

Rituximab Seems Safe in RA Lung Disease

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FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

To date, no new significant safety signals associated with rituximab therapy in patients with severe rheumatoid arthritis who also have lung disease have been identified in an ongoing observational study of such patients, according to Dr. Shouvik Dass.

Overall, the incidence of serious infections has been low and is about what would be expected in these patients, who already have significant comorbidity because of longstanding RA and preexisting lung disease, said Dr. Dass, of the department of rheumatology, University of Leeds (England).

Because interstitial lung disease and various other lung diseases are more common among patients with RA, they

may be considered contraindications to treatment with anti-tumor necrosis factor therapy, because of reports that the anti-TNF agents may cause, or at least may be associated with, major deteriorations in interstitial lung disease. Although these data are not definitive, as a result, the use of rituximab – a CD20-directed cytolytic antibody – may be increasing among patients with RA and pulmonary disease, said Dr. Dass.

“The effect of biologic therapies as a whole on lung disease is not completely clear,” he said in an interview. He also referred to data – mostly case reports– in the hematologic literature associating rituximab with worsening lung disease.

He and his associates reviewed the records of 67 patients with RA and concomitant lung disease who were treated with rituximab between 2004 and 2010 at their center, which he said has one of the largest single cohorts of RA patients treated with rituximab. The patients’ mean age was 60 years and most (56) were female. The most common pulmonary diagnosis was interstitial lung disease (ILD) in 48 patients; 14 patients had chronic obstructive pulmonary disease (COPD), and 5 patients had bronchiectasis; 2 patients also had had a previous pulmonary empyema.

All patients received two infusions of 1,000 mg rituximab with methylprednisolone per course, which was repeated when RA became active again, at intervals of no less than 6 months. Half of the patients received at least two treatment cycles.

Over a median of about 2 years of follow-up (the range was about 8 months to 6.5 years) after treatment with rituximab, there were three deaths among these patients: 2 of the 48 patients with ILD and 1 of the 14 patients with COPD. The patient with COPD died of an infective COPD exacerbation 12 months after the third cycle of rituximab. One of the patients with ILD died of pneumonia and possible acute progression of ILD, Dr. Dass said, noting that clinical and CT changes attributable to either condition were observed 4 weeks after the patient had been treated with the first cycle of rituximab. Suicide was the cause of death in the second patient with ILD, 3 months after treatment with the first course of rituximab. Another three patients had a single episode of serious respiratory tract infection, which required hospital admission or treatment with intravenous antibiotics.

Based on these cases, there were no definite new significant safety signals that were observed “beyond that which might be expected in this group of patients with longstanding severe RA and concomitant lung disease,” Dr. Dass said.

However, he pointed out that the one death caused by respiratory deterioration was temporally related to rituximab therapy.

“B-cell depletion is now an important therapy for RA, and therefore this study aims to add insight into the safety and practical usage of rituximab,” he noted in the interview. “We hope to encourage ongoing review and follow-up of such patients.”

In the United States, rituximab is marketed as Rituxan by Genentech, a member of the Roche Group, and is a registered trademark of Biogen Idec.

Dr. Dass and two of his six coauthors disclosed that they are consultants for Roche. Dr. Dass received an award from EULAR for this research. ■

Table 1. Incidence of Adverse Reactions Occurring in at Least 3% of Patients Treated With BENLYSTA 10 mg/kg Plus Standard of Care and at Least 1% More Frequently Than in Patients Receiving Placebo plus Standard of Care in 3 Controlled SLE Studies

Preferred Term	BENLYSTA 10 mg/kg + Standard of Care (n = 674) %	Placebo + Standard of Care (n = 675) %
Nausea	15	12
Diarrhea	12	9
Pyrexia	10	8
Nasopharyngitis	9	7
Bronchitis	9	5
Insomnia	7	5
Pain in extremity	6	4
Depression	5	4
Migraine	5	4
Pharyngitis	5	3
Cystitis	4	3
Leukopenia	4	2
Gastroenteritis viral	3	1

Immunogenicity
In Trials 2 and 3, anti-belimumab antibodies were detected in 4 of 563 (0.7%) patients receiving BENLYSTA 10 mg/kg and in 27 of 559 (4.8%) patients receiving BENLYSTA 1 mg/kg. The reported frequency for the group receiving 10 mg/kg may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations. Neutralizing antibodies were detected in 3 patients receiving BENLYSTA 1 mg/kg. Three patients with anti-belimumab antibodies experienced mild infusion reactions of nausea, erythematous rash, pruritus, eyelid edema, headache, and dyspnea; none of the reactions was life-threatening. The clinical relevance of the presence of anti-belimumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to belimumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to belimumab with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS
Formal drug interaction studies have not been performed with BENLYSTA. In clinical trials of patients with SLE, BENLYSTA was administered concomitantly with other drugs, including corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including azathioprine, methotrexate, and mycophenolate), angiotensin pathway antihypertensives, HMG-CoA reductase inhibitors (statins), and NSAIDs without evidence of a clinically meaningful effect of these concomitant medications on belimumab pharmacokinetics. The effect of belimumab on the pharmacokinetics of other drugs has not been evaluated [see *Pharmacokinetics*].

