Etanercept in Combination with Sulfasalazine, Hydroxychloroquine, or Gold in the Treatment of Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To prospectively determine the efficacy and safety of etanercept in combination with sulfasalazine (SSZ), hydroxychloroquine (HCQ), and gold in the treatment of rheumatoid arthritis (RA).

Methods. A prospective open-label study enrolled 119 patients with RA who had active disease despite stable therapy with SSZ (n = 50), HCQ (n = 50), or intramuscular gold (n = 19). Primary efficacy endpoints consisted of American College of Rheumatology responses at 24 and 48 weeks. Safety was established at regularly scheduled visits.

Results. Patients in each etanercept combination showed significant improvement at both 24 and 48 weeks. Toxicity withdrawals by 48 weeks included gold (n = 1): proteinuria; HCQ (n = 5): septic wrist and bilateral pneumonia, rash, optic neuritis, breast cancer, squamous cancer of the tongue; and SSZ (n = 5): otitis media, elevated liver function indicators, pericarditis, rash, and gastroenteritis. The most common adverse events not requiring discontinuation from the study were injection site reactions (43% of patients) and upper respiratory type infections (34%).

Conclusion. This study is the first to prospectively evaluate the safety of etanercept in combination with SSZ, HCQ, and gold in patients with RA. Etanercept in combination with SSZ, HCQ, or gold was efficacious and well tolerated, with a discontinuation rate of 9% (11/119) for adverse events at 48 weeks. (J Rheumatol 2006;33:213-8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ETANERCEPT COMBINATION THERAPY
SULFASALAZINE HYDROXYCHLOROQUINE GOLD

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine that plays a critical and complex role[1] in the pathogenesis of rheumatoid arthritis (RA). Etanercept, a fusion protein consisting of 2 recombinant soluble p75 TNF-α receptor monomers combined to the Fc portion of human IgG1, binds TNF-α, blocking its interaction with cell surfaces. Placebo controlled studies with etanercept have shown that etanercept is an effective therapy with a favorable side effect profile for patients with RA[2] who have failed one or more prior disease modifying antirheumatic drugs (DMARD). Subsequent studies have also shown etanercept to be safe and effective when used in combination with methotrexate (MTX)[3]. There are no published prospective studies, however, on the safety and efficacy of using etanercept in combination with other DMARD. Since many patients are treated with DMARD other than MTX[4], or have had adverse events limiting the use of MTX[5], this study was undertaken at the request of the US Food and Drug Administration to evaluate the safety and efficacy of etanercept in combination with 3 other commonly used DMARD, hydroxychloroquine (HCQ), sulfasalazine (SSZ), and intramuscular (IM) gold.

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MATERIALS AND METHODS

This study was conducted by the Rheumatoid Arthritis Investigational Network (RAIN), which brings rheumatologists at the University of Nebraska Medical Center together with rheumatologists in Nebraska, South Dakota, North Dakota, Minnesota, Illinois, California, and Oregon for the purpose of investigator-initiated clinical studies in RA. All physicians participating in this network were involved with patient enrollment and data collection, and in development of the study protocols. Enrollment occurred at 10 centers from September 1999 through November 2001.

Patient selection. Patients who were being followed at rheumatology clinics at the University of Nebraska Medical Center or the Omaha Veterans Administration Medical Center, or in the private offices of network physicians were asked to participate in this study if they met entry criteria. The protocol was approved by the Institutional Review Board at the University of Nebraska Medical Center and at other sites where applicable. All patients gave informed, written consent.

