

Lipid Test Flags Renal Impairment Risk in Lupus

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Contributing Writer

A simple serum lipid test may identify patients with systemic lupus erythematosus who are at an increased risk for renal dysfunction, according to investigators.

Data collected on 1,060 patients with SLE who were registered at the University of Toronto Lupus Databank were analyzed by Annaliese Tisseveras and her colleagues.

They found that an elevated serum total cholesterol level in the first sample obtained from patients and recorded in the databank was significantly associated with subsequent renal deterioration and death associated with kidney dysfunction (Arthritis Rheum. 2006;54:2211-9).

“Independent of any association with proteinuria or steroid therapy, an elevated total cholesterol level portends a worse renal outcome,” reported Ms. Tisseveras and her colleagues at Toronto Western

Hospital. More research is needed, they noted, but “the predictive value of an elevated cholesterol level on renal function ... cannot be discounted.”

The patients, who were mostly women, had a mean age of 36 years and a mean duration of SLE of 4 years when the first total cholesterol measurement was recorded. The first measurement ranged from 1.6 to 17.1 mmol/L, with a mean of 5.3 mmol/L (205 mg/dL).

During an average follow-up of almost

9 years, 9% of patients experienced renal deterioration, 4% developed end-stage renal disease (ESRD), and 15% died (30% of the deaths were associated with renal dysfunction). The investigators stratified patients into two groups: those with normal total cholesterol levels and those with elevated levels. They then looked at Kaplan-Meier survival estimates for each of the three outcomes—renal deterioration, ESRD, and death. The estimates for each of the outcomes, they found, were significantly different between the two groups, with worse outcomes in the group with elevated total cholesterol levels.

In multivariate analyses that included other variables, baseline proteinuria and serum creatinine level were predictive of both ESRD and renal deterioration. Total cholesterol level did not retain its significance with regard to ESRD, however, which may be due to the low number of patients with ESRD.

Total cholesterol level did, however, correlate again with death, and significantly with renal death—a finding that is “strongly supportive of a pathogenic role for hypercholesterolemia in SLE renal disease,” the investigators reported.

Patients With SLE Sought for Stem Cell Trial

Researchers are recruiting patients with severe and active systemic lupus erythematosus to participate in a pilot study involving hemopoietic stem cell transplant.

Potential participants with systemic lupus erythematosus (SLE) should be 15-40 years of age and have acceptable organ function. Participants should have 4 of the 11 American College of Rheumatology criteria for SLE but no other significant medical conditions. Patients may have active and refractory lupus affecting the kidneys, CNS, lungs, or blood. Participants also should have no evidence of malignancy, active hepatitis B virus or hepatitis C virus, or HIV infections. Written consent is required.

The treatment protocol includes priming and conditioning regimens. The priming regimen involves treatment with methylprednisolone, rituximab, cyclophosphamide, and mesna. At the end of this regimen, patients will receive a granulocyte colony-stimulating factor to mobilize stem cells for collection for transplant. Patients will undergo the conditioning regimen immediately prior to stem cell transplant.

Following transplantation, patients will be followed for 6 months and then at 9, 12, 18, and 24 months. After 2 years, patients will be followed yearly for 5 years.

The trial is being conducted at the National Institutes of Health campus in Bethesda, Md. The principal investigator is Dr. Steven Pavletic of the National Institute for Arthritis and Musculoskeletal and Skin Diseases. Physicians who know of interested patients may contact Cheryl Yarboro, R.N., by calling 301-402-6409.

—Kerri Wachter

BRIEF SUMMARY

The following is a brief summary. Before prescribing, please consult full prescribing information.

WARNINGS

Fatal Infusion Reactions: Deaths within 24 hours of RITUXAN infusion have been reported. These fatal reactions followed an infusion reaction complex, which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. (See WARNINGS and ADVERSE REACTIONS.)

Patients who develop severe infusion reactions should have RITUXAN infusion discontinued and receive medical treatment.

