Adalimumab Plus Methotrexate Versus Methotrexate Monotherapy in Early RA

Written by Toni Rizzo

Jacqueline Detert, MD, Charité Universitätsmedizin Berlin, Berlin, Germany, presented results from the High Induction Therapy with Anti-Rheumatic Drugs study [HIT HARD], which compared treatment with adalimumab plus methotrexate with methotrexate monotherapy in disease-modifying antirheumatic drug (DMARD)-naïve patients with active early rheumatoid arthritis (RA). The central question of the study was whether or not early induction therapy with a subsequent step-down strategy leads to long-term clinical effect in patients with RA.

Patients in this multicenter trial were randomized to treatment with subcutaneous (SC) adalimumab plus methotrexate (n=87) versus methotrexate alone (n=85) for the first 24 weeks. After Week 24, both groups received methotrexate monotherapy up to Week 48. The primary endpoint was DAS28 at 48 weeks. Secondary endpoints included radiological changes in the hands and feet (modified Sharp score and Ratingen score); American College of Rheumatology (ACR) 20/5/70; WHO/ILAR core set variables; safety; and changes in glucocorticoid, NSAID, and COX-2 inhibitor dosages.

Baseline characteristics were similar in both treatment groups. At baseline, the patients had a mean disease duration of 1.7 months, mean DAS28 of 6.2, mean HAQ of 1.4, and Sharp-van der Heijde total score of 8.8. A total of 76 patients in the induction group and 57 patients in the placebo group completed 48 weeks of treatment.

The combination group (induction group) had significantly decreased Disease Activity Score (DAS) 28 versus the placebo group at Weeks 8 (3.2 vs 4.5), 16 (3.0 vs 3.9), and 24 (3.0 vs 3.6; $p<0.05$ for all), but there was no significant difference between the groups during the methotrexate monotherapy phase (Weeks 32 to 48). Likewise, significantly more patients in the induction versus the placebo group achieved remission (DAS28 <2.6) during the first 24 weeks, but the difference narrowed during Weeks 32 to 48. The ACR response rates at Week 24 for the induction versus the placebo group were: ACR20 (79% vs 68%; p=NS), ACR50 (64% vs 49%; $p<0.05$), and ACR70 (48% vs 27%; $p<0.05$). The ACR response rates at Week 48 were not significantly different between the induction and the placebo groups: ACR20 (66% vs 75%), ACR50 (53% vs 51%), and ACR70 (40% vs 34%). The mean HAQ values were significantly improved in the induction versus placebo group at Weeks 8 (0.6 vs 1.0; $p<0.001$), 16 (0.6 vs 0.8; $p<0.001$), and 24 (0.5 vs 0.7; $p<0.05$) but were not significantly different at Weeks 32, 40, or 48.

Radiographic progression was significantly reduced in the induction group compared with the placebo group (total Sharp-van der Heijde score adalimumab 2.6 vs methotrexate 6.4; p=0.03) at Week 48. No new safety signals were detected.

Combination therapy with adalimumab and methotrexate was significantly superior to methotrexate alone during the initial treatment phase of 24 weeks. Reduced radiographic progression was observed at Week 48, indicating a sustained effect of combination treatment. However, reduction in disease activity, the primary endpoint, was not sustained through 48 weeks. The numerical increase in the clinical outcome parameters of the adalimumab-plus-methotrexate group from Week 40 onwards may reflect the loss of response after removal of adalimumab.

Results From the ESPOIR Cohort Study

Written by Toni Rizzo

Laure Gossec, MD, PhD, Paris Descartes University, Paris, France, presented results from the French Early Arthritis (ESPOIR) cohort study. Investigators analyzed patients who were in remission to determine if a patient's global status assessment and fatigue rating during the first year of early arthritis play a significant role in predicting structural progression over 3 years.

ESPOIR is an observational study of patients with early arthritis who had no prior disease-modifying antirheumatic drug (DMARD) therapy. Early arthritis was defined as having at least 2 swollen joints for <6 months. The outcome was change in total Sharp-van der Heijde score (SHS) from baseline to 3 years, adjusted for baseline radiographic score. Predictive variables included definitions of remission at 6 and 12 months, swollen and tender joints, C-reactive protein (CRP), global assessment, and fatigue rating (means of 6- and 12-month values). Remission definitions that were used were the ACR/EULAR Boolean remission (tender and swollen joint counts ≤1, CRP ≤1 mg/dL, and patient global ≤1/10), no-patient-reported outcome (PRO)

near-remission (remission for all criteria except patient global), and fatigue remission (≤1/10 on a visual analog scale). Kappa agreement statistics were used to compare the definitions of remission. Multiple linear regression was used for prediction by remission definitions. Multiple linear regression and stepwise selection were used for prediction of radiographic score by remission components. Analyses were restricted to patients with all relevant data, with no imputation of missing data.

