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Therapies for Active Rheumatoid Arthritis after Methotrexate Failure

James R. O'Dell, M.D., Ted R. Mikuls, M.D., M.S.P.H., Thomas H. Taylor, M.D., Vandana Ahluwalia, M.D., Mary Brophy, M.D., M.P.H., Stuart R. Warren, J.D., Pharm.D., Robert A. Lew, Ph.D., Amy C. Cannella, M.D., Gary Kunkel, M.D., Ciaran S. Phibbs, Ph.D., Aslam H. Anis, Ph.D., Sarah Leatherman, M.A., and Edward Keystone, M.D., for the CSP 551 RACAT Investigators*

ABSTRACT

BACKGROUND

Few blinded trials have compared conventional therapy consisting of a combination of disease-modifying antirheumatic drugs with biologic agents in patients with rheumatoid arthritis who have active disease despite treatment with methotrexate — a common scenario in the management of rheumatoid arthritis.

METHODS

We conducted a 48-week, double-blind, noninferiority trial in which we randomly assigned 353 participants with rheumatoid arthritis who had active disease despite methotrexate therapy to a triple regimen of disease-modifying antirheumatic drugs (methotrexate, sulfasalazine, and hydroxychloroquine) or etanercept plus methotrexate. Patients who did not have an improvement at 24 weeks according to a prespecified threshold were switched in a blinded fashion to the other therapy. The primary outcome was improvement in the Disease Activity Score for 28-joint counts (DAS28, with scores ranging from 2 to 10 and higher scores indicating more disease activity) at week 48.

RESULTS

Both groups had significant improvement over the course of the first 24 weeks ($P=0.001$ for the comparison with baseline). A total of 27% of participants in each group required a switch in treatment at 24 weeks. Participants in both groups who switched therapies had improvement after switching ($P<0.001$), and the response after switching did not differ significantly between the two groups ($P=0.08$). The change between baseline and 48 weeks in the DAS28 was similar in the two groups (–2.1 with triple therapy and –2.3 with etanercept and methotrexate, $P=0.26$); triple therapy was noninferior to etanercept and methotrexate, since the 95% upper confidence limit of 0.41 for the difference in change in DAS28 was below the margin for noninferiority of 0.6 ($P=0.002$). There were no significant between-group differences in secondary outcomes, including radiographic progression, pain, and health-related quality of life, or in major adverse events associated with the medications.

CONCLUSIONS

With respect to clinical benefit, triple therapy, with sulfasalazine and hydroxychloroquine added to methotrexate, was noninferior to etanercept plus methotrexate in patients with rheumatoid arthritis who had active disease despite methotrexate therapy. (Funded by the Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development, and others; CSP 551 RACAT ClinicalTrials.gov number, NCT00405275.)

From the Veterans Affairs (VA) Nebraska–Western Iowa Health Care System and University of Nebraska Medical Center, Omaha (J.R.O., T.R.M., A.C.C.); White River Junction VA Medical Center, White River Junction, VT (T.H.T.); Brampton Civic Hospital, Brampton, ON (V.A.), University of British Columbia and Centre for Health Evaluation and Outcome Sciences, Vancouver (A.H.A.), and University of Toronto and Mount Sinai Hospital, Toronto (E.K.) — all in Canada; VA Cooperative Studies Program (CSP) Coordinating Center, Boston (M.B., R.A.L., S.L.) and the Schools of Medicine (M.B.) and Public Health (R.A.L.), Boston University, Boston; VA CSP Clinical Research Pharmacy Coordinating Center, Albuquerque, NM (S.R.W.); George E. Whalen VA Medical Center and University of Utah School of Medicine, Salt Lake City (G.K.); and Palo Alto VA Healthcare System, Palo Alto (C.S.P.), and Stanford University School of Medicine, Stanford (C.S.P.) — both in California. Address reprint requests to Dr. O'Dell at the Veterans Affairs Nebraska–Western Iowa Health Care System, 4101 Woolworth Ave., Omaha, NE 68105, or at james.o'dell@va.gov.

*A complete list of investigators in the CSP 551 RA: Comparison of Active Therapies (RACAT) study is provided in the Supplementary Appendix, available at NEJM.org.

