Infliximab Biosimilar Appears Safe and Effective Compared With Infliximab for RA

Written by Jill Shuman

Tumor necrosis factor inhibitors (TNFis) have been a mainstay in the treatment of rheumatoid arthritis (RA) since 1998. These biological agents directly target molecules and cells involved in the pathogenesis of RA, leading to a better prognosis and clinical remission, especially in patients who are not well controlled with traditional disease-modifying antirheumatic drugs alone [Weaver AL et al. *Curr Med Res Opin*. 2006].

Because TNFis are expensive, however, there is currently much interest in lower-cost biosimilars—biological products that are highly similar to a licensed reference biological product with no clinically meaningful differences in safety, potency, and purity. Because they are not exact replicas of the reference drug, each biosimilar must be tested against its reference drug to determine its efficacy and safety in a particular therapeutic area.

Jonathan Kay, MD, University of Massachusetts Medical School, Worcester, Massachusetts, USA, presented results of a phase 3, randomized, double-blind, active comparator trial of the biosimilar BOW015 to its reference drug infliximab in patients with active RA. The trial originally enrolled 199 patients at 23 study sites in India. Almost 90% of the patients were female with a median age of 46 and a median disease duration of 3 years. All patients received a stable dose of either oral methotrexate or corticosteroids for at least 4 weeks prior to randomization, and no patient had previously used a biologic agent. No patient had active or latent tuberculosis.

Patients were randomized to receive infliximab (n = 62) or the biosimilar drug (n = 127) dosed at 3 mg/kg at baseline and at weeks 2, 6, and 14. The primary outcome of the study was the proportion of patients in either treatment group who achieved an American College of Rheumatology 20% improvement response (ACR20) at week 16.

Of the original patients, 181 completed the double-blind portion of the study (weeks 0 to 22). At 22 weeks, patients who responded to the biosimilar continued with the treatment; responders to infliximab were crossed over to the biosimilar group (n = 157, both groups). All of the responders then continued on BOW015 every 8 weeks through week 46. Nonresponders were followed only to week 26 (n = 24). The last efficacy measure was at week 54, and safety follow-up extended to week 58.

By week 16, ACR20 responses were seen in 89.8% of patients receiving infliximab and in 86.4% of those taking the biosimilar (95% CI, −19.3% to 12.6%). The durability of the response was maintained at weeks 24 and 54.

During the double-blind phase of the study, at least 1 treatment-emergent adverse event (AEs) occurred in 40.94% of the BOW015 group and in 48.39% of the infliximab group. Serious AEs were reported by 7.1% and 6.5% of the BOW015 and infliximab groups, respectively. No deaths were reported. At week 58, 53.5% of the patients in the initial BOW015 group had developed antidrug antibodies compared with 56.5% of the patients who initially received infliximab.

In conclusion, these data suggest that BOW015 was well tolerated and efficacious both as monotherapy and following an initial 12-week regimen of infliximab, with a durability of clinical response that extended over a total of 54 weeks.

Flare-Free Withdrawal of TNFis Possible in Patients With RA and Stable Low Disease Activity

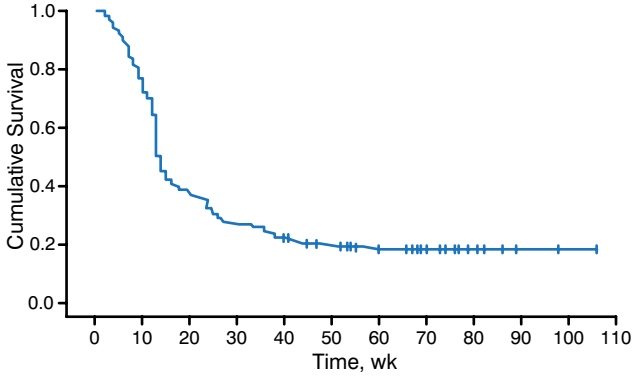
Written by Nicola Parry

Harald E. Vonkeman, MD, PhD, Medisch Spectrum Twente, Enschede, The Netherlands, shared data from the multicenter, open-label, randomized, Potential Optimalization of (Expediency) and Effectiveness of TNF-blockers trial [POET; NTR3112]. The results showed that, in patients with rheumatoid arthritis (RA) who have stable low disease activity, tumor necrosis factor inhibitors (TNFis) can be abruptly withdrawn without the disease flaring. If a disease flare does occur, TNFi therapy can once again be effectively restarted.

