RITUXAN™
Rituximab

DESCRIPTION

The RITUXAN (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures.

RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. RITUXAN is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

CLINICAL PHARMACOLOGY

General

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes.[1,2] The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL)[3] but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues.[4] CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation,[4] and possibly functions as a calcium ion channel.[5] CD20 is not shed from the cell surface and does not internalize upon antibody binding.[6] Free CD20 antigen is not found in the circulation.[2]

Pre-clinical Pharmacology and Toxicology

Mechanism of Action: The Fab domain of Rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC)[7] and antibody-dependent cellular cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.[8]

Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B-lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in non-lymphoid tissues examined.

Human Pharmacokinetics/Pharmacodynamics

In patients given single doses at 10, 50, 100, 250 or 500 mg/m² as an IV infusion, serum levels and the half-life of Rituximab were proportional to dose. In 9 patients given 375 mg/m² as an IV infusion for four doses, the mean serum half-life was 59.8 hours (range 11.1 to 104.6 hours) after the first infusion and 174 hours (range 26 to 442 hours) after the fourth infusion. The wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20 positive (normal and malignant) B-cell populations upon repeated administrations.

Rituximab at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for four doses to 166 patients. The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden. Median steady-state serum levels were higher for responders compared to nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared to those with subtype A. Rituximab was detectable in the serum of patients three to six months after completion of treatment.

The pharmacokinetic profile of Rituximab when administered as six infusions of 375 mg/m² in combination with six cycles of CHOP chemotherapy was similar to that seen with Rituximab alone.

Administration of RITUXAN resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B-cells in seven of eight patients who had received single doses of Rituximab ≥100 mg/m². [9] Among the 166 patients in the pivotal study, circulating B-cells (measured as CD19+ cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. One of the responding patients (1%), failed to show significant depletion of CD19+ cells after the third infusion of Rituximab as compared to 19% of the nonresponding patients. B-cell recovery began at approximately six months following completion of treatment. Median B-cell levels returned to normal by twelve months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following Rituximab administration. However, only 14% of patients had reductions in IgG and/or IgM serum levels, resulting in values below the normal range.

CLINICAL STUDIES

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory low-grade or follicular B-cell NHL who received 375 mg/m² of RITUXAN given as an IV infusion weekly for four doses. Patients with tumor masses >10 cm or with >5,000 lymphocytes/μL in the peripheral blood were excluded from the study. The overall response rate (ORR) was 48% (80/166) with a 6% (10/166) complete response (CR) and a 42% (70/166) partial response (PR) rate. Disease-related signs and symptoms (including B-symptoms) were present in 23% (39/166) of patients at study entry and resolved in 64% (25/39) of those patients. The median time to onset of response was 50 days and the median duration of response is projected to be 10 to 12 months.

In a multivariate analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF A subtype (58% vs. 12%), higher in patients whose largest lesion was <5 cm vs. >7 cm in greatest diameter (55% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (53% vs. 36%). ORR in patients previously treated with autologous bone marrow transplant was 78% (18/23). The following factors were not associated with a lower response rate: age ≥ 60 years. extranodal disease, prior anthracycline therapy, and bone marrow involvement.

In a second multicenter, multiple-dose study, 37 patients with relapsed or refractory B-cell NHL received 375 mg/m² of RITUXAN as an IV infusion once weekly for four doses.[10,11] The ORR was 46% with a median duration of response of 8.6 months (range 2.6 to 26.2+). Single doses of up to 500 mg/m² were well-tolerated.[9]

Twenty patients have received two courses and one patient has received three courses of RITUXAN as 4 weekly infusions of 375 mg/m² per infusion. The percentage of patients reporting adverse events upon retreatment was similar to that reported following the first course, although the incidence of specific adverse events differed (see ADVERSE EVENTS). All patients had obtained an objective clinical response (CR or PR) to the first course of RITUXAN™ (Rituximab); upon retreatment, 6 of 12 patients evaluable for response obtained a complete or partial remission.

Twenty-nine patients with relapsed or refractory, bulky (single lesion of >10 cm in diameter), low grade NHL received 375 mg/m² of RITUXAN as four weekly infusions. The overall incidence of adverse events and the incidence of Grade 3 and 4 adverse events was higher in patients with bulky disease than in patients with non-bulky disease (see ADVERSE EVENTS). Ten of 21 patients evaluable for response have obtained a complete or partial remission.