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The prognosis for patients with rheumatoid arthritis has improved dramatically over the past two decades.[1,2] The reasons for the improved prognosis include earlier diagnosis, treatment targeted to low disease activity or remission, the use of disease-modifying antirheumatic drugs (DMARDs) in combinations, and the availability of biologic therapies.[1-4] A substantial portion of patients who are diagnosed today will have a clinical remission with therapy.[1,2,5,6] Unfortunately, the cost of treating rheumatoid arthritis has also risen dramatically, and this disease is now more expensive to treat than diabetes,[7] largely as a consequence of the biologic therapies.

Most clinicians initiate therapy with methotrexate; however, only 30% of patients will have low disease activity with methotrexate alone.[6,8,9] All nine of the biologic agents approved by the Food and Drug Administration[10-20] and several combinations of conventional DMARDs[21-25] are more effective than placebo when added to methotrexate in this population, but the option most often preferred by clinicians is to add a tumor necrosis factor (TNF) inhibitor to methotrexate.[3] TNF inhibitors are considerably more expensive than are conventional DMARDs, and therefore this decision has dramatic economic consequences.

Despite the wealth of biologic agents and conventional DMARDs that can be used when methotrexate alone is insufficient, few blinded trials have compared conventional DMARDs with a biologic agent in this common clinical scenario. We compared the strategy of first adding conventional DMARDs to methotrexate with the strategy of first adding etanercept to methotrexate in patients with active disease despite methotrexate therapy.

Methods

Design

We conducted a multicenter, double-blind, noninferiority trial in which patients with active rheumatoid arthritis were randomly assigned to sulfasalazine and hydroxychloroquine added to methotrexate (triple therapy) or to etanercept (Enbrel, Amgen) added to methotrexate (etanercept–methotrexate therapy). Patients in both groups who did not have a response to the assigned therapy were switched at 24 weeks to the other therapy. Because we were evaluating which therapy to start first, we chose as the primary outcome the change in the Disease Activity Score for 28-joint counts (DAS28, with scores ranging from 2 to 10 and higher scores indicating more disease activity) at 48 weeks according to the initial therapeutic regimen to which the participants had been randomly assigned (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Study Oversight

The trial was conducted at 16 Veteran Affairs hospitals, 12 Rheumatoid Arthritis Investigational Network sites, and 8 Canadian medical centers. The Veterans Affairs Cooperative Studies Program was responsible for the collection of the data, the analysis of the data (Boston site), the provision of and payment for study medications, and the preparation and distribution of the placebo (Albuquerque site). Amgen donated the placebo etanercept but had no role in the design of the study, the collection or analysis of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Blinded sulfasalazine and placebo tablets were purchased at a reduced price from Pharmascience, which also had no role in the study.

An independent data and safety monitoring committee monitored the trial for safety and scientific integrity. The research protocol and written-informed-consent documents were approved by the institutional review board at each participating site. The first author wrote all drafts of the manuscript and made the decision to submit the manuscript for publication. All the authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of this report to the study protocol, available at NEJM.org.

Participants

From July 2007 through December 2010, we enrolled 353 participants 18 years of age or older who met 1987 American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis,[26] had been receiving methotrexate at stable doses of 15 to 25 mg weekly for at least 12 weeks, had a DAS28 of 4.4 or higher, and met inclusion criteria and had no exclusion criteria (Fig. S2 in the Supplementary Appendix; for a full

list of inclusion and exclusion criteria, see Table S1 in the Supplementary Appendix). All the enrolled participants provided written informed consent.

INTERVENTIONS

Participants continued to receive methotrexate throughout the trial, at the dose that they were receiving at the time of enrollment. Participants who were assigned to the triple-therapy group received sulfasalazine at a dose of 1 g daily for the first 6 weeks, with the dose increased thereafter to 2 g daily, and also received hydroxychloroquine, at a dose of 400 mg daily, and an injection of placebo etanercept weekly. Participants who were assigned to the etanercept–methotrexate group received an injection of etanercept at a dose of 50 mg weekly and placebo sulfasalazine and hydroxychloroquine tablets daily. If the score on the DAS28 decreased (indicating improvement) by 1.2 or more by 24 weeks, the initial therapy was continued. If the score on the DAS28 decreased by less than 1.2, the participant was switched to the alternative regimen. Sulfasalazine could be reduced to 500 mg twice a day if a participant had unacceptable side effects with the higher dose. Participants continued to receive nonsteroidal antiinflammatory agents and prednisone (≤10 mg per day) at stable doses.

