# Treat Autoimmune Hepatitis Based on History

BY SHARON WORCESTER

EXPERT ANALYSIS FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

CHICAGO – A diagnosis of autoimmune hepatitis does not necessarily mandate therapy.

Rather, a decision about therapy should be based on the natural history of the disease, according to Dr. Bruce Luxon.

Patients for whom treatment is mandatory are those with aspartate aminotransferase (AST) levels greater than 10 times the upper limit of normal, or 5 times the upper limit of normal plus gamma globulin levels greater than twice the upper limit of normal. Data from the 1970s showed that patients with these disease characteristics had a 6-month mortality of 60%, said Dr. Luxon, professor and chair of the department of internal medicine at Georgetown University, Washington.

**While a failure to normalize liver enzymes suggests residual disease, about half of those who do have normalization will still go on to have significant liver fibrosis and inflammation.**

Similarly, treatment is needed when a biopsy shows "bridging" – or multilobular – necrosis, as studies have shown that progression to cirrhosis occurs in more than 80% of such patients, and 5-year mortality is about 45%.

"In contrast, there is a group of patients whose AST and [alanine transaminase (ALT)] were quite normal or very close to normal [less than twice the normal value]. Those people had a 10-year life expectancy greater than 80%," he said, noting that these patients generally don't require treatment.

Cirrhotic patients with significant inflammation, on the other hand, might benefit from a 3 to 6-month trial of therapy to slow down progression, he said adding: "That's really a decision for a hepatologist to make."

In those who will be treated, prednisone remains the mainstay of therapy, as it has for 50 years, he noted.

It is given initially at a high dose of 60 mg for the first week (or 30 mg plus 50 mg of azathioprine, which is usually given to allow lowering of the prednisone dose). Prednisone is lowered to 40 mg for week 2 (or 20 mg and 50 mg of prednisone and azathioprine, respectively), and to 30 mg for weeks 3 and 4 (or 15 mg and 50 mg of prednisone and azathioprine, respectively).

After week 4, the dose remains 20 mg (or 10 mg and 50 mg of prednisone and azathioprine, respectively) until the clinical end point is reached.

Use of the combination therapy is associated with a much lower occurrence of corticosteroid-related side effects (10% vs. 44%), but not all patients can tolerate the azathioprine. It is fine to give prednisone monotherapy in such patients, he said.

The typical side effects of steroid therapy can occur, including weight gain, unwanted hair growth, acne, and – importantly – bone disease.

"You really want to make sure they are on calcium and vitamin D," he said, noting bisphosphonates, rather than controversial estrogen replacement, are usually prescribed as well.

Azathioprine side effects can include gastrointestinal upset, drug-induced hepatitis in rare cases, and cancer in very rare cases.

The efficacy of treatment should be evaluated on a biochemical or histological basis. But keep in mind that while a failure to normalize liver enzymes suggests residual disease, about half of those who do have normalization will still go on to have significant liver fibrosis and inflammation on biopsy. "So it's not sufficient to just normalize transaminases," he said.

Since biopsy improvement lags behind biochemical improvement by about 6 months, a repeat biopsy at that time is warranted. These serial biopsies, which are important in this disease, can also predict whether a patient can be taken off therapy, he said.

Patients with a normal liver biopsy at follow-up will have only about a 15%-20% risk of relapse, so it is reasonable to take them off treatment, he noted.

Conversely, those with interface hepatitis and inflammation on follow-up biopsy will relapse about 90% of the time and require ongoing treatment.

In most cases, autoimmune hepatitis can be controlled, although ongoing treatment might be required. About 65% of patients will remit within 18 months, while only about 10% of patients will fail treatment altogether – and those patients typically have other contributing factors, such as excessive alcohol use, concurrent viral infection such as hepatitis B or C, or an overlap syndrome.

Another 10% of patients won't tolerate treatment.

Among those who require treatment indefinitely due to relapse, maintenance therapy with 7.5 mg/day of prednisone and 2 mg per kg/day of azathioprine can be effective for maintaining control. In one study, 85% of patients who relapsed were managed effectively with this strategy at a mean follow-up of 149 months, Dr. Luxon noted.

These patients generally have survival similar to age- and gender-matched controls, so although they have to stay on these low doses of treatment for life, the treatment is quite effective.