Tumor Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) patients with RITUXAN. (See WARNINGS.)

Severe Mucocutaneous Reactions: Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with RITUXAN treatment. (See WARNINGS and ADVERSE REACTIONS.)

INDICATIONS

RITUXAN (rituximab) in combination with methotrexate is indicated to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

CONTRAINDICATIONS

RITUXAN is contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product. (See WARNINGS.)

WARNINGS (See BOXED WARNINGS.)

Severe Infusion Reactions (see BOXED WARNINGS, ADVERSE REACTIONS, and Hypersensitivity Reactions)

RITUXAN has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of RITUXAN administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.

Management of severe infusion reactions: The RITUXAN infusion should be interrupted for severe reactions. Medications and supportive care measures including, but not limited to, epinephrine, antihistamines, glucocorticoids, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen, should be available and instituted as medically indicated for use in the event of a reaction during administration. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells ($\geq 25,000/\text{mm}^3$) with or without evidence of high tumor burden. (See WARNINGS, Cardiovascular and ADVERSE REACTIONS.)

Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with RITUXAN. The majority of patients received RITUXAN in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of RITUXAN and approximately one month after the last dose.

Persons at high risk of HBV infection should be screened before initiation of RITUXAN. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following RITUXAN therapy. In patients who develop viral hepatitis, RITUXAN and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming RITUXAN therapy in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received RITUXAN in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of RITUXAN and have resulted in death.

Hypersensitivity Reactions

RITUXAN has been associated with hypersensitivity reactions (non-IgE-mediated reactions), which may respond to adjustments in the infusion rate and in medical management. Hypotension, bronchospasm, and angioedema have occurred in association with RITUXAN infusion (see Severe Infusion Reactions). RITUXAN infusion should be interrupted for severe hypersensitivity 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 hypersensitivity 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 glucocorticoids, should be available for immediate use in the event of a reaction during administration. (See WARNINGS, Management of severe infusion reactions, and Cardiovascular, and ADVERSE REACTIONS.)

Cardiovascular

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 pre-existing 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.

Renal (See BOXED WARNINGS: Tumor Lysis Syndrome [TLS] and ADVERSE REACTIONS)

RITUXAN administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome in hematologic malignancy patients. Renal toxicity has occurred in patients with high numbers of circulating malignant cells ($>25,000/\text{mm}^3$) or high tumor burden who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN is not an approved treatment regimen. If this combination is used in clinical trials extreme caution should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of RITUXAN should be considered for those with rising serum creatinine or oliguria.

Severe Mucocutaneous Reactions (See BOXED WARNINGS)

Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with RITUXAN. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy), Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 to 13 weeks following RITUXAN exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent

treatment. The safety of readministration of RITUXAN to patients with any of these mucocutaneous reactions has not been determined.

Concomitant use with biologic agents and DMARDs other than methotrexate in RA: Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in patients exhibiting peripheral B cell depletion following treatment with rituximab. Patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used concomitantly.

PRECAUTIONS

Information for Patients

Patients should be provided the RITUXAN Patient Information leaflet and provided an opportunity to read it prior to each treatment session. Because caution should be exercised in administering RITUXAN to patients with active infections, it is important that the patient's overall health be assessed at each visit and any questions resulting from the patient's reading of the Patient Information be discussed.

Laboratory Monitoring

Because RITUXAN targets all CD20-positive B lymphocytes (malignant and nonmalignant), 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 REACTIONS). The duration of cytopenias caused by RITUXAN can extend well beyond the treatment period.

Drug/Laboratory Interactions

There have been no formal drug interaction studies performed with RITUXAN. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. (See WARNINGS, Renal.) In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

Immunization

The safety of immunization with live viral vaccines following RITUXAN therapy has not been studied and vaccination with live virus vaccines is not recommended. The ability to generate a primary or anamnestic humoral response to vaccination is not known.