According to Prof Vonkeman, although TNFis have been shown to be effective in the treatment of RA, little is known about the effect of stopping this therapy in patients with stable low disease activity, particularly with respect to the likelihood of disease flare, and whether TNFis can be restarted effectively and safely. He added that, due to the risk of serious side effects and complications in patients who take TNFis and their high cost, it is important to know whether individuals in stable low disease activity can effectively stop their TNFi therapy.

The POET study therefore aimed to determine whether patients with RA in stable low disease activity can stop their TNFi therapy. It included 817 patients from 47 centers, all of whom had low RA disease activity and had been treated with a TNFi for ≥ 12 months. During the 6 months prior to the study, all patients had

Figure 1. Time to Regained Low Disease Activity After Flare in Patients Who Stopped TNFi Therapy



TNFi, tumor necrosis factor inhibitor.

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also received a stable dose of disease-modifying antirheumatic drug(s) and had ≥ 2 Disease Activity Score in 28 joints (DAS28) scores < 3.2 in this period. Patients were randomized 2:1 to either stop (65%) or continue (35%) their TNFi therapy (DAS28 flare; defined as DAS28 ≥ 3.2 with an increase ≥ 0.6 compared with the previous DAS28).

At 12 months, the data showed that 46.9% of patients who stopped their TNFi experienced a DAS28 flare, compared with 16.6% of those who continued their TNFi ($P < .001$). The median time to first flare was 24 weeks in patients who stopped taking their TNFi. However, most patients in the group who stopped their TNFi regained low disease activity quickly after a flare, at a median time of 14 weeks (Figure 1).

During the 12-month study period, flare-free discontinuation of TNFi was possible in 53% of patients with stable low RA disease activity.

Overall, these data demonstrate that abrupt discontinuation of TNFi can be safely and effectively implemented in this patient population. Additionally, if a disease flare is going to occur after TNFi withdrawal, it will occur soon, and patients can effectively restart their therapy with restoration of low disease activity, on average, by 14 weeks.

APR Improves PsA Symptoms Out to Week 104

Written by Maria Vinall

Alvin F. Wells, MD, PhD, Rheumatology and Immunotherapy Center, Franklin, Wisconsin, USA, reported results from the Efficacy and Safety Study of Apremilast to Treat Active Psoriatic Arthritis (PsA) [PALACE4; NCT01307423]. Up to week 104, apremilast (APR) monotherapy produced clinically relevant improvements in the symptoms, physical function, and skin manifestations of PsA in patients who had not taken disease-modifying antirheumatic drugs (DMARDs).

PsA occurs in about 30% of patients with psoriasis and is prevalent in an estimated 0.3% to 1.0% of the general population [Gladman DD et al. *Ann Rheum Dis.* 2005]. The manifestations of PsA, including enthesitis, dactylitis, swollen and tender joints, and psoriasis, are associated with impaired physical function and health-related quality of life [Carneiro S et al. *J Rheumatol.* 2013; Sakkas LI et al. *Semin Arthritis Rheum.* 2013; Strand V et al. *Health Qual Life Outcomes.* 2013; Gladman DD et al. *Ann Rheum Dis.* 2005].

APR is an oral phosphodiesterase 4 inhibitor that regulates inflammatory mediators associated with the pathogenesis of PsA [Schafer PH et al. *Br J Pharmacol.* 2010]. PALACE4 was a phase 3, double-blind, randomized, placebo-controlled, parallel-group study designed to evaluate the long-term efficacy and safety of APR treatment compared with placebo over 104 weeks. The study consisted of 3 treatment phases with a planned overall study duration of up to 5 years.

To be eligible, patients were required to be DMARD-naïve adults with documented PsA with a duration ≥ 3 months and with ≥ 3 swollen joints and ≥ 3 tender joints. Patients with active tuberculosis or a history of incompletely treated tuberculosis, malignancy, or joint disease other than PsA were excluded. Participants were randomized (1:1:1) to receive placebo (n = 176), APR 20 mg BID (n = 175), or APR 30 mg BID (n = 176).

Efficacy assessments included the American College of Rheumatology 20%/50%/70% improvement response criteria (ACR20/50/70) and the Health Assessment Questionnaire Disability Index (HAQ-DI). Safety assessments included adverse events (AEs) and clinical laboratory parameters at scheduled visits during each treatment phase (weeks 0, 4, 16, and 24 during the placebo-controlled phase; weeks 28, 40, and 52 during the blinded active treatment phase; and weeks 65, 78, 91, and 104 during the long-term open-label phase). There were no significant differences in baseline