INDICATIONS AND USAGE

RITUXAN is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma.

CONTRAINDICATIONS

RITUXAN is contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product. (See WARNINGS.)

WARNINGS

RITUXAN is associated with hypersensitivity reactions which may respond to adjustments in the infusion rate. Hypotension, bronchospasm, and angioedema have occurred in association with RITUXAN infusion as part of an infusion-related symptom complex. RITUXAN infusion should be interrupted for severe reactions and can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-threatening reactions have been able to complete the full course of therapy. (See DOSAGE and ADMINISTRATION.) Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids should be available for immediate use in the event of a reaction during administration.

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during RITUXAN therapy and should be monitored throughout the infusion and immediate post-infusion period.

PRECAUTIONS

Laboratory Monitoring: Complete blood counts (CBC) and platelet counts should be obtained at regular intervals during RITUXAN therapy and more frequently in patients who develop cytopenias (see ADVERSE EVENTS).

Drug/Laboratory Interactions: There have been no formal drug interaction studies performed with RITUXAN.

HAMA/HACA Formation: Human anti-murine antibody (HAMA) was not detected in 67 patients evaluated. Less than 1.0% (3/355) of patients evaluated for human anti-chimeric antibody (HACA) were positive. Patients who develop HAMA/HACA titers may have allergic or hypersensitivity reactions when treated with this or other murine or chimeric monoclonal antibodies.

Immunization: The safety of immunization with any vaccine, particularly live viral vaccines, following RITUXAN therapy has not been studied. The ability to generate a primary or anamnestic humoral response to any vaccine has also not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN, or to determine its effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following RITUXAN therapy.

Pregnancy Category C: Animal reproduction studies have not been conducted with RITUXAN. It is not known whether RITUXAN can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore, RITUXAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

Pediatric Use: The safety and effectiveness of RITUXAN in children have not been established.

ADVERSE REACTIONS

Safety data are based on 315 patients treated in five single-agent studies of RITUXAN. This includes patients with bulky disease (lesions >10 cm), those who have received more than one course of RITUXAN, and patients receiving 375 mg/m² for eight doses.

Infusion-Related Events: An infusion-related symptom complex consisting of fever and chills/rigors occurred in the majority of patients during the first RITUXAN infusion. Other frequent infusion-related symptoms included nausea, urticaria, fatigue, headache, pruritus, bronchospasm, dyspnea, sensation of tongue or throat swelling (angioedema), rhinitis, vomiting, hypotension, flushing, and pain at disease sites. These reactions generally occurred within 30 minutes to 2 hours of beginning the first infusion, and resolved with slowing or interruption of the RITUXAN infusion and with supportive care (IV saline, diphenhydramine, and acetaminophen). The incidence of infusion-related events decreased from 80% (7% Grade 3/4) during the first infusion to approximately 40% (5% to 10% Grade 3/4) with subsequent infusions. Mild to moderate hypotension requiring interruption of RITUXAN infusion with or without the administration of IV saline occurred in 32 (10%) patients. Isolated occurrences of severe reactions requiring epinephrine have been reported in patients receiving RITUXAN for other indications. Angioedema was reported in 41 (13%) patients and was serious in one patient. Bronchospasm occurred in 25 (8%) patients; one-quarter of these patients were treated with bronchodilators. A single report of bronchiolitis obliterans was noted.

Immunologic Events: RITUXAN induced B-cell depletion in 70 to 80% of patients and was associated with decreased serum immunoglobulins in a minority of patients. The incidence of infection does not appear to be increased. During the treatment period, 50 patients in the pivotal trial developed 68 infectious events; 6 (9%) were Grade 3 in severity and none were Grade 4 events. Of the

6 serious infectious events, none were associated with neutropenia. The serious bacterial events included sepsis due to Listeria (n=1), Staphylococcal bacteremia (n=1) and polymicrobial sepsis (n=1). In the post-treatment period (30 days to 11 months following the last dose), bacterial infections included sepsis (n=1); significant viral infections included herpes simplex infections (n=2) and herpes zoster (n=3).

Retreatment Events: Twenty-one patients have received more than one course of RITUXAN™ (Rituximab). The percentage of patients reporting any adverse event upon retreatment was similar to the percentage of patients reporting adverse events upon initial exposure. The following adverse events were reported more frequently in retreated subjects: asthenia, throat irritation, flushing, tachycardia, anorexia, leukopenia, thrombocytopenia, anemia, peripheral edema, dizziness, depression, respiratory symptoms, night sweats, and pruritus.

