Belimumab May Be First Biologic Okayed for SLE

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ROME — What a difference a year makes.

At last year's rain-drenched EULAR gathering in Copenhagen, earlier optimism regarding the prospects for biologic therapies for systemic lupus erythematosus gave way to a pervasive pessimism. Highly encouraging studies had been followed by a rash of negative major clinical trials, which dashed many observers' hopes that biologics would have a clinically meaningful impact in SLE. But that was then.

"It's a year later now. The sun has been shining every day in Rome, and I can tell you that there are now a lot of reasons to think biologics are going to make a real difference in the treatment of lupus," Dr. Ronald van Vollenhoven said. Clearly, the most exciting recent development is that the anti–B cell cytokine agent belimumab (Benlysta) achieved its primary end points in two separate, exceptionally large phase III clinical trials.

"Safety was excellent in those trials; that's really a great component of the story. So I think belimumab is very likely to become the first registered biologic for SLE," predicted Dr. van Vollenhoven, senior physician in the department of rheumatology and chief of the clinical trials unit of the Karolinska Institute, Stockholm.

If so, belimumab would also be the first new therapy of any sort approved for SLE in more than 40 years.

Dr. van Vollenhoven, who was on the steering committees of both the BLISS-76 (Belimumab in Subjects With Systemic Lupus Erythematosus–76) and BLISS-52 trials, characterized the demonstrated treatment effect of the anti–B cell cytokine agent as "modest." But he noted that there is a caveat.

"If the effect size isn't so big, how relevant is the treatment clinically? It's a reasonable question. I think the modest effect size is a function of the primitive outcome measures we have for SLE. The [problem with the lupus trials has been]—and still is—that our instruments aren't very good," the rheumatologist said. "I think we're picking up a signal and the signal is weak, but it's not because the true effect is weak. It's just because our instruments are blunt. The true effect is probably much better than we think."

Atacicept, another anti–B cell cytokine agent, is now in a phase III randomized clinical trial for SLE, he said.

There is further encouraging news. At the Rome congress, Dr. Daniel J. Wallace presented positive results from the phase IIB EMBLEM trial of epratuzumab, a humanized anti-CD22 monoclonal antibody. Unlike rituximab, an anti-CD20 monoclonal antibody that completely obliterates B cells, epratuzumab reduced them by about half in the study.

The EMBLEM trial was a 12-week, multicenter, double-blind, randomized study involving 227 patients with moderate to severe SLE who were already on standard therapy. The key finding was that patients who received a cumulative intravenous dose of 2,400 mg of epratuzumab—either as 600 mg weekly (37 people) or 1,200 mg every other week (37 people)—had a responder rate twice that of controls on placebo (38 people).

Early data from the EMBLEM trial show that epratuzumab halved, rather than eliminated, B cell numbers.

DR. WALLACE

EMBLEM's responder rate index end point was a novel composite outcome measure that was aimed at overcoming the sort of limitations Dr. van Vollenhoven cited. It's defined as a reduction of all baseline BILAG grade A disease to grade B-D, and BILAG grade B to grade C or D, in all body systems; no BILAG worsening in other organ systems; no deterioration in SLEDAI or physicians' global disease activity assessments; and no increase in corticosteroids and/or immunosuppressive agents over baseline levels. Overall, the responder rate index was 43.2 for the 74 patients on a total of 2,400 mg of epratuzumab vs. 21.1 for those on placebo. Especially impressive were the epratuzumab-induced reductions in neuropsychiatric and cardiorespiratory symptoms of SLE, which are often particularly resistant to conventional therapies, observed Dr. Wallace of the University of California, Los Angeles.

"This is a very encouraging result from a relatively small first trial that needs to be confirmed," Dr. van Vollenhoven said. "The size of the treatment effect is pretty impressive. There was a strong positive effect for a total dose of 2,400 mg, but 3,600 mg was not effective. That's a little bit strange. I can't quite put my head around that."

Dr. van Vollenhoven offered the following updates on the status of other major classes of biologic agents in terms of their prospects as SLE therapies:

▶ **Anti–interferon-alpha.** High serum levels of interferon-alpha are present in SLE. It is produced by plasmacytoid dendritic cells in response to stimulation by immune complexes. Several companies currently have anti–interferon-alpha agents in clinical trials for SLE. The key issue will be safety: Interferon-alpha plays key roles in viral immunity and tumor defenses, Dr. van Vollenhoven noted.

▶ **Anti–interleukin-6.** Tocilizumab (RoActemra) achieved improvements in SLEDAI and arthritis in a recent National Institutes of Health phase I study in 16 SLE patients (Arthritis Rheum. 2010;62:542-52). Neutropenia was a frequent limiting side effect. Additional interleukin-6 and interleukin-6 receptor antagonists are in early clinical trials.

