Will a Deluge of New Biologics Change RA Care?

BY BRUCE JANCIN
Denver Bureau

SNOWMASS, COLO. — The many biologic agents for rheumatoid arthritis now in mid- to late-stage development are likely to have little impact on clinical practice unless they are priced substantially lower than those now available, Dr. Mark C. Genovese said at a symposium sponsored by the American College of Rheumatology.

The new agents' potential impact on clinical practice will depend on their cost.

DR. GENOVESE

These agents will enter an increasingly crowded biologics marketplace. Data from the phase II and III clinical trials reported to date provide no evidence that the investigational tumor necrosis factor–α inhibitors and anti-CD20 agents are substantially more effective, safer, better tolerated, or more convenient than the ones physicians prescribe today. And that leaves only one major aspect open to competition: expense, said Dr. Genovese, cochief of the division of immunology and rheumatology at Stanford (Calif.) University.

The UCB drug certolizumab (Cimzia) is expected to be the next anti-TNF agent to receive marketing approval for RA. Next to come will probably be Centocor's golimumab, a fully human monoclonal antibody.

Lots of data have been presented on these two agents, with lots more to come. The ACR 20, ACR 50, and ACR 70 response rates are very good—but not profoundly better than the rates for the current anti-TNF biologics. The same holds for the safety profiles. Golimumab, however, has a potential edge in convenience: It appears to be effective when given every 4 weeks rather than every 2 weeks. A subcutaneous version is also being developed, the rheumatologist noted.

Two agents—the humanized monoclonal antibody ocrelizumab and the fully human monoclonal antibody of atumumab—both deplete peripheral B-cells. Thus far the efficacy appears fairly similar for all three, Dr. Genovese said.

In terms of biologics with novel mechanisms of action, on the horizon is tocilizumab (Actemra), a humanized monoclonal antibody that works in RA by blocking the interleukin-6 receptor. Two of the five phase III studies have been presented, with two more to come this June at EULAR in Paris. Dr. Genovese was principal investigator of the largest—the Tocilizumab in Combination With Traditional DMARD (TOWARD) study—which involved 1,220 patients with moderate-to-severe RA who had an inadequate response to a variety of conventional DMARD therapies. The subjects were randomized in a double-blind fashion to placebo or IV tocilizumab at 8 mg/kg every 4 weeks.

"Tocilizumab offers an incredibly useful approach to reducing inflammation, reducing structural damage, and improving symptoms and signs. The efficacy is as we've come to expect of biologics. It looks like there's lots of flexibility regarding the use of background conventional DMARDs," he commented.

Tocilizumab's impact on clinical practice will depend on the outcome of future studies that will look closer at these safety issues and at how well the biologic works in nonresponders to anti-TNF therap, the application for which most physicians will want to use it first, he said.

Baminercept binds to the lymphotoxin alpha1/beta2 and to LIGHT ligands on activated B and T cells and natural killer cells. In this way it inhibits formation of ectopic lymphoid structures involved in the autoimmune inflammatory cascade. In a 47-patient, short-term, double-blind, placebo-controlled phase II trial sponsored by Biogen Idec, baminercept elicited what Dr. Genovese termed "impressive" responses, with persistent benefits seen 8 weeks after the final dose of the subcutaneously administered, once-monthly biologic.

Belimumab (LymphoStat-B) is a monoclonal antibody that binds to BLyS, a B lymphocyte costimulator of normal and autoimmune B cells.

Dr. Genovese is on the speakers bureaus of Abbott Laboratories, Genentech, Bristol-Myers Squibb Co., Wyeth, and Amgen Inc. He has received research grants from most of those companies as well as Centocor Inc., Biogen Idec, Sereno, and Roche. ■

Durable Responses Seen for Abatacept in RA Patients

BY NANCY WALSH
New York Bureau

BOSTON — The safety and efficacy of abatacept were maintained throughout 5 years of treatment for patients with rheumatoid arthritis, with more than one-third of those who remained in the long-term extension phase of a multicenter trial achieving an ACR 70 response.

The initial double-blind trial enrolled 339 patients with rheumatoid arthritis (RA) who had had an inadequate response to methotrexate, randomizing them to receive 2 mg/kg abatacept, 10 mg/kg abatacept, or placebo for 1 year. They also received background methotrexate in doses of 10-30 mg/week, Dr. Rene R. Westhovens reported in a poster session at the annual meeting of the American College of Rheumatology.