Physicians should review the vaccination status of patients with RA being considered for RITUXAN treatment and follow the Centers for Disease Control and Prevention (CDC) guidelines for adult vaccination with non-live vaccines intended to prevent infectious disease, prior to therapy. For patients with NHL, the benefits of primary and/or booster vaccinations should be weighed against the risks of delay in initiation of RITUXAN therapy.

Use in patients with RA who had no prior inadequate response to TNF antagonists: While efficacy of RITUXAN was supported in two well-controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, a favorable risk/benefit relationship has not been established in this population. The use of RITUXAN in patients with RA who have no prior inadequate response to one or more TNF antagonists is not recommended. (See CLINICAL STUDIES, Rheumatoid Arthritis.)

Retreatment in patients with RA: Safety and efficacy of retreatment have not been established in controlled trials. A limited number of patients have received two to five courses (two infusions per course) of treatment in an uncontrolled setting. In clinical trials in patients with RA, most of the patients who received additional courses did so 24 weeks after the previous course and none were retreated sooner than 16 weeks.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term animal studies have been performed to establish the carcinogenic potential of RITUXAN. Studies also have not been completed to assess mutagenic potential of RITUXAN, or to determine potential 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

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Animals were administered rituximab via the intravenous route during early gestation (organogenesis period; post-coitum days 20 through 50). Rituximab was administered as loading doses on post-coitum days 20, 21, and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on post-coitum days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in exposures of 0.8-fold a human 2 g dose based on AUC. Although rituximab has been shown to cross the monkey placenta, there was no evidence of teratogenicity under the conditions of the experiment.

Nonteratogenic effects: Results from the embryo-fetal developmental toxicology study described above showed that rituximab treatment produced a decrease in lymphoid tissue B cells in the offspring of treated dams.

A subsequent pre- and postnatal developmental toxicity study in cynomolgus monkeys was completed to assess developmental toxicity and the recovery of B-cells and immune function in infants exposed to rituximab in utero. Rituximab was administered from early gestation (post-coitum day 20) through lactation (post-partum day 28). Due to the possibility of anti-drug antibody development with such a long dosing period, the animals were divided into 3 sets of dosing periods: one set received rituximab (20 or 100 mg/kg weekly) from post-coitum day 20 through delivery and post-partum day 28 (~25 weeks); a second set received rituximab (20 or 100 mg/kg weekly) from post-coitum day 50 through post-coitum day 76 (8 weeks); a third set received rituximab (20 or 100 mg/kg weekly) from post-coitum day 76 through delivery and post-partum day 28 (~8 weeks). For each of these dosing periods, a loading dose was administered for the first 3 days of the period at doses of 15 or 75 mg/kg/day. The decreased B cells and immunosuppression noted in the offspring of pregnant animals treated with either 20 or 100 mg/kg/week rituximab showed a return to normal levels and function within 6 months post-birth. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Rituximab was excreted in the milk of lactating cynomolgus monkeys. 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 pediatric patients have not been established.

Geriatric Use

Among the 517 patients in the phase 3 RA study, 16% were 65 to 75 years old and 2% were 75 years old and older. The RITUXAN ACR 20 response rates in the older (age ≥ 65 years) vs. younger (age < 65 years) patients were similar (53% vs. 51%, respectively). Adverse reactions, including incidence, severity, and type of adverse reaction were similar between older and younger patients.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The following serious adverse reactions, some with fatal outcomes, have been reported in patients treated with RITUXAN (see BOXED WARNINGS and WARNINGS): severe or fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, hepatitis B reactivation with fulminant hepatitis, other viral infections, hypersensitivity reactions, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

Post-Marketing Reports

The following adverse reactions have been identified during post-approval use of RITUXAN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these

reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to RITUXAN.

Hematologic: prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia, hyperviscosity syndrome in Waldenström's macroglobulinemia.

Cardiac: fatal cardiac failure.

Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarthralgia and vasculitis with rash.

Infection: increased in fatal infections in HIV-associated lymphoma.

Skin: severe mucocutaneous reactions.

Gastrointestinal: bowel obstruction and perforation.

Adverse Reactions in Patients with Rheumatoid Arthritis

In general, the adverse events observed in patients with RA were similar in type to those seen in patients with non-Hodgkin's lymphoma (see WARNINGS, PRECAUTIONS and other sections under ADVERSE REACTIONS). Specific safety considerations in this indication are discussed below.

Where specific percentages are noted, these data are based on 938 patients treated in Phase 2 and 3 studies of RITUXAN (2 × 1000 mg) or placebo administered in combination with methotrexate.

Table 1
Incidence of All Adverse Events* Occurring in $\geq 2\%$ and at Least 1% Greater Than Placebo Among Rheumatoid Arthritis Patients in Clinical Studies Up to Week 24 (Pooled)

Preferred Term	Placebo + MTX N=398 n (%)	RITUXAN + MTX N=540 n (%)
Abdominal Pain Upper	4 (1)	11 (2)
Anxiety	5 (1)	9 (2)
Arthralgia	14 (4)	31 (6)
Asthenia	1 (<1)	9 (2)
Chills	9 (2)	16 (3)
Dyspepsia	3 (<1)	16 (3)
Hypercholesterolemia	1 (<1)	9 (2)
Hypertension	21 (5)	43 (8)
Migraine	2 (<1)	9 (2)
Nausea	19 (5)	41 (8)
Paresthesia	3 (<1)	12 (2)
Pruritus	5 (1)	26 (5)
Pyrexia	8 (2)	27 (5)
Rhinitis	6 (2)	14 (3)
Throat Irritation	0 (0)	11 (2)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Urticaria	3 (<1)	12 (2)

*Coded using MedDRA.

Infusion Reactions

In RITUXAN RA placebo-controlled studies, 32% of RITUXAN-treated patients experienced an adverse event during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse events during the 24-hour period following the second infusion, RITUXAN or placebo, decreased to 11% and 13%, respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of RITUXAN-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion reactions following the second infusion of RITUXAN or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1% of patients in either treatment group. Acute infusion reactions required dose modification (stopping, slowing or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion reactions decreased with subsequent courses of RITUXAN. The administration of IV glucocorticoids prior to RITUXAN infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to RITUXAN infusions.

Infections

In RA clinical studies, 39% of patients in the RITUXAN group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis. The only infections to show an absolute increase over placebo of at least 1% were upper respiratory tract infections, which affected 7% of RITUXAN-treated patients and 6% of placebo-treated patients and rhinitis, which affected 3% of RITUXAN-treated patients and 2% of placebo-treated patients.

The incidence of serious infections was 2% in the RITUXAN-treated patients and 1% in the placebo group. One fatal infection (bronchopneumonia) occurred with rituximab monotherapy during the 24-weeks placebo-controlled period in one of the Phase 2 RA studies.

Cardiac Events

The incidence of serious cardiovascular events in the double-blind part of the clinical trials was 1.7% and 1.3% in RITUXAN and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all rituximab regimens (3/769=0.4%) as compared to none in the placebo treatment group (0/389).

Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the infusion and RITUXAN should be discontinued in the event of a serious or life-threatening cardiac event.

Immunogenicity

A total of 54/930 patients (5%) with RA tested positive for HACA. Of these, most became positive by week 24. Following the first course, however, some became positive at week 16 or after 24 weeks. Some patients tested positive after the second course of treatment. Limited data are available on the safety or efficacy of RITUXAN retreatment in patients who develop HACA. One of 10 HACA-positive patients who received retreatment with RITUXAN experienced a serious acute infusion reaction (bronchospasm). The clinical relevance of HACA formation in rituximab-treated patients is unclear.

OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m² have been given in dose-escalation clinical trials.

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