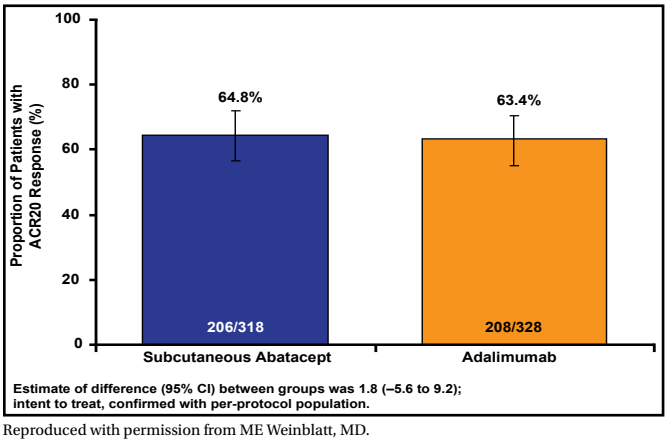
The Phase 3b AMPLE study is a randomized, investigator-blinded, 24-month trial with a 12-month primary efficacy endpoint. In total, 646 biologic-naïve patients with active RA and inadequate response to MTX were stratified by disease activity and randomized 1:1 to either abatacept 125 mg SC (without an intravenous load) weekly or adalimumab 40 mg SC biweekly, in combination with a stable dose of MTX.

Baseline characteristics were similar in both groups. The 646 patients had a mean disease duration of about 1.8 years. Both abatacept and adalimumab showed comparable efficacy and kinetics of clinical response over the course of 1 year. At 4 weeks, 42.5% of patients in the abatacept group achieved ACR20 response versus 47.6% in the adalimumab group. At 12 months, 64.8% of the abatacept group and 63.4% of the adalimumab group achieved the primary endpoint of ACR20 response, confirming abatacept noninferiority.

Rates for low disease activity (28-joint Disease Activity Score [DAS28]-C-reactive protein [CRP] score ≤3.2) at Year 1 were 59.3% for abatacept and 61.4% for adalimumab. The respective numbers for remission (DAS28-CRP <2.6) were 43.3% versus 41.9%. AMPLE also included measures for changes in radiographic scores and rates of nonprogressors at Year 1. The mean joint space narrowing score (standard deviation [SD]) was 0.28 (1.92) in the abatacept group (n=290) versus 0.39 (2.50) in the adalimumab group (n=289). Numbers for radiographic nonprogressors were 246/290 (84.8%) and 256/289 (88.6%), respectively.

According to Dr. Weinblatt, SC abatacept was noninferior to adalimumab (64.8% vs 63.4%) in the primary outcome measure of ACR20 at 1 year (Figure 1). Comparable responses, including similar onset, were seen across all efficacy variables, including the ACR core components. Other than fewer discontinuations due to adverse events and serious adverse events in the SC abatacept group and significantly (p=0.006) less frequent local injection-site reaction complaints in abatacept patients, safety outcomes were balanced.

Figure 1. SC Abatacept Is Noninferior to Adalimumab.



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Etanercept Proves Clinically Superior to Discontinuation: Results from the DOSERA Trial

Written by Maria Vinall

Results from the late-breaking Study Comparing the Effect on Disease Activity When Reducing or Discontinuing Etanercept in Subjects with RA [DOSERA; NCT00858780] were reported by Ronald F. van Vollenhoven, MD, Karolinska Institute, Stockholm, Sweden. The results showed that in patients with rheumatoid arthritis (RA) and stable low disease activity on methotrexate plus etanercept, continued treatment with etanercept at 25 or 50 mg/week provides a significantly higher likelihood of maintaining a stable disease state over 48 weeks than placebo. Discontinuation of etanercept leads to worsening.

Etanercept has been shown to have sustained efficacy over 3 years, and it has a favorable safety profile [Klareskog L et al. *Ann Rheum Dis* 2006]. Its efficacy in combination with methotrexate in the treatment of RA is well established [Rexhepi S et al. *Arthritis Res Ther* 2012]; however, it is not known whether etanercept must be continued to maintain low disease activity/remission (LDA/REM) or if the continuation of methotrexate alone or with a lower dose of etanercept might be equally effective.

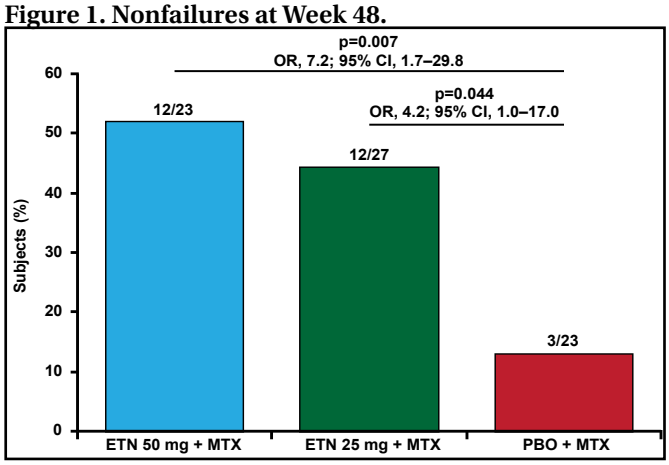
This was a randomized, double-blind, 3-arm study conducted in 5 Northern European countries. Adult patients with RA treated with stable background methotrexate (7.5 to 25 mg/week) plus etanercept (50 mg/week) for ≥14 months, with a 28-joint Disease Activity Score (DAS28) ≤3.2 for at least 11 months were randomized (1:1:1) to methotrexate plus etanercept 50 mg/week (etanercept50), etanercept 25 mg/week (etanercept25), or placebo. The primary study outcome was the proportion of patients in the etanercept50 group who were nonfailures at 48 weeks. Failure was defined as DAS28 >3.2 and increased by 0.6 or disease progression determined by investigator or subject. Secondary outcomes included comparisons of nonfailure and DAS28 outcomes for all 3 groups, and time to failure. The primary outcome was analyzed using a Generalized Estimating Equation model and expressed as the odds ratio (OR; 95% CI) for achieving nonfailure. Patients were followed for 2 months without major changes in therapy to ensure stable LDA/REM and stratified based on LDA/REM status. Seventy-three patients were randomized, 70% were women, mean age was 57 years, and mean duration of etanercept treatment was 3.88 years. Twenty percent of subjects were in remission and 5% had low disease