In those who fail therapy, it might be useful to increase prednisone to 60 mg/day and azathioprine to 150 mg/day. If there is still no response, it is worth trying mycophenolate mofetil or a calcineurin inhibitor such as tacrolimus, although these have only been assessed in small pilot studies and haven't proved very successful, he said.

Dr. Luxon had no relevant disclosures to report. ■

# SLE: Belimumab Safety, Efficacy Sustained Over 6 Years

BY DIANA MAHONEY

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

LONDON – Belimumab therapy in patients with active systemic lupus erythematosus was well tolerated and associated with sustained disease improvement over 6 years, judging from the findings of a continuation study of a phase II randomized controlled trial.

Hyped regularly as the first new drug approved for the treatment of systemic lupus erythematosus (SLE) in 50 years, belimumab has been shown to reduce disease activity and flares in serologically active patients when combined with standard therapy versus placebo, said Dr. Michelle A. Petri, director of the lupus center at Johns Hopkins University, Baltimore. Belimumab inhibits B-lymphocyte stimulator. Among the "unanswered questions" about the recently approved monoclonal antibody, however, are the durability of the disease improvement and the drug's safety over time, she said.

To examine long-term safety and efficacy of the drug, Dr. Petri and her colleagues conducted a follow-up study of patients who participated in a 1-year phase II randomized controlled trial (Arthritis Rheum. 2009;61:1168-78) and who continued treatment for up to 6 years. After the randomized phase of the trial, all of the patients entered the open-label extension phase of the trial during which they were continued on one of three belimumab (Benlysta) doses – 1 mg/kg, 4 mg/kg, or 10 mg/kg. At study week 80, a total of 296 of the patients entered the continuation phase during which they all received 10-mg/kg doses of the drug, Dr. Petri explained. As of July 2010, a total of 200 patients remained in the study, she said.

**VITALS**

**Major Finding:** The rate of severe disease flares in seropositive patients treated with belimumab decreased from 17% at year 1 to 5% at year 6 with no increase in the adverse event rate during that period.

**Data Source:** An open-label continuation study of a phase II randomized controlled trial of belimumab in patients with serologically active systemic lupus erythematosus to assess safety and efficacy at 6 years.

**Disclosures:** Dr. Petri disclosed receiving research support and consultancy fees for Human Genome Sciences/GlaxoSmithKline.

Focusing specifically on the subset of seropositive SLE patients (positive for antineutrophil antibody or positive for anti–double-stranded DNA ) in whom the B-cell–directed therapy is considered to be most effective, the investigators measured disease activity using the SLE Flare Index (SFI), the British Isles Lupus Assessment Group (BILAG) 1A/2B flares, the SLE Responder Index (SRI), and biomarkers (complement and autoantibodies), and assessed adverse events at each study visit, Dr. Petri said. "Over 6 years, patient response rates improved, the frequency of new flares decreased significantly, and the rate of adverse events remained stable or declined, compared to year 1," she said.

The SRI rate increased from 46% at year 1 to 55%-61% through year 6; the frequency of 1 new BILAG A or 2 new B flares decreased from 35% at 1 year to 11% at year 6; and the frequency of SFI flares decreased from 76% at 1 year to 42% at year 6, Dr. Petri said. Additionally, the rate of severe flares, which was 17% at year 1, decreased to 5% at year 6. "Patients had to be really sick to get into this study in the first place, so to see the severe flares disappear to that degree is really clinically important," she said.

The proportion of patients with increased complement 3 or 4 and decreased anti-Sm, anti–double-stranded DNA, and anticardiolipin antibodies increased over time, suggesting a sustained or improved therapeutic response, Dr. Petri said. Concomitant corticosteroid use decreased by a mean of 34% from baseline, with an absolute reduction of 4.7 mg/day at year 6, over baseline.

Belimumab is not indicated as a standalone, first-line therapy but rather as an adjunct therapy in patients who have not responded to the standard of care, "especially in whom there is evidence that B cells are driving disease activity, such as anti-DNA or low complement," she said.

Despite some study design flaws, the safety and tolerability data suggest that, in "the appropriately targeted SLE population, belimumab has the potential to be a widely used, steroid-sparing background therapy."

Yet to be addressed "meaningfully" in clinical trials are the safety and efficacy of belimumab in black patients, as well as the drug's effects on patients with lupus nephritis or central nervous system involvement – both of which were excluded from this and the pivotal trials that led to FDA approval of the drug – as well as pediatric and pregnant patients, Dr. Petri said in an interview. ■