Participants were seen every 6 weeks for monitoring of laboratory values and adverse events. At the time of enrollment and every 12 weeks, the Health Assessment Questionnaire II[27] was administered, a count of joints with disease activity was performed, and pain was assessed. At the time of enrollment and every 24 weeks, the DAS28 was calculated, the physician's global assessment (an overall assessment of disease) was performed, quality-of-life and functional surveys were administered, and radiographs were obtained. Adherence to study medications was assessed by means of tablet counts in returned bottles and with the use of diaries in which participants noted injection dates.

OUTCOMES

The primary outcome was the change in the DAS28 at 48 weeks according to the initial regimen. The DAS28 is a composite index of the number of swollen and tender joints, the erythrocyte sedimentation rate, and a visual-analogue scale of patient-reported disease activity.[28] A decrease in the DAS28 of 1.2 or more was considered to be a clinically meaningful improvement.[29]

The originally proposed primary outcome was the difference in the proportion of participants who had a DAS28 of 3.2 or less at week 48. In response to unexpectedly low enrollment, the protocol was amended in October 2008 to change the primary outcome from a binary outcome to a continuous outcome in order to increase the power of the study. Funding constraints mandated ending enrollment before the revised sample-size target of 450 was reached.

Secondary outcomes included radiographic progression (according to the van der Heijde modification of the Sharp score, which ranges from 0 to 380, with higher scores indicating more extensive disease[30]); the proportion of participants with a DAS28 of 3.2 or less, a value that is consistent with low disease activity[29]; American College of Radiology (ACR) 20, 50, and 70 responses, indicating 20%, 50%, and 70% reductions, respectively, in the number of both tender and swollen joints and equivalent improvement in at least three of five other criteria[31]; responses on the Clinical Disease Activity Index, which is a composite score of the sum of tender and swollen joints (28 joints) and the patient and physician global assessments (each scored with the use of a visual-analogue scale ranging from 0 to 10 cm)[32]; and functional outcomes, as measured with the use of the Health Assessment Questionnaire II.[29]

Posterior–anterior hand and wrist images and anterior–posterior forefoot images were obtained at baseline, 24 weeks, and 48 weeks and were scored independently by two trained readers. The readers were not aware of the treatment the participant was receiving or of the week of treatment during which the images were obtained. The mean of the scores from the two readers was used.

STATISTICAL ANALYSIS

The comparisons between the study groups were performed with the use of Student's t-test for continuous measures and the chi-square test (or Fisher's exact test) for categorical measures. The primary comparison was between triple therapy and etanercept–methotrexate therapy. We tested the one-sided hypothesis that triple therapy

would not be inferior to etanercept–methotrexate therapy, with rejection of the null hypothesis if the upper limit of a one-sided 95% confidence interval for the difference between the groups in the change from baseline to 48 weeks (triple therapy minus etanercept–methotrexate therapy) would be less than 0.6. This value is half of 1.2, which is the value associated with the minimal clinically important change in the DAS28.[29]

We estimated that with 450 participants, the study would have 90% power to detect a between-group difference in the change from baseline to 48 weeks of 0.3, at a type I error of 5%, using formula 3.2.3 in Chow et al.[33] The protocol prespecified that the test for noninferiority in the primary analysis would use a two-factor analysis of variance with factors for treatment regimen and for switching the regimen at 24 weeks and the interaction term. Also prespecified in the protocol was an analysis without adjustment for switching. The results of the two analyses were similar. We report the results of both analyses, but we consider the analysis without adjustment for switching to be more appropriate, given that the purpose of the study was to compare the two strategies according to the treatment received at the time of randomization. The one-sided confidence interval was based on the least-square-means estimate of the difference in the change and its standard error. Missing data on outcomes were not imputed; all the analyses were performed on an intention-to-treat basis with data from patients who completed the 48-week assessment.

Per-protocol analyses that were restricted to the subgroup of participants who adhered to the study treatment (defined as taking at least 80% of each prescribed study medication over the course of 48 weeks) were performed for the primary outcome (continuous variable: change in the DAS28). Planned exploratory analyses (with the use of Student's t-test or the chi-square test) compared the two groups with respect to the Health Assessment Questionnaire II score; the ACR20, ACR50, and ACR70 responses; the scores on the DAS28 indicating low disease activity and remission[28]; scores on the Clinical Disease Activity Index[32]; and modified Sharp scores (the sum of the scores for erosion and joint-space narrowing), as assessed by means of imaging.

