One-Year Results of the SWEFOT Trial

Prof. Ronald van Vollenhoven, Karolinska Institute, Stockholm, Sweden, presented 1-year data from the SWEFOT trial (NCT00603525), an open-label, randomized, controlled trial that was designed to compare 2 treatment strategies in rheumatoid arthritis (RA) patients who failed treatment with methotrexate (MTX) monotherapy.

In SWEFOT, 487 patients with early RA (symptom duration <1 year) received MTX monotherapy (maximum dose 20 mg/week) for a maximum of 4 months. Patients who had not achieved DAS28 <3.2 by Month 4 but who could tolerate MTX (n=258) were randomly assigned to receive one of two treatment protocols. Patients in Group 1 (n=130) received MTX plus sulfasalazine 1000 mg BID and hydroxychloroquine 400 mg daily. Patients in Group 2 (n=128) received MTX plus infliximab (3 mg/kg/infusion, rounded up to the nearest 100 mg, given at Weeks 0, 2, and 6 and every 8 weeks thereafter). DMARD dose could be adjusted for intolerance. The frequency (but not the dose) of the infliximab infusion could be increased based on response. A single switch within each group was allowed only for intolerance. Sulfasalazine and hydroxychloroquine could be replaced by cyclosporine A (2.5-5.0 mg/kg BID); infliximab could be replaced by etanercept (50 mg weekly).

The primary (EULAR good response) and secondary (EULAR moderate response, ACR responses, and others) outcomes were assessed at Month 12. Analysis was based on the intent-to-treat population (ITT). Data also were analyzed using a modified ITT (mITT) population that included only patients who received at least one dose of the study drug. For patients who discontinued during the study, nonresponder imputation was used for dichotomous variables, and last-observation-carried-forward was used for continuous variables.

At 12 months, significantly ($p<0.01$) more patients in Group 2 (42%) achieved a EULAR good response versus those in Group 1 (26%). The percentage of EULAR total responders also was significantly higher in Group 2 (64% vs 52% Groups 2 and 1, respectively; $p<0.05$). ACR 20, 50, and 70 responses are shown in Table 1.

Table 1. Patients Achieving ACR Response by Treatment Group.

	ACR 20	ACR 50	ACR 70
Group 1	33%	16%	8%
Group 2	49%	29%	13%

* $p<0.05$ vs Group 1

Responses using the mITT population yielded similar results with stronger statistical significance.

"After the disease has been confirmed in a patient, we start by treating it with methotrexate," said Prof. van Vollenhoven, who also is a member of the SWEFOT steering committee. "But for the group of patients who don't respond well to MTX, it's more effective to add a biological medicine than to combine MTX with an older drug."

Results of the COMET Trial

The COMET trial, the first biologic rheumatoid arthritis (RA) clinical trial to use remission as a primary endpoint, is a 2-year double-blind, randomized trial that included active RA patients (DAS28 ≥3.2) with a disease duration ≥3 months and ≤2 years who were methotrexate-naïve. Patients received either etanercept plus methotrexate (MTX) or MTX monotherapy. MTX was titrated beginning at Week 4 to a maximum of 20 mg/week at Week 8. The primary study efficacy endpoints were the proportion of patients achieving DAS28 remission (<2.6) and change from baseline in modified Total Sharp Score (mTSS) at Week 52. Other endpoints included low disease activity (DAS28 ≤3.2), radiographic non-progression (mTSS ≤0.5), and percentage of patients achieving a normal HAQ score (≤0.5).

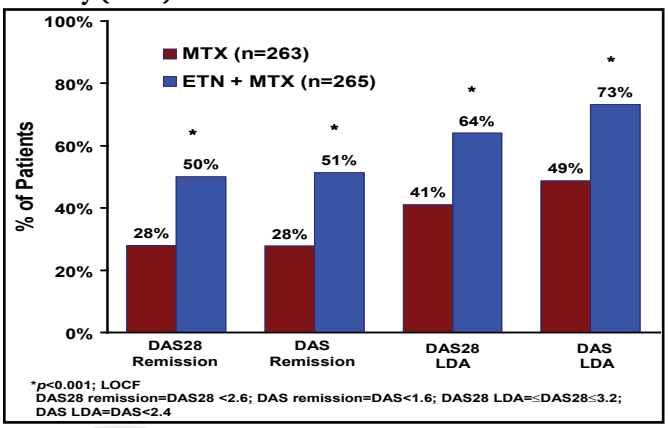
Paul Emery, MD, PhD, University of Leeds, Leeds, UK, presented the initial 52-week data from the COMET trial which showed that etanercept in combination with MTX was superior to MTX alone in providing clinical remission, radiographic non-progression, and normalized function.

