In Primary Anti-TNF Failure, Switch It Up

BY SALLY KOCH KUBETIN

EXPERT ANALYSIS FROM A RHEUMATOLOGY SEMINAR

SANTA MONICA, CALIF. – Rheumatoid arthritis patients with a true primary failure on a first-time trial of tumor necrosis factor inhibitor therapy should change to treatment with a biologic that has a different mechanism of action. The likelihood is great that trying a second anti-TNF agent will result in just another failure and delay the initiation of effective treatment, according to Dr. Daniel E. Furst.

The key is to be sure that failure to respond to the first anti-TNF agent is not secondary to another cause, such as too low a dose, he said at a meeting sponsored by Skin Disease Education Foundation and the University of Louisville.

An estimated 60%-70% of patients who begin treatment with an anti-TNF agent are still on the agent at the end of 1 year. Although some patients have to stop treatment because of problems with their insurance and other reasons, primary and secondary failure play a role, he said.

One cannot recognize a treatment failure unless one undertakes therapy with a treatment target in mind, usually remission or low disease activity levels. Treating-to-target goals have been shown to improve outcome and to lower rates of organ damage in diabetes and hypertension. Treating to target was the watchword of new treatment guidelines issued jointly earlier this year by the American College of Rheumatology and the European League Against Rheumatism (RHEUMATOLOGY NEWS, October 2010, p. 33). The guidelines were published jointly in the EULAR journal Annals of the Rheumatic Diseases (2010;69:1580-8) and the ACR's Arthritis & Rheumatism (2010;62:2569-81).

Evidence that treating to target in RA is effective dates back to 1998, and this therapeutic approach has become more important in the biologics era of care. The goals of treating to target, as outlined by ACR/EULAR, are to aim for complete remission of low disease activity; to see the patient monthly for at least the first 3-6 months, depending on disease activity; to use a combination of validated response measures; to consider comorbidities; to aim for sustained remission; and to get informed consent.

So how does one tell whether a patient's lack of response to an anti-TNF agent is a true primary failure or is secondary to something else that may be correctable, such as a longer therapeutic trial?

Findings from a secondary analysis of TEMPO (Trial of Etanercept and Methotrexate With Radiographic Patient Outcomes) data show that about half of the patients who had not responded by 12 weeks to treatment with etanercept or methotrexate, either as monotherapy or in combination, were still likely to respond by 24 weeks with either treatment (Ann. Rheum. Dis. 2008;67:1444-7).

"If there is a hint of a response, treat beyond the usual 12 weeks," advised Dr. Furst, who is the Carl M. Pearson Professor of Medicine at the University of California, Los Angeles.

Some patients may need a higher dose of the anti-TNF agent than they have been receiving. A chart review presented by Dr. Furst and colleagues at the 2008 annual meeting of the ACR showed that increasing the adalimumab dose from 40 mg subcutaneously every other week for 5 months to 40 mg every week for 6 months can increase the number of patients with good EULAR responses. Of 48 patients who originally had received 40 mg of adalimumab subcutaneously every other week for 5 months, 20 had good response and 28 achieved moderate or no EULAR responses. An increase in the dose to 40 mg every week for 6 months resulted in a good EULAR response in 8 of 28 nonresponders, which included 4 of 12 patients who originally had no response to the lower-dose adalimumab (Arthritis Rheum. 2008;58[suppl.]:abstract 999).

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A video interview with Dr. Daniel E. Furst is available at www.rheumatologynews.com/.

One can improve treatment response to infliximab by decreasing the interval between doses. But increasing the dose and leaving the interval the same does not have the desired effect. Other data from Dr. Furst's research suggest that in the case of etanercept, increasing dose does not improve efficacy (Arthritis Rheum. 2007;56[suppl.]:abstract 726).

