Statin Found to Improve Raynaud's in Scleroderma

BY MARY ANN MOON Contributing Writer

torvastatin raised the number of circulating endothelial precursors in a pilot study of 14 patients with systemic sclerosis, significantly improving the symptoms of Raynaud's phenomenon, reported Dr. Masataka Kuwana of Keio University, Tokyo, and associates.

Compared with healthy control subjects, patients with scleroderma had a

nts who develop severe infusion reactions should have RITUXAN infusion

cal treatment Tumor Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fail 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.)

IICALIONS IVXAN (Rituximab) in combination with methotrexate is indicated to reduce ns and symptoms in adult patients with moderately to severely active umatoid arthritis who have had an inadequate response to one or more "antagonist therapies.

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 uticaria, 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 anaphylacticid events. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or manite cell lymphoma.

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, bronchotilators, 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 rumbers of circulating malignant cells (<25,000/mm²) 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

Infections Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death the force reacted in some softents with hometologic malingancies treated with BTI IVAN

been reported in some patients with hematologic malignancies treated with RITUXAN. majority of patients received RITUXAN in combination with chemotherapy. The fain time to the diagnosis of hepatitis was approximately 4 months after the tition of RITUXAN and approximately one month after the last dose.

WARNINGS

INDICATIONS

markedly reduced number of circulating endothelial precursors (CEPs), and their CEPs tended to have an impaired maturation potential when stimulated by angiogenic factors.

Dr. Kuwana and associates theorized that "insufficient mechanisms of vascular repair, due to defective vasculogenesis, contribute to the pathogenic process" underlying scleroderma patients' Raynaud's symptoms, digital ulcers, and gangrene. If so, raising the number of CEPs and stimulating CEP kinetics might improve the vasculopathy.

Statins have been shown to increase CEPs and stimulate their kinetics in patients with coronary heart disease, so the researchers conducted a prospective pilot study to assess whether statins would have the same effect in scleroderma. They assessed 14 women aged 36-75 years (mean age, 57 years), half of whom had diffuse systemic sclerosis and half of whom had limited cutaneous systemic sclerosis. All

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. *tologic:* prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia viscosity syndrome in Waldenstrom's macroolobulinemia.

Cardiac: fatal cardiac failure. Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis and vasculitis with rash.

Infection: increased in fatal infections in HIV-associated lymphoma. Skin: severe mucocutaneous reactions.

Suit severe induccularities reactions: Castrointestinal: 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-hodgin's lymphoma (see WARNINGS, PRECAUTIONS and other sections under ADVERSE REACTIONS). Specific safety considerations in this indication are discussed below.

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

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

referred Term	Placebo + MTX N=398 n (%)	RITUXAN + MTX N=540 n (%)
bdominal Pain Upper	4 (1)	11 (2)
nxiety	5 (1)	9 (2)
rthralgia	14 (4)	31 (6)
sthenia	1 (<1)	9 (2)
hills	9 (2)	16 (3)
vspepsia	3 (<1)	16 (3)
ypercholesterolemia	1 (<1)	9 (2)
ypertension	21 (5)	43 (8)
ligraine	2 (<1)	9 (2)
ausea	19 (5)	41 (8)
aresthesia	3 (<1)	12 (2)
ruritus	5 (1)	26 (5)
yrexia	8 (2)	27 (5)
hinitis	6 (2)	14 (3)
hroat Irritation	0 (0)	11 (2)
pper Respiratory		
Tract Infection	23 (6)	37 (7)
rticaria	3 (<1)	12 (2)

*Coded using MedDRA.

*Coded using MedDRA. Thusion 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, puritus, uricaria/rash, angloedema, sneezing, throat infusition, coupared to 19% of placebo-treated patients following the "first patient" of the patient of these acute infusion reactions following the second infusion of RITUXAN or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions required dates following their first placebo infusion of RITUXAN or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions required dose modification (stopping, slowing or placebo, respectively, after the first course. The proportion of patients experienced acute infusion reactions frequire for using reactions, however, there was no clear RITUXAN. The administration of NJ gluccoorticolds prior to RITUXAN infusions reduced the incidence and severity of such reactions, however, there was no clear entrution reactions. Patients in clinical studies also received antihistamines and acetaminopen prior to RITUXAN infusions. **B** Adverse there and the second induced in the provention of acute infusion reactions required to server the provention of acute infusion reactions. Patients in clinical studies also received antihistamines and acetaminopen 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 treated patients and rhinitis, wh 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 R4 studies.

Cardiac Events 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%) escompared 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 RTIUXAN should be discontinued in the event of a serious or life-threatening cardiac event.

A total of 54/990 patients (5%) with RA tested positive for HACA. Of these, m became nositive by week 24. Following the first course, however, some became In test or brock provide the provided of th 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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the patients had Raynaud's phenomenon. Atorvastatin treatment resulted in a sta-

tistically significant 1.7- to 8.0-fold increase in the number of CEPs. The CEP numbers returned to extremely low baseline levels after cessation of atorvastatin, however.

In addition, "reductions in the up-regulated levels of angiogenic factors and vascular endothelial activation/injury markers were observed during treatment," Dr. Kuwana and associates noted.

Raynaud's symptoms improved significantly during treatment, along with patients' activity levels and ratings of disability and pain. No patient developed new ulcers during treatment. These symptoms recurred when therapy was stopped, however, and patients quickly began developing new digital ulcers.