Eligibility criteria included: age between 19 and 75 years; RA fulfilling

the American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria[6]; active disease as defined by the presence of ≥ 6 tender and ≥ 6 swollen joints; taking stable doses of either SSZ (up to 3 g/day), HCQ (up to 400 mg/day), or IM gold (25 mg or 50 mg every 2–4 weeks) for > 4 weeks; ability to self-inject study drug or have someone who could do so; stable doses of corticosteroids ≤ 10 mg/day prednisone for > 4 weeks; mono-nonsteroidal antiinflammatory drug (NSAID) therapy less than or equal to the maximum recommended daily dose; and laboratory criteria as follows: AST/ALT ≤ 1.2 times upper limit of normal; hemoglobin ≥ 8.5 g/dl and stable for 3 months if < 10 g/dl, platelets ≥ 125,000/mm^3; white blood cell (WBC) count ≥ 3500 cells/cm^3; serum creatinine ≤ 2.0 mg/dl; and urinalysis with negative blood, protein, and ≤ 10 WBC/high power field. Patients were not eligible if they had previously received etanercept, antibody to TNF-α, anti-CD4 antibody, or diphtherial interleukin 2 fusion protein (DAB IL-2); had received any investigational drugs or biologics within 4 weeks of the screening period; received cytoxan, cyclosporine, or azathioprine within 6 months; or received any DMARD other than SSZ, HCQ, or gold within 2 weeks of screening. Other exclusion criteria included: active or chronic infections; women of childbearing age not using adequate contraception; pregnant or lactating women; concurrent medical diseases including uncompensated congestive heart failure, myocardial infarction within 12 months, angina pectoris, uncontrolled hypertension, severe pulmonary disease requiring medical or oxygen therapy, diabetes, history of cancer other than resected basal and squamous cell carcinoma and *in situ* cervical cancer within 5 years, human immunodeficiency virus infection, substance abuse or psychiatric disease that would interfere with the ability to comply, or any other condition judged by the subject's physician that would cause this study to be detrimental to the patient.

Study design. We enrolled 119 patients with active RA in this open-label safety trial of etanercept plus HCQ (50 patients), SSZ (50 patients), and gold (19 patients). The numbers of patients enrolled in each of these groups was determined by the FDA's request to Immunex. Therefore it was not powered to detect differences in efficacy among the groups. This was a 24-week trial with the option of a 24-week extension for those showing at least a 20% improvement in ACR criteria[7]. All patients in all 3 groups received etanercept 25 mg subcutaneously twice weekly in conjunction with their respective stable dose of DMARD. Subjects were supplied with a diary to record dates and times of study doses, any adverse events, and concomitant medications. Diaries were reviewed and patients were evaluated by a physician every 6 weeks. Erythrocyte sedimentation rate (ESR) was checked with each visit, while other laboratory tests and a Health Assessment Questionnaire (HAQ) were performed every 12 weeks. Patients were followed for an additional 30 days past the date of discontinuation or study end. Etanercept was supplied free of charge to all patients during the initial 24 weeks and the second 24 weeks.

Evaluation criteria. The primary outcome of the study was evaluation of the type and grade of adverse events using the National Cancer Institute common toxicity criteria. Adverse events were tabulated and summarized according to body system as well as severity grade. The secondary objective was to evaluate efficacy as measured by ACR20 response[7]. Efficacy was determined by an intent-to-treat (ITT) analysis. Patients who withdrew for toxicity or for any other reason before 24 weeks were considered efficacy failures; all other data were analyzed using last observation carried forward (LOCF). The ACR core criteria for clinical response requires a 20% improvement in both the tender and the swollen joint counts and a 20% improvement in 3 of the following 5 indicators: patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ score, ESR, and patient's assessment of pain.

For the ACR core criteria, we utilized a validated modified joint count[8] in which 38 joints were scored. This validated joint count scores the proximal interphalangeal and metacarpophalangeal joints, wrists, elbows, knees, ankles, and metatarsophalangeal joints. The patient's assessment of global status, overall pain score, and physician's global assessment were scored using a visual analog scale, with 0 being normal and 10 representing severe problems.

Individual components of ACR core set[7] disease activity measures and the ACR20, ACR50, and ACR70 responses were also reported in this study. Difference among the groups for these outcomes was analyzed by chi-square test.

Toxicity monitoring. All patients were questioned about adverse events, and their diaries were reviewed at each followup visit. Interruption of etanercept for less than 2 weeks (4 doses) was allowed for Grade 3 systemic toxicity/adverse events not alleviated by symptomatic intervention. If Grade 3 toxicity recurred, or if patients missed more than 4 doses, they were discontinued from the study. No dose reductions of etanercept were allowed.

Concurrent therapy. No changes in DMARD, NSAID, or prednisone therapy were allowed once enrolled. Supplemental pain medicines and intraarticular or soft tissue injections were allowed (with the following restrictions: no injections were given 24 hours before a complete joint examination, any joint injected less than 4 weeks prior to a complete joint examination was counted as a tender and swollen joint for that examination, maximum steroid dose ≤ 40 mg methylprednisolone, and repeat injections were spaced at least 2 weeks apart). Joint injections within 4 weeks of the 24 and 48-week timepoints were discouraged.

