

Most monoclonal antibodies are administered intravenously, although a few are now being administered subcutaneously (under the skin). In general, monoclonal antibodies cause fewer side effects than traditional chemotherapy drugs because they are more targeted to cancer cells. Typically, the most common side effects occur during intravenous infusion when the drugs are administered for the first time, with subsequent infusions usually better tolerated. Infusion reaction symptoms may include headache, fever, chills, flushing, nausea, and dizziness. More severe allergic symptoms include hives, chest tightness, trouble breathing, and swelling of the face, lips, tongue, or throat. In order to minimize reactions, pre-medication with acetaminophen, antihistamine, and sometimes a corticosteroid, is standard. If a reaction is noted during the infusion, the rate of administration can be adjusted and more of the pre-medication drugs can be given to relieve symptoms.

Rituximab (Rituxan or Mabthera)

Rituximab was the first monoclonal antibody to receive FDA approval, which was for the treatment of relapsed non-Hodgkin's lymphoma in 1998. It is prescribed off-label for WM and is now commonly used as single agent therapy as well as in combination therapies and as maintenance therapy for both first-line and relapsed/refractory treatment. Rituximab targets the CD20 surface antigen on B-cells.

Two schedules for single agent rituximab have been studied: the standard one, in which one weekly infusion of 375 mg/m^2 is administered for 4 weeks; and the extended one, in which responding patients receive 4 more weekly infusions during weeks 12-16. With the standard schedule, the reported overall response rate was 30-60%, with a duration of response of 8-11 months in both first-line and relapsed/refractory patients. With the extended schedule, the overall response rate was 35-45%, with a duration of response of 16-29 months.

Recently, subcutaneous administration of rituximab was FDA approved for several blood cancers and can also be prescribed off-label for WM. The subcutaneous formulation is called Rituxan Hycela and is given by injection in 5-7 minutes rather than the typical several hours needed for intravenous infusion. The approval stipulates that the subcutaneous option can be used only after patients have received at least one treatment of rituximab intravenously. In clinical trials the effectiveness of the subcutaneous formulation was equivalent to that of intravenous rituximab, and the most common side effects of subcutaneous administration included nausea, infections, and neutropenia (low neutrophil count).

About 40-50% of WM patients treated with rituximab experience a transient increase in serum IgM levels—the IgM "flare" phenomenon. This flare occurs mostly during the first months of treatment but may persist for several months; it is not associated with a higher risk of treatment failure, and physicians should be cautious not to interpret flare as a lack of response or even disease progression. Patients with symptomatic hyperviscosity should receive plasmapheresis prior to treatment, or rituximab should be avoided during the first one or two cycles until IgM declines to a safer level.

Late-onset neutropenia (low neutrophil count) has been observed with rituximab, mostly when combined with chemotherapy. The underlying mechanism is not well understood. Reactivation of hepatitis B virus has also been observed, and screening for prior hepatitis B exposure is recommended Hepatitis B carriers should be closely monitored for clinical and laboratory signs and symptoms of active infection during therapy and for several months afterward.

Because of the relatively lower rate of response in WM patients with high IgM levels and the risk of IgM flare, single-agent rituximab should be avoided in patients with high IgM levels but may be considered for WM patients with disorders secondary to WM, such as IgM neuropathy, or in frail patients less likely to tolerate chemotherapy.

Rituximab has been combined with alkylating agents, nucleoside analogs, proteasome inhibitors, immunomodulators, and targeted pathway therapies. It is a part of almost every regimen for both first-line and relapsed/refractory WM.

Biosimilars for rituximab have been approved in Europe and the US. A biosimilar is a biological product that is highly similar to and has no clinically meaningful difference from an existing approved reference product. As patent protections for rituximab and similar drugs are expiring, biosimilars are being developed to provide more treatment options, increase access to medications, and potentially lower health care costs through competition. Trade name examples of rituximab biosimilars include Rixathon and Truxima and should be considered equivalent.
There has been controversy as to the exact role of rituximab maintenance therapy in WM. Maintenance therapy is prolonged treatment given after the initial treatment course (usually combination rituximab therapy) has taken effect and reduced the disease burden. The typical maintenance rituximab dosing schedule in WM has been a single infusion every 3 months for 2 years, although other dosing schedules have been used.

A major hypothesis for the use of maintenance therapy is to prolong the amount of time before disease progression occurs and re-treatment becomes necessary. Maintenance therapy has been more thoroughly researched for the common indolent lymphoma called follicular lymphoma.

The use of maintenance rituximab was recently reported in a study that examined the outcome of 248 rituximab-naïve WM patients who responded to rituximab-containing regimens, 35% of whom received maintenance. The median number of infusions over a 2-year period of maintenance rituximab was 8. Responses improved in 10% of patients overall. Both progression-free survival and overall survival were longer in patients on maintenance. (Progression-free survival is the length of time during and after treatment that a patient lives with the disease but does not show signs or symptoms of disease progression, while overall survival is the length of time after diagnosis that a patient survives.) An increased number of infections was observed, along with reduction of IgA and IgG. A prospective randomized clinical trial aimed at clarifying the role of rituximab as maintenance therapy in WM patients is currently underway in Germany and is evaluating the impact of 2 years of rituximab maintenance vs. observation alone after initial therapy with rituximab and bendamustine.

Ofatumumab (Arzerra)

Ofatumumab is a fully human monoclonal antibody that targets a different region on the CD20 surface antigen than rituximab, and in cells expressing low levels of CD20, it is more potent.

Two studies have looked at the role of ofatumumab in WM patients, including those who were intolerant to rituximab. These studies demonstrated that ofatumumab could be successfully administered as either a single-agent or as combination therapy, although infusion reactions similar to those from rituximab have occurred. A test dose of ofatumumab with appropriate pre-medication should be considered in patients with rituximab intolerance. There is a risk of IgM flare with ofatumumab, and precautions similar to those used for rituximab should be considered in patients who have evidence of hyperviscosity or who have significantly elevated IgM levels.

Obinutuzumab (Gazyva)

Obinutuzumab is a humanized monoclonal antibody approved for the treatment of chronic lymphocytic leukemia and follicular lymphoma. It is supposedly better at activating the complement pathway to destroy CD20-expressing B-cells and has been tested in clinical trials that included WM patients.

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About the IWMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer-led, nonprofit 501(c)(3) organization with an important mission: to offer mutual support and encouragement to the Waldenstrom's macroglobulinemia community and others with an interest in the disease; to provide information and educational programs that address patients' concerns; and to promote and support research leading to better treatments and ultimately, a cure.

More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF and its affiliate organizations can be found on our website, www.iwmf.com.

The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a Business Office at 6144 Clark Center, Ave., Sarasota, FL 34238. The Office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.