SLE Drug Pipeline: An Embarrassment of Riches

BY BRUCE JANCIN
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SNOWMASS, COLO. — The drug pipeline is suddenly chock-full of biologic agents, good news for rheumatologists, who have been waiting more than 3 decades since the last approval of a new therapy for SLE. Some of these agents have completed promising phase II clinical trials and are well along in phase III.

"For many years, I would give talks on the latest developments in mouse models and speculate about what might happen in patients. Today, I can talk about real clinical data on a new generation of biologic therapies for lupus," Dr. David Wofsy marvelled at a symposium sponsored by the American College of Rheumatology.

He offered up what he emphasized were personal and highly opinionated "shoot from the hip" predictions as to the first-generation biologic induction therapies for lupus most likely to emerge from the pack: the anti-CD20 agent ocrelizumab, abatacept (Orencia), and—as a long shot—an anti–tumor necrosis factor agent such as etanercept.

"I think the best chance for a new major step forward in induction therapy lies in these three agents," said Dr. Wofsy, the George A. Zimmermann Distinguished Professor of Rheumatology and director of the clinical trials center at the University of California, San Francisco.

As for his predictions regarding likely first-generation biologic maintenance therapies, he named the anti–B-lymphocyte stimulator (anti-BlyS) agent belimumab (LymphoStat-B), atacicept, and abetimus sodium (Riquent), formerly known as LJP 394, as the top candidates.

B cells make a compelling target for therapeutic research because of the multiple mechanisms by which they are believed to contribute to SLE: presentation of antigen, regulation of T-cell activation, differentiation into antibody-producing plasma cells, and stimulation of proinflammatory cytokines.

Furthest along in development are the anti-CD20 monoclonal antibodies. And of these, the one surrounded by the most buzz is rituximab (Rituxan), already approved for rheumatoid arthritis. An audience show of hands indicated most have used rituximab in lupus patients—and most believed it worked.

"It's a very widespread belief in our community that rituximab is effective in lupus. I have to warn you to be careful about that. We got the big surprise from the CellCept trial. The literature on anti-CD20 is pretty lean at this point," said Dr. Wofsy, who is also a former ACR president. "My hope mirrors yours, but I'm very cautious in this area because we continue to get disappointing surprises."

Indeed, while 34 of 35 rituximab-treated lupus patients reported in the literature responded with peripheral B-cell depletion, 4 of them experienced sustained depletion for longer than 12 months. That raises safety concerns. And human antichimeric antibody production has been a problem.

Rituximab's role in treating SLE should be clarified within the year, upon completion of two ongoing phase III trials: Explorer in patients with active nonrenal lupus, and Lunar in lupus nephritis patients.

Ocrelizumab is a second-generation anti-CD20 agent in ongoing clinical trials. As a humanized monoclonal antibody, it is likely to have fewer safety issues.

Another focus of research into lupus therapy is abatacept: This agent prevents costimulation of T cells, and it appears to have synergistic efficacy when combined with a brief course of cyclophosphamide. "In the mouse models of lupus, nothing compares to this," said Dr. Wofsy, who did the original animal studies.

Current or upcoming clinical trials include Bristol-Myers Squibb Co.–sponsored studies of abatacept in SLE patients without nephritis and abatacept plus mycophenolate mofetil in lupus nephritis, as well as an NIH-sponsored study of abatacept plus short-course cyclophosphamide vs. cyclophosphamide alone for lupus nephritis to be conducted by Dr. Wofsy and coworkers.

"It will take a while longer to know about abatacept, but I think the strong preclinical data and its effectiveness in rheumatoid arthritis gives us some hope," he said.

Preliminary data on research with anti–tumor necrosis factor–α therapy suggest TNF's inflammatory effect in the kidney might be an important mediator in lupus renal flares. A trial of infliximab as short-duration induction therapy is underway in Europe. Dr. Wofsy and colleagues are about to start a clinical trial with etanercept.

"Until those trials are in, I would discourage anybody from doing it, but there are some anecdotes that have at least opened our eyes to the possibility," the rheumatologist continued.

Riquent was developed solely as a relatively safe therapy for the purpose of maintaining remission. This novel agent binds specifically to B cells that make anti-DNA antibodies, tolerizing them and causing selective B-cell anergy and death. The appeal of Riquent lies in its power to reduce autoantibodies without global immune suppression.

A 230-patient phase II trial proved negative. However, La Jolla Pharmaceutical Co. saw positive signals in the data and has completed enrollment in a phase III trial involving more than 700 lupus nephritis patients with high-affinity anti-DNA antibodies who were in remission at baseline. The primary end point is time to renal flare.