Higher doses of anti-TNF agents are associated with higher rates of nonserious adverse events, especially with adalimumab and infliximab. Data from package inserts show that infliximab has a 5.3% rate of serious adverse events, which is higher than that seen with adalimumab (2%), etanercept (1%), golimumab (1.9%), and certolizumab (3%). Data from the French RATIO registry show that, during 57,711 people-years of biologic use in 2004-2007, there were 69 cases of tuberculosis in patients who took anti-TNF agents for a variety of reasons, including RA. After adjustment for confounding risk factors, the incidence rate for TB in patients on any anti-TNF drug was shown to be 116.7 cases per 100,000 person-years of use (Arthritis Rheum. 2009;60:1884-94).

The bottom line is that not only are anti-TNF agents less effective after a primary failure, but the rate of adverse events increases as well, judging from data reported at the annual meeting of the European League Against Rheumatism in 2008 by Dr. Luba Nalysnyk of United BioSource Corp. Dr. Nalysnyk and associates performed a meta-analysis of 16 articles and 15 abstracts involving 5,306 patients. In the meta-analysis, primary failure of an anti-TNF agent occurred in 48% of patients. A second anti-TNF agent did not work in 66% of those patients, and another 66% of those patients developed adverse events in response to the second agent.

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Biologic Agent Improved Sleep in Ankylosing Spondylitis

BY SHARON WORCESTER

FROM ARTHRITIS CARE AND RESEARCH

The anti–tumor necrosis factor–alpha agent golimumab significantly reduced sleep disturbance and improved health-related quality of life in a randomized placebo-controlled trial of 356 patients with ankylosing spondylitis.

The investigators assessed sleep disturbance using the Jenkins Sleep Evaluation Questionnaire (JSEQ), which asks patients how many times in the past month they have had trouble falling asleep, awakened several times per night, had trouble staying asleep (including waking far too early), and/or awakened after their usual amount of sleep feeling tired and worn out. On the scale, the possible answers for each question were 0 (not at all), 1 (1-3 days), 2 (4-7 days), 3 (8-14 days), 4 (15-21 days), and 5 (22-31 days). Thus, the total JSEQ score ranges from 0 to 20, with higher scores indicating greater sleep disturbance.

Study participants, who had moderate-to-severe sleep disturbance at baseline because of underlying pain associated with AS, were randomized to receive either placebo or treatment with 50 mg or 100 mg of golimumab subcutaneously every 4 weeks.

Most of the study participants were men. Their mean time since AS diagnosis was 11 years for the placebo group and 8 years for each golimumab group. The mean baseline JSEQ score was 10 for the placebo group, 10 for the 50-mg group, and 11 for the 100-mg group.

Compared with those in the placebo group, those in the golimumab groups had significantly greater median improvement from baseline on the 0- to 20-point JSEQ at the 14-week follow-up (–3.0 vs. 0.0 point change), and the improvement was sustained at 24-week follow-up (–3.0 vs. –1.0 point change), Dr. Atul Deodhar, medical director of the rheumatology clinic at the Oregon Health & Science University, Portland, and colleagues reported.

The effect was similar with both the 50- and 100-mg golimumab dose, the investigators noted (Arthritis Care Res. 2010:62:1266-71).

The findings of this study – which is a secondary analysis of the previously reported GO-RAISE study that evaluated golimumab in AS patients – also showed that changes in the JSEQ scores during the course of the study significantly correlated with changes from baseline on Short Form–36 Health Survey summary scores, Bath AS Functional Index scores, Bath AS Disease Activity Index, inflammation assessments, and total and night back-pain scores.

Improvements in the night back-pain scores were the strongest predictor of improvement in sleep disturbance as measured by JSEQ scores.

Golimumab (Simponi) has Food and Drug Administration approval for treatment – with methotrexate – of moderately to severely active rheumatoid arthritis in adults; in the treatment of active psoriatic arthritis, in which it can be given with or without methotrexate; and in the treatment of active ankylosing spondylitis. ■

VITALS

Major Finding: Compared with patients in the placebo group, those in the golimumab groups had significantly greater median improvement from baseline on the 0- to 20-point JSEQ at 14 weeks' follow-up (–3.0 vs. 0.0 point change); the improvement was sustained at 24-week follow-up (–3.0 vs. –1.0 point change).

Data Source: A randomized, placebo-controlled study of 356 patients with ankylosing spondylitis.

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