RESULTS

PARTICIPANTS

There were no significant differences in baseline characteristics between the two groups (Table 1). There were also no significant between-group differences in baseline characteristics in the subgroup of 309 patients who completed the 48-week assessments and were included in the efficacy analyses. The mean baseline dose of methotrexate (19.6 mg per week) was higher than the mean baseline dose in most trials — reflecting the desire to enroll participants in our study only after an adequate trial of methotrexate. The rates of withdrawal from the study were balanced between the groups (Fig. S2 in the Supplementary Appendix). Participants in the triple-therapy group adhered to treatment 78% of the time, and participants in the etanercept–methotrexate group adhered 79% of the time.

PRIMARY OUTCOME

Among the 309 participants for whom 48-week DAS28 scores were available, the difference between the groups in the mean (±SD) change in the DAS28 from baseline to 48 weeks was 0.17±0.15; triple therapy was noninferior to etanercept–methotrexate therapy, since the 95% upper confidence limit of 0.41 was below the noninferiority margin of 0.60 ($P=0.002$ for noninferiority) (Fig. S3B in the Supplementary Appendix). In analyses that were adjusted for a switch in treatment at 24 weeks among patients who did not have adequate improvement with the therapy to which they had been assigned, the results were similar (difference in change, 0.01±0.16; 95% upper confidence limit, 0.27; $P<0.001$ for noninferiority) (Fig. S3A in the Supplementary Appendix). In the subgroup of participants who adhered to treatment, triple therapy was also noninferior to etanercept–methotrexate therapy ($P<0.001$) (Fig. S3A and S3B in the Supplementary Appendix). We did not find a differential treatment response or a significant difference in improvement according to sex (data not shown).

SWITCHING

Both groups had significant improvement over the course of the first 24 weeks ($P=0.001$ for the comparison with baseline). Switching to the alter-

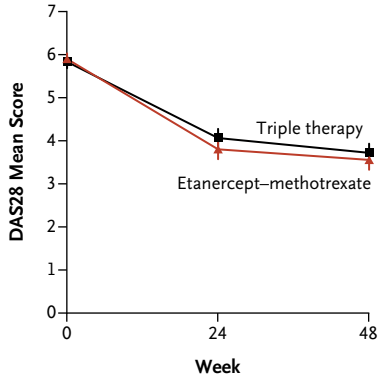
Table 1. Baseline Characteristics of the Participants.*

Characteristic	Triple Therapy (N=178)	Etanercept–Methotrexate (N=175)
Age — yr	57.8±13.0	56.0±13.2
Female sex — no. (%)	77 (43.3)	85 (48.6)
White race — no. (%)†	161 (90.4)	146 (83.4)
Body-mass index‡	29.9±5.9	29.3±6.6
Current smoker — no. (%)	46 (25.8)	46 (26.3)
Positive for rheumatoid factor — no. (%)	117 (65.7)	117 (66.9)
Time since diagnosis — yr	5.5±9.3	4.9±8.0
Assessments§		
DAS28	5.8±0.9	5.9±0.9
Patient's global assessment	5.4±2.2	5.6±1.9
Physician's global assessment	6.0±2.3	6.1±2.0
Swollen-joint count	11.1±5.3	11.3±5.2
Tender-joint count	13.4±6.6	13.3±6.4
Health Assessment Questionnaire II score	1.4±0.8	1.5±0.8
Erythrocyte sedimentation rate — mm/hr	27.4±21.0	29.7±23.5
Clinical Disease Activity Index	36.0±11.5	36.4±11.2
Modified Sharp score	20.4±29.2	16.3±22.0
Concomitant medications		
Methotrexate		
Mean dose — mg/wk	19.5±5.0	19.7±4.5
Distribution — no. (%)		
10 or 12.5 mg/wk¶	3 (1.7)	4 (2.3)
15 or 17.5 mg/wk	55 (30.9)	52 (29.7)
20 or 22.5 mg/wk	77 (43.3)	95 (54.3)
25 mg/wk	43 (24.2)	23 (13.1)
Oral glucocorticoids — no. (%)	84 (47.2)	87 (49.7)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in any baseline characteristic.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The Disease Activity Score for 28-joint counts (DAS28) ranges from 2 to 10, with higher scores indicating more disease activity. The patient's and physician's global assessments are self-reported and physician-reported, respectively, overall assessments of disease with the use of a visual-analogue scale that ranges from 0 to 10 cm. The swollen-joint and tender-joint counts are the number of swollen and tender joints, respectively, out of 28 joints assessed. Scores on the Health Assessment Questionnaire II range from 0 to 3, with higher scores indicating greater disability. Scores on the Clinical Disease Activity Index range from 0 to 76, with higher scores indicating more disease activity. Scores on the van der Heijde modification of the Sharp score range from 0 to 380, with higher scores indicating more extensive disease.
¶ This dose was used in patients who had unacceptable side effects with higher doses.