RESULTS

We enrolled 119 patients with active RA in this open-label safety trial of etanercept, with 50 patients each in the SSZ and HCQ treatment groups and 19 patients in the IM gold treatment group. Baseline characteristics of the 3 treatment groups are given in Table 1. There was no significant difference in mean patient age, HAQ score, or tender or swollen joint counts among the groups. There were lower percentages of women and rheumatoid factor positivity and slightly lower mean ESR in the gold treatment group.

Overall, 10 patients (8.4%) dropped out of the study by 24 weeks, and another 15 patients (12.6%) by 48 weeks because of lack of efficacy, patient desire, or protocol violations (Figure 1). In the SSZ group, 2 patients were discontinued at 18 weeks for protocol violations, 6 others were discontinued at various times because of failure to meet ACR20 criteria, and one patient completed only the first 24 weeks despite meeting criteria for ACR50. In the HCQ group, one patient discontinued at 18 weeks because of patient desire, 9 others discontinued at various times because of efficacy failure, and one patient completed only the first 24-week study period despite meeting ACR50 criteria. In the gold group, one patient discontinued at Week 12 for a protocol violation, 2 patients discontinued as efficacy failures, and 2 completed only the first 24 weeks despite meeting ACR50 criteria at that time.

Treatment related toxicity. The primary objective of this study was to evaluate the safety of etanercept given in combination with SSZ, HCQ, and IM gold. Adverse events requiring withdrawal occurred in 10% of patients (n = 5) in the SSZ group, 10% (n = 5) in the HCQ group, and 5% (n = 1) in the gold group. In the SSZ group, one patient discontinued at Week 6 for otitis media; 3 discontinued at Week 12 for pericarditis, rash, and severe gastroenteritis, respectively; and another patient discontinued at Week 46 for increased liver function test results. Two of these 5 patients

Table 1. Baseline patient characteristics. Unless otherwise indicated, all values represent mean and standard deviation range.

Characteristic	SSZ, n = 50	HCQ, n = 50	Gold, n = 19
Age, yrs (range)	47.0 (24–74)	49.7 (28–73)	51.5 (41–72)
Female, n (%)	39 (78)	38 (76)	10 (53)
Caucasian, n (%)	44 (88)	46 (92)	19 (100)
Disease duration, yrs	8.1 ± 6.0	8.7 ± 7.8	16.1 ± 8.7
RF +, n (%)	45 (90)	38 (76)	9 (47)
Patients taking steroids, %	58	68	53
Tender joints (0–36)	16.5 ± 8.1	16.4 ± 7.8	19.3 ± 6.4
Swollen joints (0–36)	17.7 ± 7.5	17.1 ± 7.5	15.8 ± 7.6
ESR, mm/h	34.5 ± 25.9	30.6 ± 21.2	22.0 ± 17.2
HAQ score	1.32 ± 0.62	1.33 ± 0.67	1.23 ± 0.53

RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire.