▶ **Rituximab.** Early, uncontrolled studies were "exciting and encouraging," recalled Dr. van Vollenhoven, who led several of them. Then came the failed phase III, randomized, double-blind, controlled EXPLORER and LUNAR trials, which contributed prominently to the glum global prospects for biologic therapy of a year ago. EXPLORER established that rituximab (Rituxan) is unlikely to be of benefit in nonrenal lupus. Many rheumatologists have concluded that LUNAR showed the same for lupus nephritis, but Dr. van Vollenhoven, who was on the trial's steering committee, remains unconvinced. In as-yet-unpublished data, he has shown that rituximab works quite slowly in lupus nephritis, with about one-half of treated patients showing a partial response after 1 year, and complete responses being seen only after about 2 years. LUNAR, he noted, was a 1-year trial, so it didn't capture the late responses. "It could be that rituximab doesn't work in lupus nephritis. But I'll reserve my judgment because I've seen such good responses that it still seems to me to be a pretty good option," he said. ■

Disclosures: *Dr. van Vollenhoven serves as a consultant to GlaxoSmithKline and Human Genome Sciences, which are developing belimumab, and he has received research grants from most of the other companies which make biologics for rheumatologic diseases. Dr. Wallace is a consultant to UCB, which is developing epratuzumab and funded the EMBLEM trial.*

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romyelitis optica, Dr. Birnbaum said at the meeting.

High-dose IV methylprednisolone is used to treat both forms of myelitis. Following that, patients at Hopkins are placed on steroid-sparing immunosuppressive regimens, which may include azathioprine, mycophenolate mofetil, or rituximab.

Both forms of SLE myelitis are unlike myelitis that is seen in multiple sclerosis (MS) patients, which tends to be transverse and does not cause the rapid devastation that is seen in gray matter myelitis.

Currently, however, myelitis in SLE and MS patients is often lumped together under the rubric of "lupoid sclerosis," Dr. Birnbaum said.

That's a mistake, he said.

"Under no circumstances should any of these patients be exposed to the armamentarium used to treat MS. Lupoid sclerosis does not exist for these SLE patients," he said.

Interferon, a mainstay of MS treatment, "causes flares and can lead to catastrophic worsening of SLE and SLE CNS disease," Dr. Birnbaum said.

The findings are based on a record review of 22 SLE patients who presented with myelitis to the lupus center or transverse myelitis center at Hopkins in 1994-2007.

Dr. Birnbaum and his colleagues recognized the syndromes through an analysis of histories, physical exams, lab values, follow-up care, and MRIs.

If gray matter myelitis—and how to treat it—was more widely recognized, 'hundreds of young women would be saved from permanent paralysis.'

The team discovered that 11 patients had gray matter myelitis, and 11 had white matter myelitis. There were no statistically significant differences between the two groups with regard to age, gender, or ethnicity. Most were women.

Of the 11 patients with gray matter myelitis, 10 presented for urinary retention. Because of the presence of fevers, "all of these patients were unfortunately and erroneously diagnosed as having urinary tract infections. By the time immunosuppressive treatment was initiated, there had likely already been irreversible injury," according to the study report.

Patients with gray matter myelitis, compared with those with white matter myelitis, had higher median white blood cell counts (385.5 cells/mL vs. 10 cells/mL; *P* less than .01); higher median neutrophilic pleocytosis (71% neutrophilia vs. 15% neutrophilia; *P* less than .08); higher median total protein levels (254 mg/dL vs. 57 mg/dL; *P* less than .01); and lower central spinal fluid glucose levels (33 mg/dL vs. 54 mg/dL; *P* less than .02), according to the study report.

Cerebrospinal fluid profiles in gray matter myelitis were indistinguishable from CSF profiles in bacterial meningitis, although none of the patients had meningeal signs or positive bacterial, viral, or fungal cultures.

If obtaining an MRI is not feasible, Dr. Birnbaum said, "the spinal tap can support evidence of gray matter myelitis."

He added that in cases in which the differential includes both meningitis and myelitis, concomitant administration of corticosteroids and antibiotics is appropriate. Both are commonly administered for worsening TB meningitis in order to simultaneously eliminate the infection and quiet the cytokine storm it produces.

In all, 12 MRIs were available for patients with gray matter myelitis, and 23 for patients with white matter myelitis.

Cord swelling was seen in 91.7% (11) of the gray matter MRIs and in 21.7% (5) of the white matter images; postgadolinium enhancement was seen in 25% (3) of the gray matter MRIs and in 42.9% (10) of white matter images. ■