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. There are no adequate and well-controlled clinical studies using BENLYSTA in pregnant women. Immunoglobulin G (IgG) antibodies, including BENLYSTA, can cross the placenta. Because animal reproduction studies are not always predictive of human response, BENLYSTA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Women of childbearing potential should use adequate contraception during treatment with BENLYSTA and for at least 4 months after the final treatment.

Nonclinical reproductive studies have been performed in pregnant cynomolgus monkeys receiving belimumab at doses of 0, 5 and 150 mg/kg by intravenous infusion (the high dose was approximately 9 times the anticipated maximum human exposure) every 2 weeks from gestation day 20 to 150. Belimumab was shown to cross the placenta. Belimumab was not associated with direct or indirect teratogenicity under the conditions tested. Fetal deaths were observed in 14%, 24% and 15% of pregnant females in the 0, 5 and 150 mg/kg groups, respectively. Infant deaths occurred with an incidence of 0%, 8% and 5%. The cause of fetal and infant deaths is not known. The relevance of these findings to humans is not known. Other treatment-related findings were limited to the expected reversible reduction of B cells in both dams and infants and reversible reduction of IgM in infant monkeys. B-cell numbers recovered after the cessation of belimumab treatment by about 1 year post-partum in adult monkeys and by 3 months of age in infant monkeys. IgM levels in infants exposed to belimumab in utero recovered by 6 months of age.

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to BENLYSTA, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-681-6296.

Nursing Mothers
It is not known whether BENLYSTA is excreted in human milk or absorbed systemically after ingestion. However, belimumab was excreted into the milk of cynomolgus monkeys. Because maternal antibodies are excreted in human breast milk, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of breastfeeding to the infant and the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of BENLYSTA have not been established in children.

Geriatric Use
Clinical studies of BENLYSTA did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Use with caution in elderly patients.

Race
In Trial 2 and Trial 3, response rates for the primary endpoint were lower for black subjects in the BENLYSTA group relative to black subjects in the placebo group [see *Clinical Studies*]. Use with caution in black/African-American patients.

OVERDOSAGE
There is no clinical experience with overdosage of BENLYSTA. Two doses of up to 20 mg/kg have been given by intravenous infusion to humans with no increase in incidence or severity of adverse reactions compared with doses of 1, 4, or 10 mg/kg.

PATIENT COUNSELING INFORMATION
See Medication Guide.

Advice for the Patient
Patients should be given the Medication Guide for BENLYSTA and provided an opportunity to read it prior to each treatment session. It is important that the patient's overall health be assessed at each infusion visit and any questions resulting from the patient's reading of the Medication Guide be discussed.

Mortality: Patients should be advised that more patients receiving BENLYSTA in the main clinical trials died than did patients receiving placebo treatment [see *Warnings and Precautions*].

Serious Infections: Patients should be advised that BENLYSTA may decrease their ability to fight infections. Patients should be asked if they have a history of chronic infections and if they are currently on any therapy for an infection [see *Warnings and Precautions*]. Patients should be instructed to tell their healthcare provider if they develop signs or symptoms of an infection.

Hypersensitivity/Anaphylactic and Infusion Reactions: Educate patients on the signs and symptoms of anaphylaxis, including wheezing, difficulty breathing, peri-oral or lingual edema, and rash. Patients should be instructed to immediately tell their healthcare provider if they experience symptoms of an allergic reaction during or after the administration of BENLYSTA [see *Warnings and Precautions*].

Depression: Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or other mood changes. [see *Warnings and Precautions*].

Immunizations: Patients should be informed that they should not receive live vaccines while taking BENLYSTA. Response to vaccinations could be impaired by BENLYSTA [see *Warnings and Precautions*].

Pregnancy and Nursing Mothers: Patients should be informed that BENLYSTA has not been studied in pregnant women or nursing mothers so the effects of BENLYSTA on pregnant women or nursing infants are not known. Patients should be instructed to tell their healthcare provider if they are pregnant, become pregnant, or are thinking about becoming pregnant [see *Use in Specific Populations*]. Patients should be instructed to tell their healthcare provider if they plan to breastfeed their infant [see *Use in Specific Populations*].

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