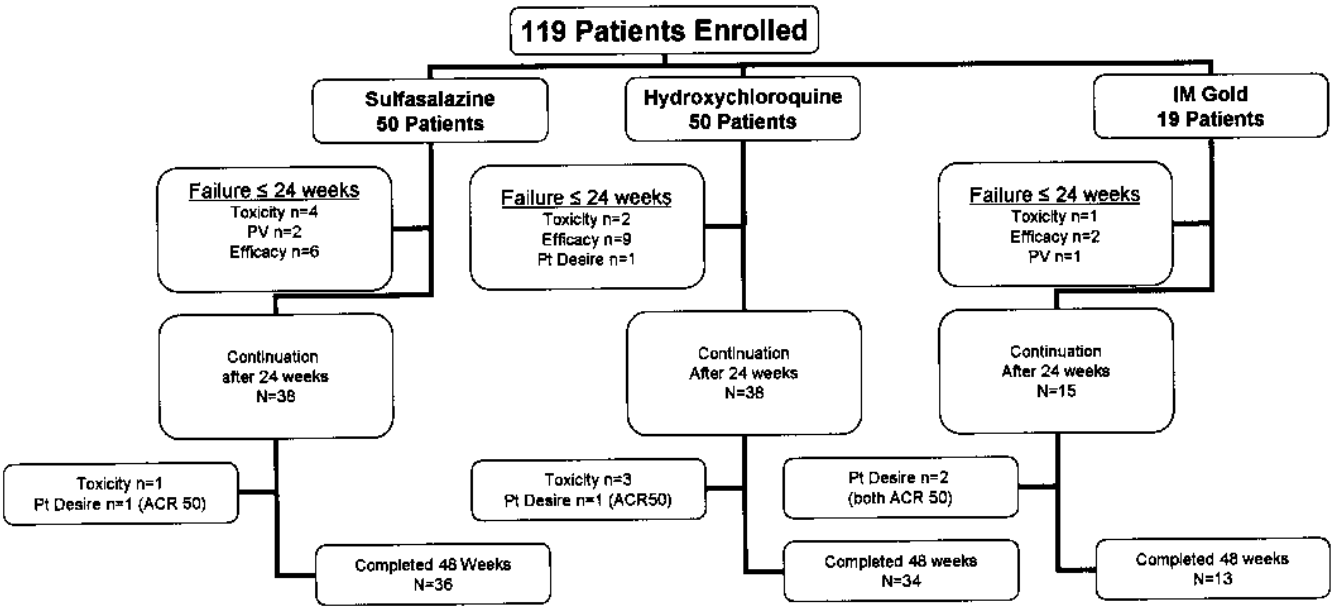

Figure 1. Procedure of patients enrolled in the study.

met ACR70 criteria, one met ACR50, and one met ACR20 prior to withdrawal. In the HCQ group, one patient was withdrawn at 12 weeks for a septic wrist and bilateral pneumonia; another was withdrawn at 12 weeks for newly diagnosed breast cancer; one patient was withdrawn at Week 26 for newly diagnosed squamous cell cancer of the tongue; one was withdrawn at 32 weeks for rash and intractable diarrhea; and another patient was withdrawn at Week 36 for optic neuritis. Two of these 5 patients met ACR70 criteria and another met ACR20 criteria prior to discontinuation. In the gold treatment group, one patient who met ACR20 criteria discontinued at Week 18 for proteinuria.

The most common adverse reactions not requiring withdrawal were injection site reactions (43% of patients), upper respiratory infections including otitis media and sinusitis (35%), ecchymosis (15%), and other infections mainly involving respiratory and genitourinary systems (16% of patients). Figure 2 shows the categories of adverse events encountered in each treatment group over 48 weeks. No cases of tuberculosis, fungal infections, or blood dyscrasias were observed in this study. There were no deaths.

Treatment outcomes. The ACR20 response was a secondary outcome measure during this trial. The ACR20, ACR50, and ACR70 responses at 24 weeks are presented in Figure 3A. There were no significant differences for ACR20 responses among the drug combination groups at either 24 or 48 weeks (Figure 3B). The mean ACR20 response for all groups was 67% at 24 weeks and 54% at 48 weeks. Also, there was lit-