Hematologic Events: During the treatment period (up to 30 days following last dose) severe thrombocytopenia occurred in 1.3% of patients, severe neutropenia occurred in 1.9% of patients, and severe anemia occurred in 1.0% of patients. A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following RITUXAN therapy were reported.

Cardiac Events: Four patients developed arrhythmias during RITUXAN infusion. One of the four discontinued treatment because of ventricular tachycardia and supraventricular tachycardias. The other three patients experienced trigeminy (1) and irregular pulse (2) and did not require discontinuation of therapy. Angina was reported during infusion and myocardial infarction occurred 4 days post-infusion in one subject with a prior history of myocardial infarction.

Table 1.

Adverse Events ≥5% of Patients (N=315)

	Incidence All Grades	
	N	%
Any Adverse Event	**275**	**87**
Body As A Whole		
Fever	154	49
Chills	102	32
Asthenia	49	16
Headache	43	14
Throat Irritation	19	6
Abdominal Pain	18	6
Cardiovascular System		
Hypotension	32	10
Digestive System		
Nausea	55	18
Vomiting	23	7
Hemic and Lymphatic System		
Leukopenia	33	11
Thrombocytopenia	25	8
Neutropenia	21	7
Metabolic and Nutritional System		
Angioedema	41	13
Musculo-Skeletal System		
Myalgia	21	7
Nervous System		
Dizziness	23	7
Respiratory System		
Rhinitis	25	8
Bronchospasm	24	8
Skin and Appendages		
Pruritus	32	10
Rash	31	10
Urticaria	24	8

Severe and life-threatening (Grade 3 and 4) events were reported in 10% (32/315) of patients. The following Grade 3 and 4 adverse events were reported: neutropenia (1.9%), chills (1.6%), leukopenia and thrombocytopenia (1.3% for each), hypotension, anemia, bronchospasm, and urticaria (1.0% for each), headache, abdominal pain, arrhythmia (0.6% for each), and asthenia, hypertension, nausea, vomiting, coagulation disorder, angioedema, arthralgia, pain, rhinitis, increased cough, dyspnea, bronchiolitis obliterans, hypoxia, asthma, pruritus, and rash (one patient each, 0.3%).

The following adverse events occurred in ≥1.0% but <5.0% of patients, in order of decreasing incidence: flushing, arthralgia, diarrhea, anemia, cough increase, hypertension, lacrimation disorder, pain, hyperglycemia, back pain, peripheral edema, paresthesia, dyspepsia, chest pain, anorexia, anxiety, malaise, tachycardia, agitation, insomnia, sinusitis, conjunctivitis, abdominal enlargement, postural hypotension, LDH increase, hypocalcemia, hypesthesia, respiratory disorder, tumor pain, pain at injection site, bradycardia, hypertonia, nervousness, bronchitis, and taste perversion.

The proportion of patients reporting any adverse event was similar in patients with bulky disease and those with lesions <10 cm in diameter. However, the incidence of dizziness, neutropenia, thrombocytopenia, myalgia, anemia and chest pain was higher in patients with lesions >10 cm. The incidence of any Grade 3 and 4 event was higher (31% vs. 13%) and the incidence of Grade 3 or 4 neutropenia, anemia, hypotension, and dyspnea was also higher in patients with bulky disease compared with patients with lesions <10 cm.

OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses higher than 500 mg/m² have not been tested.

DOSAGE AND ADMINISTRATION

Usual Dose:

The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22). RITUXAN may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. (See Administration.)**

Instructions for Administration

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

RITUXAN solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 12 hours. No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Hypersensitivity reactions may occur (see WARNINGS). Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of RITUXAN™ (Rituximab). Premedication may attenuate infusion-related events. Since transient hypotension may occur during RITUXAN infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to RITUXAN infusion.

First Infusion: The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: Subsequent RITUXAN infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated.

Stability and Storage: RITUXAN vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight.

HOW SUPPLIED

RITUXAN is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials.
Single unit 100 mg carton: Contains one 10 mL vial of RITUXAN (10 mg/mL).
NDC 50242-051-21
Single unit 500 mg carton: Contains one 50 mL vial of RITUXAN (10 mg/mL).
NDC 50242-053-06

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