

Lupus Patient Subgroups Benefit From Rituximab

BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – Rituximab has a place in the treatment of certain subsets of patients with lupus, but generally the biologic agent has proved disappointing for this disease, according to Dr. R. John Looney.

The chimeric monoclonal antibody against the protein CD20 has worked very well in certain autoimmune diseases, and it is approved for a number of indications including refractory rheumatoid arthritis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

Rituximab is commonly used in relapsing and remitting multiple sclerosis, and early trial data suggest that the agent may have promise in the management of type 1 diabetes, said Dr. Looney, a professor of medicine at the University of Rochester (N.Y.).

In the “amazingly negative” EXPLORER (A Study to Evaluate the Efficacy and Safety of Rituximab in Patients With Severe Systemic Lupus Erythematosus) trial, however, overall clinical response rates did not differ significantly in rituximab- and placebo-treated nonrenal lupus patients (Arthritis Rheum. 2010;62:222-33).

And in the LUNAR (A Study to Evaluate the Efficacy and Safety of Rituximab in Subjects With ISN/RPS Class III or IV Lupus Nephritis) trial, patients with lupus nephritis who were treated with rituximab had a modest improvement in proteinuria, compared with those who received placebo, but only a small, non-statistically significant improvement in overall renal outcomes of about 11%, compared with those who received placebo, according to data re-

ported at conferences, including the annual conference of the American College of Rheumatology in 2009, Dr. Looney said.

“So rituximab has been a remarkably effective drug in certain types of autoimmune disease, but it has been a relative failure in lupus,” he added.

An exception is in patients with antibodies associated with neuromyelitis optica, he said.

Neuromyelitis optica (NMO), which can also present as a primary disease, is remarkably responsive to rituximab, and there is a subset of lupus patients who have the NMO IgG/aquaporin-4 antibody that is associated with the disease, he said.

“If you’re looking at a patient with lupus who develops optic neuritis or if they develop transverse myelitis, you have to think about whether they are in a subgroup with these NMO antibodies,” he said, noting that these patients will tend to have longitudinally extensive transverse myelitis that extends over three vertebral bodies, and they will tend to be positive for aquaporin-4.

“In this subgroup, we have moved to using rituximab early in the course of disease if [these patients] have been very refractory to other treatments,” he said.

Dr. Looney said he also continues to use rituximab in severe refractory systemic lupus erythematosus, particularly in patients with central nervous system disease or lupus nephritis, as well as in patients with refractory idiopathic thrombocytopenic purpura (ITP).

Although rituximab is not approved for ITP, it is widely used as a secondary therapy for this condition, he said.

Dr. Looney disclosed that he has been an advisor for Genentech. ■

Bosentan May Reduce Skin Fibrosis in Scleroderma

BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – Bosentan, which has been shown to prevent digital ulcers in systemic sclerosis, also may have beneficial effects on skin fibrosis.

In a small, prospective, open-label study, treatment with the dual endothelin receptor antagonist was associated with a significant reduction in skin thickening as measured by the modified Rodnan skin score (mRSS), according to Dr. Annegret Kuhn.

The mean change from baseline in the mRSS in the 10 systemic sclerosis patients in the study was 6.4 points on the 0-51 point scale, said Dr. Kuhn of Westfälische Wilhelms-Universität Münster (Germany).

Significant responses were seen in patients with both diffuse and limited disease, and there also was significant healing of digital ulcers. No differences were seen from baseline and week 24, however, on 20-MHz ultrasound, fist-closure evaluation, U.K. systemic sclerosis functional score, or the modified sclerosis health assessment questionnaire (SHAQ) and its visual analogue scale (Rheumatology [Oxford] 2010;49:1336-45).

Patients were treated with 62.5 mg of bosentan twice daily for 4 weeks, then with 125 mg twice daily for 20 weeks. This regimen is similar to the dosing used in the RAPIDS-1 and -2 (Randomized Placebo-Controlled Study on Prevention of Ischemic Digital Ulcers in Systemic Scleroderma-1 and -2) trials, which demonstrated the drug’s efficacy

for the prevention of digital ulcers. Bosentan is currently approved for use in the United States for pulmonary artery hypertension, and – based on the RAPIDS-1 trial (Arthritis Rheum. 2004;50:3985-93) – it was also approved in Europe in 2007 for prevention of digital ulcers.

