However, in 2002 concerns began to appear regarding the possibility of an association between anti-TNF therapy and an increased risk of lymphoma in this patient population [Brown SL et al. *Arthritis Rheum* 2002]. Assessing this risk is difficult because individuals with RA already have a 2 to 3 times higher risk of lymphoma compared with the general population, and this risk increases with increasing disease severity [Baecklund E et al. *Arthritis Rheum* 2006]. To date, neither clinical trials [Leombruno JP et al. *Ann Rheum Dis* 2009] nor observational studies [Setoguchi S et al. *Arthritis Rheum* 2006; Wolfe F and Michaud K. *Arthritis Rheum* 2007; Askling J et al. *Ann Rheum Dis* 2009] have shown such a relationship.

The purpose of this prospective cohort study was to determine whether the use of anti-TNF therapy influences the risk of lymphoma. The study population comprised patients with RA but without prior lymphoproliferative malignancy who were being treated in routine clinical practice in the United Kingdom. Cohort 1 included patients newly exposed to anti-TNF therapy. Cohort 2 included biologic-naïve patients starting or changing to a disease-modifying antirheumatic drug (DMARD). Patient characteristics are shown in Table 1. All participants were followed with both physician and patient questionnaires and linked with the National Health Service cancer and death registry for lymphoma or death. The current results represent follow-up through September 30, 2010. The primary study outcome was risk of first lymphoma in patients ever exposed to anti-TNF therapy versus those exposed to nonbiologic DMARD only. The secondary outcome was the risk of non-Hodgkin lymphoma only.

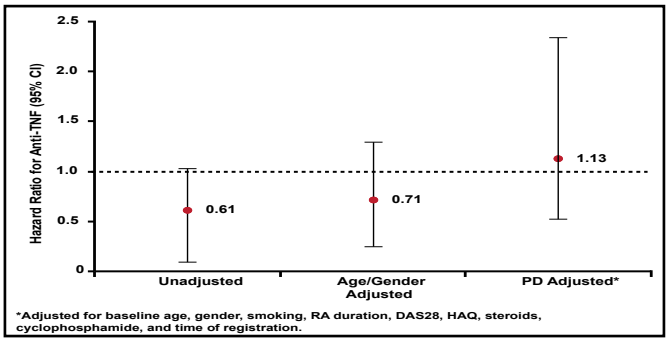
Table 1. Baseline Characteristics.

	nbDMARD n=3465	Anti-TNF n=11987
Follow-up (total patient-years)	13,186	66,353
Median follow-up, patient-years (IQR)	4.5 (2.6–5.9)	6.4 (4.8–7.4)
Mean age, years (SD)	60 (12)	56 (12)
Women, n (%)	2545 (73)	9145 (76)
Ever smoked, (%)	64	60
Median RA disease duration years (IQR)	6 (1–15)	11 (6–19)
Mean DAS score (SD)	5.3 (1.1)	6.6 (1.0)
Mean HAQ (SD)	1.5 (0.7)	2.0 (0.6)
Oral steroids (%)	23	44
Median # prior DMARDs (IQR)	2 (1, 3)	4 (3, 5)
Lymphoma, n Rate/100,000 person-years (95% CI)	20 152 (93–234)	64 96 (74–123)
Hodgkin lymphoma, n Non-Hodgkin lymphoma, n	4 16	9 55

DAS=Disease Activity Score; HAQ=Health Assessment Questionnaire; IQR=interquartile range; nbDMARD=nonbiologic disease-modifying antirheumatic drug; RA=rheumatoid arthritis; SD=standard deviation; TNF=tumor necrosis factor.

There was no increased risk for lymphoma with anti-TNF treatment compared with nonbiologic DMARD only. The adjusted HR for anti-TNF treatment was 1.13 (Figure 1). In the DMARD group 20% had Hodgkin lymphoma versus 14% in the anti-TNF group. A very similar pattern of risk was noted when limited to non-Hodgkin lymphoma (HR=1.26).

Figure 1. Hazard for Lymphoma (nbDMARD Referent).



DAS=Disease Activity Score; HAQ=Health Assessment Questionnaire; nbDMARD=nonbiologic disease-modifying antirheumatic drug; RA=rheumatoid arthritis; TNF=tumor necrosis factor.
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The strengths of the study include it being a large, national cohort with detailed patient data from the National Health Service registry and a propensity model that allowed for adjustment of a large number of covariates. It was limited by a reporting lag, possible screening bias, and the fact that it did not include data on changes in disease activity over time. Further follow-up is recommended to allow for longer latency.

Head-to-Head Biologics Trial Shows No Difference Between Abatacept and Adalimumab

Written by Rita Buckley

Outcomes from the Abatacept Versus Adalimumab Head-to-Head [AMPLE; NCT00929864] trial demonstrated comparable efficacy between subcutaneous (SC) abatacept and adalimumab on background methotrexate (MTX). Michael E. Weinblatt, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented key efficacy and safety results from the trial.

Dr. Weinblatt said that AMPLE is the first head-to-head study in rheumatoid arthritis (RA) patients that is powered to compare biologic disease-modifying antirheumatic drugs (DMARD) on a background of MTX in subjects who have failed MTX therapy and are naïve to biologic DMARD therapy. The hypothesis was that 12 months of treatment with SC abatacept would be noninferior to adalimumab. The primary endpoint was the proportion of subjects meeting the American College of Rheumatology 20% improvement criteria (ACR20) at 12 months.

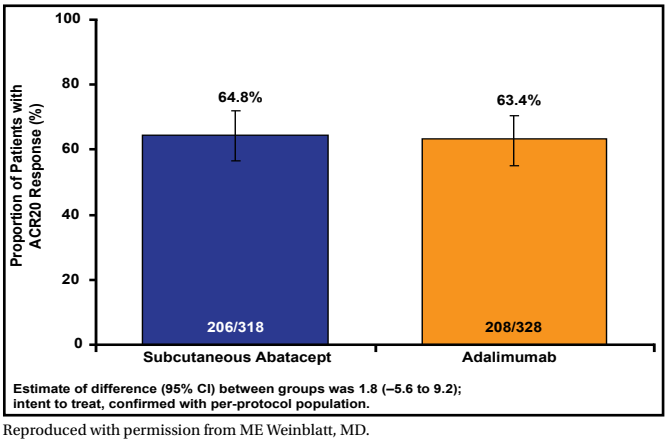
The Phase 3b AMPLE study is a randomized, investigator-blinded, 24-month trial with a 12-month primary efficacy endpoint. In total, 646 biologic-naïve patients with active RA and inadequate response to MTX were stratified by disease activity and randomized 1:1 to either abatacept 125 mg SC (without an 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