Data for a total of 528 patients were evaluable for clinical efficacy (etanercept+MTX, n=265; MTX alone, n=263) and for 476 patients for radiographic efficacy (etanercept+MTX, n=246; MTX alone, n=230). At Week 52, significantly ($p<0.001$) more patients in the etanercept+MTX group (50%; 132/265) achieved DAS28 remission versus in the MTX alone group (28%, 73/263; Figure 1). A significantly ($p<0.001$) greater proportion of patients in the combination therapy group (64%) also achieved DAS28 ≤3.2 versus the MTX alone group (41%; Figure 1).

Combination therapy also resulted in significantly ($p<0.001$) lower radiographic progression than MTX monotherapy (mean mTSS changes from baseline: 0.27 for etanercept+MTX and 2.44 for MTX alone). Radiographic non-progression was achieved by 80% (196/246) of patients receiving combination therapy and 59% (135/230) receiving MTX alone ($p<0.001$). The proportion of patients

achieving HAQ ≤0.5 was significantly (p<0.001) greater in the combination group (55%, 140/256) versus the MTX group (39%, 93/241).

Figure 1. DAS28 and DAS Remission and Low Disease Activity (LDA).



Serious adverse events were reported by 33 patients (12%) in the combination group and 34 (13%) in the MTX group. There were no differences in the rates of serious infections or malignancies and no cases of tuberculosis or demyelinating disease.

"Until recently, we did not know whether remission was a realistic", said Prof. Emery. "We now have results which show that not only is clinical remission achievable in a significant number of patients, but radiographic and functional remission are also achievable. These exciting results lead to the next therapeutic step in aiming for multiple measures of remission as our treatment goal, no longer just one".

Effect of Previous Bisphosphonate Use on Response to Zoledronic Acid

The HORIZON Pivotal Fracture Trial (NCT00049829) was a 3-year, double-blind, randomized, placebo-controlled trial in which patients received a 15-minute infusion of zoledronic acid 5 mg (n=3889) or placebo (n=3876) at baseline and at 12 and 24 months. Results, previously reported by Black and colleagues, showed that once-yearly zoledronic acid significantly reduces the risk of vertebral, hip, and other fractures [Black D et al. *N Engl J Med* 2007].

Richard Eastell, MD, PhD, University of Sheffield, Sheffield, UK, presented the results of a planned subanalysis from HORIZON that evaluated the effect of prior bisphosphonate use on the primary endpoints of new vertebral fracture (in patients who were not taking concomitant osteoporosis medications) and non-vertebral fractures (in all patients). Markers of bone turnover were also evaluated.

Bisphosphonates had been used by 565 patients (14.5%) in the zoledronic acid group and 557 patients (14.4%) in the placebo group. The duration of the washout period was dependent on previous use (eg, 2 years if previous use was ≥48 weeks).

Over 3 years, the incidence of vertebral fracture was significantly (p<0.0001) lower in the zoledronic acid group versus the placebo group regardless of prior bisphosphonate.

Significant (p<0.001) reductions in the incidence of non-vertebral fractures also were seen in bisphosphonate-naïve patients who were treated with zoledronic acid (n=237, 7.60%) versus placebo (n=337, 10.88%), but not in patients who previously had used bisphosphonates (n=54, 10.11% vs n=50, 9.80%).

Over 3 years, changes in markers of bone turnover were similar between the bisphosphonate use groups. Reductions from baseline at Month 36 in serum levels of c-telopeptides, bone alkaline phosphatase, and N-terminal propeptide of type I collagen with zoledronic acid relative to placebo were 53.8%, 30.0%, and 48.4%, respectively, in the bisphosphonate-naive group, and 49.3%, 16.1%, and 50.1%, respectively, in the previous bisphosphonate use group.

The benefits of once-yearly zoledronic acid that were observed during a 3-year period were robust on vertebral fractures, bone turnover markers, and bone mineral density, regardless of whether patients had previously received bisphosphonate treatment. Zoledronic acid had a favorable safety profile and generally was well tolerated.

The AMBITION Study

Although studies have shown current anti-TNF treatments to be superior to short-term methotrexate (ie, before 24 weeks), none has shown superiority at Week 24. Graeme Jones, MD, PhD, University of Tasmania, Hobart, Australia, lead investigator of the AMBITION study (NCT00109408), presented data that showed that after 24 weeks, tocilizumab (an anti-IL-6 receptor antibody that inhibits IL-6 signaling) monotherapy was clinically superior to methotrexate (MTX) monotherapy in patients with rheumatoid arthritis (RA) who have not failed previous MTX or biologic treatment.