Belimumab was found to have no effect on time to flare or SLE Disease Activity Index in a randomized trial involving 449 patients with mild to moderate active SLE. In response, sponsor Human Genome Sciences Inc. created a novel combined end point, applied it retroactively, and declared the study a success. The new combined primary end point is being used in two ongoing phase III trials of the anti-BlyS agent, each double the size of the earlier one.

The new end point consists of at least a 4-point improvement on the SLE Disease Activity Index, no new 1A/2B British Isles Lupus Assessment Group domain scores, and no worsening in Physician Global Assessment.

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DR. WOFSY

While Dr. Wofsy said the company's persistence is laudable, he was highly critical of the new combined end point, as well as the fact that the earlier negative trial has never been published, although it was first presented in 2005.

"This trial has been subjected to spin unlike any other trial I've ever seen," he said. "I think this novel end point is a disservice to the community. It doesn't translate into anything meaningful to anybody who takes care of lupus patients." He added that if the phase III trials prove positive, "that may be a business triumph but it won't be a scientific breakthrough."

"In the end, if you can't make lupus nephritis better with these risky immunosuppressive drugs, you probably don't have a drug," Dr. Wofsy asserted.

Like belimumab, atacicept blocks the BlyS pathway. But atacicept also blocks the APRIL (a proliferation-inducing ligand) pathway, thereby more effectively blocking signals to B cells. B-cell levels in treated patients fall by about 50%, as with belimumab, but atacicept-treated patients also show a 50% reduction in IgM and 20% decrease in IgG.

"But if atacicept is more effective, it may also be more toxic. Only time and more studies will tell. There's an array of B-cell therapies out there that are under investigation, and no one can tell you which one is going to be best," Dr. Wofsy said.

Both atacicept and belimumab are agents that are more likely to sustain a remission than induce it, in his view.

Other potential biologic therapies in lupus include anti-CD3, -4, or -22, anti-B7, anti-C5, anti-interleukin-10, and agents directed at the interleukin-6 receptor. Stem cell transplantation is also under investigation.

Dr. Wofsy serves as a consultant to Serono and Zymo-Genetics and is organizing the phase II-III clinical trials of atacicept for SLE. He is also a consultant to Bristol-Myers Squibb regarding abatacept, and to Genentech/Biogen Idec/Roche regarding rituximab and ocrelizumab. ■

Minipulse Cyclophosphamide Favored in Lupus Nephritis

BY BRUCE JANCIN
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SNOWMASS, COLO. — Most American physicians who treat systemic lupus erythematosus have been overly slow to adopt the low-dose, less toxic minipulse intravenous cyclophosphamide regimen pioneered in the landmark Euro-Lupus Nephritis Trial, Dr. David Wofsy said at a symposium sponsored by the American College of Rheumatology.

"I think we should move away from traditional, [National Institutes of Health]–style cyclophosphamide. If you're going to use cyclophosphamide, I would favor using [the Euro-Lupus Nephritis Trial cyclophosphamide regimen] at this point without hesitation," said Dr. Wofsy, professor of medicine at the University of California, San Francisco, and a former ACR president.

For many years, the standard therapy for lupus nephritis has been the high-dose pulse intravenous cyclophosphamide (Cytoxan) regimen that has shown to be effective in an NIH trial. This regimen typically involves dosing monthly for 6 months at 0.5-1.0 g/m^2, followed by two pulses at 3-month intervals, then maintenance therapy with azathioprine. It's a highly toxic regimen associated with increased infections, leukopenia, cancer, infertility, alopecia, and cystitis.

In the ELNT, investigators led by Dr. Frederic A. Houssiau of Catholic University of Louvain, Brussels, demonstrated that a more modest cyclophosphamide regimen can achieve the same efficacy with fewer adverse effects (Arthritis Rheum. 2004;50:3934-40).

The European minipulse regimen consists of six pulses of 500 mg given at 2-week intervals, followed by azathioprine. Patients tend to be deeply grateful to be done with cyclophosphamide after just 12 weeks.

Some American physicians have criticized the ELNT because its Northern European patient population isn't representative of the lupus patients they see. But, according to Dr. Wofsy, the ELNT is actually a much better trial methodologically than the NIH study upon which high-dose pulse therapy is based. "My own feeling is that it's time to begin using cyclophosphamide in a gentler way. These [ELNT] data support that strongly," he continued.

Patients and physicians alike look longingly at the bursting-full SLE drug development pipeline, eager for the day when they can finally discard cyclophosphamide in favor of agents that are less toxic and/or more effective. But there is reason to believe that cyclophosphamide may continue to play an important role in the coming biologic therapy era.

Preliminary evidence suggests at least two of the investigational biologics—rituximab (Rituxan) and atacicept—may have unique synergistic benefit when used with cyclophosphamide. This synergistic effect isn't present when either biologic is combined with mycophenolate mofetil (CellCept), Dr. Wofsy said. ■