activity. Mean DAS28 score at the start of etanercept treatment was 5.0.

After 48 weeks, the proportion of nonfailures was 52% for etanercept50 (OR, 7.2; 95% CI, 1.7 to 29.8; p=0.007 vs placebo) and 44% for etanercept25 (OR, 4.2; 95% CI, 1.0 to 17.0; p=0.044 vs placebo; Figure 1). Median time to failure was 6 weeks from randomization for placebo, and 48 and 36 weeks for etanercept50 and etanercept25, respectively. Adverse events were similar between the groups and no unexpected safety signals were noted.

The data suggest that induction-maintenance may be possible with etanercept for some RA patients, even in established disease.

Figure 1. Nonfailures at Week 48.



ETN=etanercept; MTX=methotrexate; PBO=placebo.
Adapted from RF van Vollenhoven, MD.

IMPROVED: Final Study Results of Combination Treatment in Patients with Early RA and UA

Written by Maria Vinall

Final results of the Induction Therapy with Methotrexate and Prednisone in Rheumatoid or Very Early Arthritis Disease [IMPROVED] study, reported by Lotte Heimans, MD, Leiden University Medical Center, Leiden, The Netherlands, showed that patients with rheumatoid arthritis (RA) and undifferentiated arthritis (UA) achieved similarly greater rates of remission after early initial treatment with combination therapy (methotrexate [MTX] and prednisone). Patients who failed to achieve early remission benefited more when switched to a treatment strategy with adalimumab than with multiple disease modifying antirheumatic drugs (DMARDs), with virtually no radiographic damage progression in all patients.

The objectives of the IMPROVED trial were to assess if induction of remission and drug-free remission is possible with initial combination therapy in early RA and UA, to determine which strategy results in more remission if the initial combination fails, and to compare results in RA and UA patients. The study included adult patients with RA (2010 criteria; n=479) of <2 years duration or rheumatologist-determined UA (n=122). The goal was remission (Disease Activity Score [DAS] <1.6).

All patients were initially treated with MTX (25 mg QW) and prednisone (60 mg QD tapered to 7.5 mg QD over 7 weeks). Prednisone was tapered then discontinued for patients with a DAS <1.6 at 4 months. MTX was tapered for patients with a DAS <1.6 at 8 months. If remission was lost after 8 months, prednisone was restarted at 7.5 mg QD. Patients not in remission at 4 months were randomized to Arm 1 (MTX + prednisone + sulfhasalazine 2000 mg QD + hydroxychloroquine 400 mg QD [poly DMARDs + prednisone]; n=83) or Arm 2 (MTX + adalimumab [ADA] 40 mg every 2 weeks; n=78). Patients in either arm achieving remission at 8 months had their treatments tapered to MTX monotherapy. If not in remission after 8 months, patients in Arm 1 switched to ADA plus MTX and patients in Arm 2 increased ADA to 40 mg QW.

At baseline, RA patients had significantly (p≤0.02) higher DAS and Health Assessment Questionnaire scores compared with UA patients; 68% of RA patients were positive for anticitrullinated protein antibody plus (ACPA+) compared with 3% of UA patients (p<0.001). Mean age was 52 years; 70% of RA and 61% of UA patients were women; mean symptom duration was ~17 weeks. Proportions of remission and radiographic progression measured by Sharp/van der Heijde score (SHS) after 1-year follow-up were compared between the different treatment strategies.

Early remission (4 months) was achieved by 61% of all patients (Figure 1). At 1 year, 68% of those 61% were in remission and 32% were in drug-free remission. Significantly more patients in arm 2 (MTX + ADA, 41%) achieved remission at 1 year compared with those in arm 1 (poly DMARDs + prednisone, 25%; p=0.01). There was no difference between RA (62%) and UA (65%) patients who achieved early remission (p=0.46) or 1 year remission (53% vs 58%, respectively; p=0.1). Damage progression was minimal. Only 33 patients showed a 1-point progression on SHS. Toxicity was comparable between the 2 randomized arms.

In this treat-to-remission cohort, early remission more often led to remission at 1 year (radiological damage progression after 1 year and drug-free remission). Also, remission-steered therapies led to minimal radiographic damage in UA and RA patients regardless of the treatment employed.