Abatacept was given as a 30-minute infusion on days 1, 15, and 30, and every 30 days thereafter.

By week 52, 63% of patients receiving the higher dose of abatacept had achieved an ACR 20 response, compared with 36% of those receiving placebo. Moreover, 42% and 21% of those receiving 10 mg/kg of the active drug achieved ACR 50 and 70 responses, respectively, compared with 20% and 8% of those receiving placebo (Arthritis Rheum. 2005;52:2263-71).

Of the 235 patients who completed the double-blind phase of the trial, 219 entered the long-term open-label phase, during which all participants received the 10-mg/kg dose of abatacept plus methotrexate. Among these 219 patients, 84, 68, and 67 were from the original 10-mg/kg, 2-mg/kg, and placebo groups, respectively. Their mean age was 56 years, 74% were female, and their mean disease duration was 10 years. At 5 years, 130 (59%) remained on the drug, reported Dr. Westhovens of University Hospital Gasthuisberg Leuven (Belgium).

The improvements in ACR 20, ACR 50, and ACR 70 responses seen in the 10-mg/kg group in the blinded phase of the trial were maintained at year 5, with response rates of 83%, 65%, and 40%.

During the blinded phase, 55% of patients in the 10-mg/kg group had clinically meaningful improvements in physical function, defined as an increase of 0.3 units or more on the modified Health Assessment Questionnaire Disability Index. This was maintained by 53% at year 5.

The types and incidence of serious adverse events were similar in the double-blind and 5-year cumulative study periods, according to Dr. Westhovens. There were 20 serious adverse events per 100 patient-years reported among patients receiving the active treatment during the double-blind phase of the trial, and 19 serious adverse events per 100 patient-years during the open-label phase.

With almost 60% of patients still participating in the study at 5 years, responses remain durable, demonstrating that "abatacept provides long-term clinical benefits to patients with active RA," Dr. Westhovens wrote.

He disclosed that he received consulting fees from Bristol-Myers Squibb Co., the sponsor of the study. ■

Maneuvers, Not Imaging, Can Confirm Sacroiliac Joint Syndrome

BY BRUCE JANCIN
Denver Bureau

SNOWMASS, COLO. — Reserve an anesthetic block to diagnose sacroiliac joint syndrome for those patients having at least three positive pain-provoking tests on physical examination, Dr. Zacharia Isaac urged at a symposium that was sponsored by the American College of Rheumatology.

'The SI joint syndrome truly is a dysfunction syndrome because there really is no imaging test that's going to show you that the SI joint is the pain generator.'

"You can avoid a lot of needless diagnostic injections of the SI joint if you examine the patient using a cohort of provocative exam maneuvers," according to Dr. Isaac, medical director of the comprehensive spine care center at Brigham and Women's Hospital, Boston.

Sacroiliac joint syndrome (SIJS) accounts for around 15% of cases of low back pain, making it the third most common cause after discogenic pain and facet syndrome.

"The SI joint syndrome truly is a dysfunction syndrome because there really is no imaging test that's going to show you that the SI joint is the pain generator. A SPECT [single photon emission computed tomography] scan will not show you a hot SI joint. There will not be a lot of arthritis involving this joint. There will not be a bone scan or any other imaging that will confirm the diagnosis for you. You will not find erosions on MRI. This is not sacroiliitis in any way," the physical and rehabilitation medicine specialist stressed.

SIJS is characterized by low back and buttock pain that can refer to the groin and thigh. Hip findings are unimpressive. If symptoms are present above the level of the L5 transverse process, it's unlikely the SI joint is the cause. The syndrome often arises posttrauma or intra- or postpartum.

Among the pain-provocative maneuvers useful in identifying suitable candidates for the preferred method diagnostic anesthetic block are Patrick's test, in which the heel of one leg is crossed atop the opposite knee and the top knee is pressed down in an attempt to elicit pain in the sacroiliac area. Another is Gaenslen's test: While the supine patient holds one knee and hip flexed into the abdomen, the other leg hangs over the edge of the examining table as the physician presses down on it to hyperextend the hip and produce pain in the SI joint.

Precise reproduction of the pain upon palpation of a particular spot over the sacral sulcus is another useful indicator of SIJS. Other provocative exam maneuvers include standing extension, SI joint compression, and the joint distraction test.

Dr. Isaac emphasized that the diagnostic intra-articular injection of local anesthetic into the SI joint needs to be performed under fluoroscopic guidance. A positive test is one that results in relief of the familiar pain. ■