All but one patient completed the 12-

'Drugs that exert potent stimulatory effects on CEP kinetics could augment vasculogenesis as a therapeutic intervention for ischemic complications.'

week course of once-daily atorvastatin (10 mg) while continuing on their regular medication regimens. None had any adverse events. but one woman withdrew from the study because her total cholesterol level declined excessively, to less than 100

mg/dL, the investigators said (Arthritis Rheum. 2006;54:1946-51). These beneficial drug effects are likely due to the recruitment of CEPs into the periphery and the repair of injured endothelium. Statins may increase both the proliferation and the mobilization of CEPs and may prevent CEP senescence and apoptosis within the bone marrow, the researchers reported.

"However, it is also possible that the observed clinical changes were mediated through other effects of statins, such as anti-inflammation mechanisms and the improvement of mature endothelial function," Dr. Kuwana and colleagues noted.

Although the number of CEPs increased dramatically with atorvastatin, it never reached the level reported in healthy subjects. Also, atorvastatin failed to improve the impaired maturation potential of the CEPs, the researchers acknowledged. "These observations indicate that although atorvastatin is certainly capable of improving CEP dysfunction in systemic sclerosis patients, its effects are limited.

"In addition to statins, ... drugs that exert potent stimulatory effects on CEP kinetics, such as granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor, could augment vasculogenesis as a therapeutic intervention for ischemic complications in patients with systemic sclerosis," according to Dr. Kuwana and associates.

CEPs, which are derived from bone marrow, are required for the formation of blood vessels and also contribute to vascular healing at sites of vascular injury or ischemia by working together with existing mature endothelial cells.

treatment. The safety of readministration of RITUXAN to patients with any of these mucocutaneous reactions has not been determined. BRIEF SUMMARY The following is a brief summary. Before prescribing, please consult full prescribing 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 rituriand. Patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used concomitantly. sion Reactions: Deaths within 24 hours of RITUXAN infusion have een reported. These fatal reactions followed an infusion reaction complex, hich included hypoxia, pulmonary infiltrates, acute respiratory distress notrome, mycardial infraction, ventricular fibrillation, or cardiogenic shock, pproximately 80% of fatal influsion reactions occurred in association with the rst infusion, Gee WARNINGS and ADVERSE FRACTIONS.)

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.

Questions resulting normal and an analysis of the provided statement o

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n mmunization with live viral vaccines following RITUXAN therapy has ied and vaccination with live virus vaccines is not recommended. ierenrate a primary or anamnestic humoral response to vaccination rimation with li rimary or anam pility to generate a p rently being studied.

This currently being studied. Physicians should review the vaccination status of patients with RA being considered for RTUXAN 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 weighted against the risks of delay in initiation of RTUXAN 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 triats in patients with RA with prior inadequate response to non-biologic DMARDs, a favorable risk benefit relationship has not been established in this population. The use of RTUXAN 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 dids oz 24 weeks after the previous course and none were retreated sooner than 16 weeks.

retreated sooner than to 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 effects on fertility in males or themated during treatment and for up to 12 months following RITUXAN therapy. methods during treatment and for up to 12 months tollowing HIUXAN 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-cotitum days 20 truogh 50). Rituximab was administered as loading doses on post-coitum days 20 truogh 50). Rituximab was administered as loading doses on post-coitum days 20 truogh 50, Altavianab at 20, 50 or 100 mg/kg/day, and then weekly on post-coitum days 20 truogh 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.

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 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 uterc. Rituximab was administered from early gestation (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 weekk)) from post-coitum day 20 through eleves, a third set received rituximab (20 or 100 mg/kg weekk)) form post-coitum day 26 through delivery and post-partum day 28 (-25 weeks); a second set received rituximab (20 or 100 mg/kg weekk)) from post-coitum day 26 through delivery and post-partum day 28 (-8 weeks); for the centered rituximab (20 or 100 mg/kg weekk)) from post-coitum day 26 through delivery and post-partum day 28 (-8 weeks); for post-coitum day 26 through delivery and post-partum day 28 (-8 weeks); for post-coitum day 26 through delivery and post-partum day 28 (-8 weeks); for post-coitum day 26 (-8 weeks); for the period at doses of 15 or 75 mg/kg/day. The decreased B cells and timunousuppression noted in the offspring of pregnant animals reproductive studies and function within 6 months post-brith. However, there are no adequate and well-control withe potential benefit justifies the potential risk to the fetus.

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 265 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

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

Use an of expression adverse reactions, some with fatal outcomes, have been reports in patients treated with RITUXAN (see BOXED WARNINGS and WARNINGS): sever or fatal infusion reactions, tumor lysis syndrome, severe mucocultaneou reactions, hepatitis B reactivation with fulminant hepatitis, other viral infection hypersensitivity reactions, cardiac arrhythmias, renal toxicity, bowel obstructio and perforation.

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

discontinuation of RITUXAN and have resulted in death. Hypersensitivity Reactions RITUXAN been associated with hypersensitivity reactions (non-lgE-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 some data Solve reduction in rate (e.g., from 100 mg/hr to Sol 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 alse to complete the full equicocorticoids, should be exailable for immediate use in the event of a reaction during administration. (See WARNINGS, Management of severe infusion reactions, and Cardiovascular, and ADVERSE REACTIONS.) Cardiovascular

Teactions, and variables and the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should be discontinued in the event of serious 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.

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 maignant cells (>25,000/mm) or high tumor burden who experience tumor lysis syndrome and in patients with NHL administered oncomitant 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 for those with rising serum creatining or oliguria. Severe Muccoutaneous Reactions (See BOXED WARNINGS)

for those with rising serum creatinine or oliguria. Severe Mucocutaneous Reactions (See BOXED WARNINGS) Mucocutaneous reactions, some with fala outcome, have been reported in patients treated with RITUXAN. These reports include paraneoplastic pempligus (an uncommon disorder which is a manifestation of the patients underlying mailgnancy). Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobulious 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

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.

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 NIe virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of RITUXAN and have resulted in death.