Remission data were available for 776 patients, and complete data were available for 520 patients. Among the patients with complete data, after 3 years, DAS28 decreased from 5.2±1.3 to 2.9±1.4, HAQ score decreased from 1.0±0.7 to 0.5±0.6, global assessment (0 to 10) decreased from 6.0±2.5 to 2.9±2.6, fatigue rating (0 to 10) decreased from 4.8±2.8 to 3.4±2.0, and SHS radiographic total score increased from 5.4±7.7 to 13.6±14.7. At 3 years, 57% of the patients were receiving methotrexate, and 16% were receiving biologic therapies.

Of the 776 patients, 7.4% achieved ACR/EULAR remission, 18.7% achieved no-PRO near remission, and 3.1% achieved fatigue remission (ie, with a fatigue score lower than 1/10). Of the 520 patients, 6.7% achieved ACR/EULAR remission, 18.7% achieved no-PRO near remission, and 3.1% achieved fatigue remission. Agreement between ACR/EULAR and the other remission definitions was moderate: ACR/EULAR versus no-PRO near remission – kappa, 0.48 (95% CI, 0.37 to 0.58); ACR/EULAR versus fatigue remission – kappa, 0.41 (95% CI, 0.23 to 0.58).

In the comparison of the remission models for the prediction of radiographic score, only swollen joint count and CRP were predictive of radiographic score. The PROs were not significant. Additional analysis of global cutoff in patients in no-PRO near remission (n=97) demonstrated no correlation between patient global and radiographic progression (Spearman correlation 0.025; p=0.575).

This analysis had several limitations. The comparison of models was not straightforward. There was a potential lack of power because of the low number of patients in remission. Fatigue remission is not a feasible outcome with a cutoff of 1/10.

No-PRO near remission was more frequent than ACR/EULAR Boolean remission in patients with early arthritis (18.7% vs 6.7%). Fatigue remission was rare (3.1%). Swollen joint count and acute-phase reactants were strong drivers of radiographic progression. Patients' global assessments had limited additional predictive value for radiographic progression. Further research is warranted.

2-Year Results from the GO-RAISE Trial

Written by Toni Rizzo

The Multicenter Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis trial [GO RAISE] evaluated the efficacy and safety of golimumab in patients with active ankylosing spondylitis (AS). Objectives of this analysis, presented by D. van der Heijde, MD, Leiden University Medical Center, Leiden, The Netherlands, were to assess AS Disease Activity Score (ASDAS) major improvement and inactive disease and their association with improvements in Health Related Quality of Life (HRQoL), and work productivity in patients with AS after 2 years of treatment with golimumab.

A total of 356 patients with AS according to the modified New York criteria were randomized to golimumab 50 mg or 100 mg or placebo every 4 weeks. Patients with <20% improvement in total back pain and morning stiffness at Week 16 entered early escape (EE), with placebo-treated patients receiving golimumab 50 mg, and golimumab 50 mg patients switching to golimumab 100 mg. Improvement in HRQoL, work productivity, and employability were analyzed by ASDAS major improvement (≥2.0) and inactive disease (<1.3) status at Weeks 14, 24, 52, and 104. HRQoL was assessed using the Physical Component Summary Score (PCS) and Mental Component Summary Score (MCS) of the SF-36. Productivity was assessed by a visual analog score (VAS; 0=no impact, 10=high impact).

Median improvements in ASDAS scores were significantly greater in the combined golimumab arms compared with the placebo arm at Weeks 14 (1.6 vs 0.4; p<0.001) and 24 (1.7 vs 0.3; p<0.001). The mean ASDAS score was improved (range 1.9 to 2.3) in all arms at Weeks 52 and 104, after the placebo crossover (all patients receiving golimumab). At Weeks 52 and 104, ASDAS inactive disease was achieved by 33.9% and 41.6% and ASDAS major improvement was achieved by 49.1% and 52.9% of all patients, respectively. Among patients who achieved ASDAS inactive disease, 57.1% and 65.5% had PCS ≥50 and 64.8% and 74.4% had MCS ≥50 at Weeks 52 and 104, respectively. Among patients who achieved ASDAS major improvement, 37.9% and 48.3% had PCS ≥50 and 62.1% and 65.31% had MCS ≥50 at Weeks 52 and 104, respectively.

Patients with inactive disease versus those without inactive disease had greater improvements in productivity