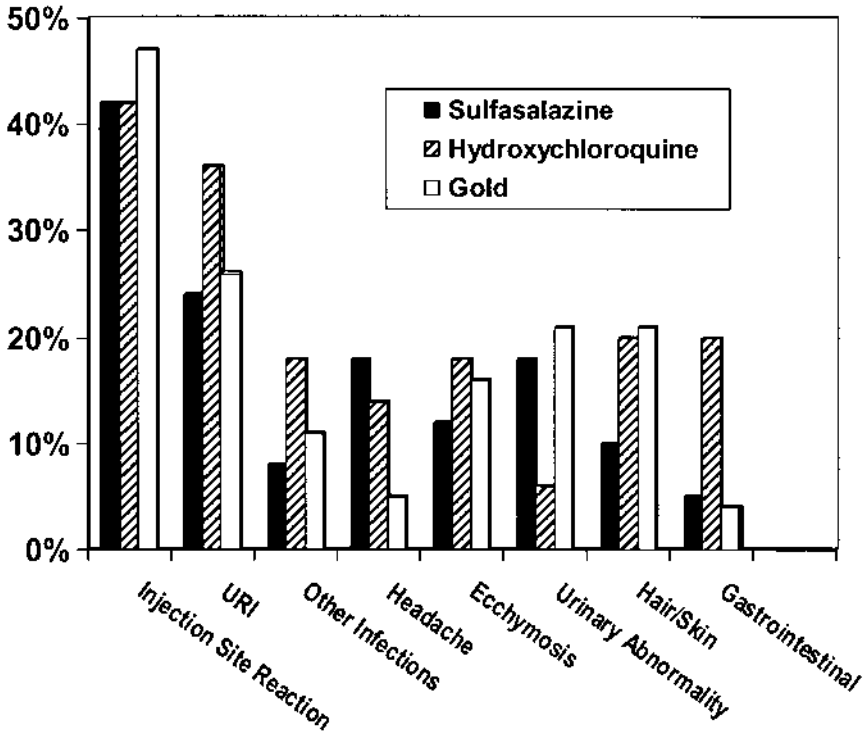

Figure 2. Categories of most common adverse events at 48 weeks (percentages of patients). URI: upper respiratory infections, including otitis media and sinusitis. Other infections included mainly lower respiratory and genitourinary infections. The majority of urinary abnormalities consisted of proteinuria or hematuria. Hair/skin involvement most often consisted of rash, hives, or alopecia.

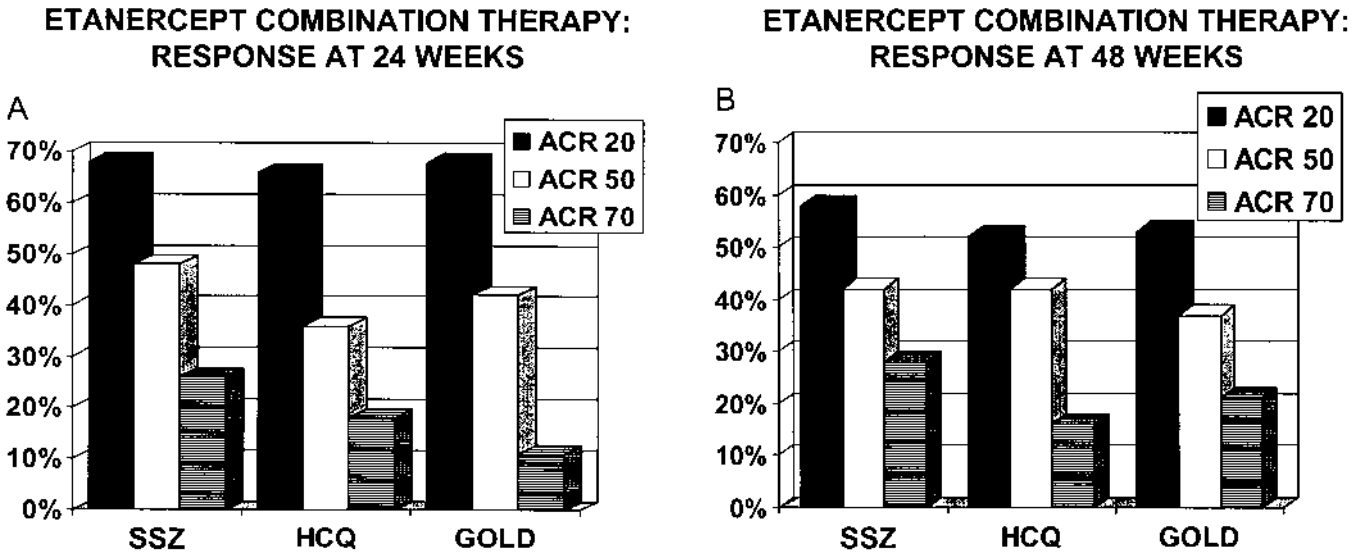

Figure 3. Response to treatment according to ACR20%, ACR50%, and ACR70% improvement criteria among patients receiving etanercept in combination with sulfasalazine (SSZ), hydroxychloroquine (HCQ), or gold at 24 weeks (A) and at 48 weeks (B).

tle variability noted among treatment groups for ACR50 responses. ACR70 responses showed some differences, with SSZ/etanercept combination patients showing the highest ACR70 response rate at both 24 and 48 weeks. Gold/etanercept combination patients had the lowest ACR70 response at 24 weeks, but improved notably by 48 weeks (Figure 3B). Evaluation of the mean ACR core set variables, presented in Table 2, also revealed significant improvement in each of the 7 individual components over 24 weeks for all 3 drug/etanercept treatment groups.