The RAPIDS-2 trial that was published this year (Ann. Rheum. Dis. 2011;70:32-8), included treatment for at least 24 weeks, and confirmed the preventive effects seen in RAPIDS-1. Bosentan was not found in either trial to be associated

with improved healing in existing ulcers, however.

“Iloprost remains the best treatment for digital ulcers in systemic scleroderma,” Dr. Kuhn said,

But bosentan is recommended for prevention, and it may also improve fibrosis,

she noted.

Guidelines that were developed this year by a group of German experts on scleroderma call for first-line treatment with iloprost for the healing of existing ulcers, with repeated infusions for long-term care. They also call for the use of bosentan for prevention, and note that current experimental treatments include sildenafil and atorvastatin, she said.

Treatment of underlying disease (such as Raynaud’s phenomenon, vasculopathy, and the like) is also important, as are general preventive measures including nicotine abstinence, cold protection, physical treatments, lymphatic draining, elimination of sympathomimetics, and vasoconstrictors.

Dr. Kuhn had no financial disclosures to report. ■

Patients treated with bosentan in an open-label trial had significant reductions in skin thickening on the modified Rodnan skin score.

Patient Subgroup Response to Belimumab Remains Unclear

BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – For now, the lupus patients most likely to respond to recently approved belimumab may be those with moderate to severe disease without renal or central nervous system involvement who have failed to respond to standard therapy, according to Dr. R. John Looney.

More specific details on which patients are most likely to benefit will require further experience with the drug, he said at the meeting.

Belimumab (Benlysta), which was approved in March, is the first new drug for systemic lupus erythematosus (SLE) in 50 years. It has a very good safety profile, although the effect size, while statistically significant, is relatively small, with an average difference in response rate of only about 12 percentage points between

treatment and placebo groups in trials. Belimumab is a fully human monoclonal antibody that inhibits B-lymphocyte stimulator, said Dr. Looney, professor of medicine at the University of Rochester (N.Y.).

Still, that reflects improvement of about 25%-30%, he noted.

The standard dosage is 10 mg/kg, given intravenously every 2 weeks for three times, then every 4 weeks, in addition to standard care.

Keep in mind that the onset is somewhat slow, so this “may not be a drug you would use in a flaring patient,” Dr. Looney said. In addition, it has not been studied in severe renal or central nervous system disease, or in combination with cyclophosphamide, he noted.

Furthermore, no particular subgroup has yet been identified in whom the drug has particular benefits, so it is a bit of a challenge to determine which pa-

tients should be put on this drug.

“I would consider it in patients with moderate to severe, nonrenal, nonneurologic disease who have failed standard therapy,” Dr. Looney said, explaining that he would consider those to be patients with continued disease activity or patients in whom steroids can’t be tapered or stopped despite treatment.

“So I look at this as a drug that might help me get my patients who are on hydroxychloroquine and let’s say CellCept [mycophenolate] or Imuran [azathioprine], down to a manageable dose of steroids,” he added.

Determining how long to treat, however, is a challenge.

“We have no good way to look at an individual patient and say they are better and they are better because they are on belimumab,” Dr. Looney said, noting that based on belimumab trial data, three out of four patients who were respon-

ders at 1 year would have been responders on placebo, so further study is needed to help guide treatment duration.

“I would also really like to see predictors of response,” he said, noting that such predictors have thus far not been reported.

Further analysis of existing data may be useful for identifying subgroups who will respond best to belimumab. Additional studies in renal and CNS disease would also be useful.

“It may be that you add this drug to current therapies [in renal and CNS patients] and they do that much better,” Dr. Looney said, noting that it would also be useful to look at belimumab treatment in conjunction with cyclophosphamide and rituximab as well “to see what happens when B cells are targeted in two different ways.”

Dr. Looney disclosed that he has been an advisor for Genentech. ■