Table 2. Mean American College of Rheumatology core set changes at 24 weeks.

	SSZ	HCQ	Gold
Tender joints	–12.45 ± 8.09	–12.03 ± 7.71	–15.26 ± 7.67
Swollen joints	–13.28 ± 7.20	–11.87 ± 6.88	–9.73 ± 8.37
HAQ	–0.56 ± 0.77	–0.71 ± 0.65	–0.75 ± 0.45
ESR	–19.19 ± 20.43	–16.56 ± 11.82	–11.88 ± 10.98
Patient global score	–3.30 ± 2.43	–2.83 ± 2.98	–2.02 ± 2.35
Physician global score	–3.87 ± 1.90	–3.57 ± 1.97	–3.41 ± 1.90
Pain scale	–3.64 ± 2.64	–2.99 ± 2.54	–2.85 ± 2.22

DISCUSSION

Treatment of RA in the last decade has changed greatly with the introduction of TNF-α antagonist drugs such as etanercept. Etanercept has been shown to be effective and to have a favorable side effect profile when used as monotherapy or in combination with MTX[2,3,9,10]. In practice, rheumatologists add etanercept to existing therapy in patients with active RA[11]. Since combination conventional DMARD therapy is ubiquitous[4], many patients have etanercept added to DMARD other than MTX, although there is a paucity of published information on these combinations. In this open trial we have demonstrated a favorable side effect profile and significant improvement in clinical measures when etanercept is initiated in patients with active RA despite SSZ, HCQ, or IM gold. Our results are reminiscent of those seen when etanercept was added to treatment of patients with active disease despite MTX[3], but should be interpreted with the knowledge that this was an open trial.

The primary objective of this open trial was to investigate the safety of etanercept in combination with SSZ, HCQ, and gold in a relatively healthy population of patients with active RA. The frequency and kind of side effects (Figure 2) were similar to those seen in previous clinical trials with etanercept and with the other DMARD[3,5,10]. Postmarketing reports have raised concerns about infections in general[12-14] and especially tuberculosis[15,16], lymphoma[17], congestive heart failure[18], demyelinating disease[19], other opportunistic infections[20,21], and autoimmune disease. With these issues in mind, 3 patients in our study experienced toxicities that require further comment. One patient (HCQ group) developed a septic wrist (Group B streptococcus) and quickly developed bilateral pneumonia. After a difficult, prolonged hospital course the patient is now reasonably well controlled on conventional DMARD combination therapy. The second patient (HCQ group) developed optic neuritis and had her etanercept discontinued. She has had no further problem to suggest a demyelinating disease with one year of followup. The third patient (SSZ group) developed pericarditis as described by her primary care physician with no other signs of lupus. She discontinued therapy and followup. Further information on this patient including antinuclear antibody and DNA antibody data is not available. Two patients (HCQ group) developed cancer (breast and tongue), but no case of lymphoma was reported. Because current experience with etanercept suggests that the overall frequency of serious adverse events (serious infection, lymphoma, cancer, demyelinating disease, etc.) is low, patients need to be studied in properly powered clinical trials to adequately determine etanercept's safety in combination with other DMARD. Because trials of this size are often more costly and difficult to perform, continued postmarketing surveillance data may also be helpful in determining the significance of serious side effects found in clinical practice.

Since this was an open-label study without a placebo-treated group it is difficult to make definitive statements about the efficacy of etanercept in these patients. However, the ACR response rates (Figure 3) and the improvements in all of the ACR core components (Table 2) were clinically significant. Of interest, about 10% of patients in all groups lost their ACR20 response by 48 weeks (Figure 3B). This contrasts with the fact that ACR50 and ACR70 responses were durable or increased with time. This was most marked for ACR70 responses in the gold group, which doubled at 48 weeks.

We believe this trial has demonstrated that etanercept can safely be added to DMARD other than MTX with the potential for significant clinical improvement. Randomized blinded trials will be necessary to rigorously prove the efficacy of this approach.

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