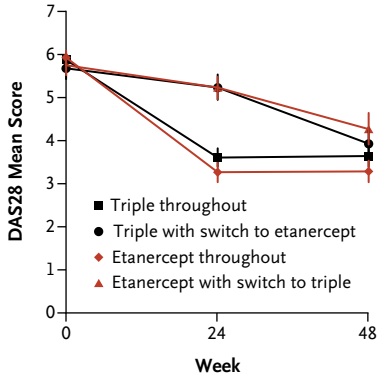
native therapy at 24 weeks owing to a clinically insignificant response occurred with equal frequency in the two groups, with 44 of 163 participants (27.0%) switching from triple therapy to etanercept–methotrexate therapy and 44 of 165 (26.7%) switching from etanercept–methotrexate therapy to triple therapy. Both groups of participants who switched had improvement in the DAS28 with the alternative therapy by week 48 ($P<0.001$ for both comparisons) (Fig. 1B).

A Change in DAS28 According to Initial Treatment



No. Evaluated			
Triple therapy	178	157	154
Etanercept–methotrexate	175	161	155

B Change in DAS28 According to Initial and Subsequent Treatment



No. Evaluated			
Triple throughout	134	113	115
Triple with switch to etanercept	44	44	39
Etanercept throughout	131	117	114
Etanercept with switch to triple	44	44	41

Figure 1. Mean Scores on the DAS28.

Panel A shows the mean scores on the Disease Activity Score for 28-joint counts (DAS28, with scores ranging from 2 to 10 and higher scores indicating more disease activity) according to the regimen to which the participants were randomly assigned at the beginning of the study. Triple therapy was noninferior to etanercept–methotrexate therapy (P=0.002). Panel B shows the mean scores according to the therapies received during the course of the 48-week intervention period. Both groups of participants who switched therapies at 24 weeks (represented by the top two curves: triple therapy to etanercept–methotrexate and etanercept–methotrexate to triple therapy) had significant improvement after the switch (P<0.001 for each), with no significant difference in the amount of improvement (P=0.08). In both panels, I bars indicate 95% confidence intervals.

ACR AND DAS28 RESPONSES

There were no significant differences between the two groups in ACR 20 and ACR 50 responses at either 24 or 48 weeks (Table 2, and Fig. S4 in the Supplementary Appendix). A larger percentage of participants in the etanercept–methotrexate group had an ACR 70 response at 24 weeks, but the difference was not maintained at 48 weeks. DAS28 responses favored etanercept–methotrexate therapy at 24 weeks but did not differ significantly from those in the triple-therapy group at 48 weeks.

RADIOGRAPHIC RESULTS

There was no significant difference between the two groups in radiographic progression over the course of 48 weeks (Table 2). Participants in the triple-therapy group had a mean progression of 0.54 Sharp score units, and participants in the etanercept–methotrexate group had a mean progression of 0.29 Sharp score units (P=0.43). Radiographic progression as assessed on the basis of cumulative probability was not distinguishable between the two groups (Fig. S4 in the Supplementary Appendix).

FUNCTIONAL OUTCOMES

Both regimens resulted in clinically significant improvement in physical function (Table 2). All the participants, regardless of whether they continued the initial therapy or switched at 24 weeks, had a significant improvement in the score on the health assessment questionnaire at the end of the trial (Table S3A in the Supplementary Appendix).

ADVERSE EVENTS AND DISCONTINUATION OF MEDICATION

Table 3 shows the adverse events and serious adverse events that were reported during the intervention period and for 4 weeks after completion of the blinded intervention. Results are presented according to the therapy that the participant was receiving at the time of the event. After accounting for switching, 222 participants were exposed to triple therapy, and 219 to etanercept–methotrexate therapy. The frequencies of adverse events were similar in the two groups (Table S4 in the Supplementary Appendix). Gastrointestinal disorders occurred more frequently with triple therapy, whereas infections and skin and subcutaneous disorders occurred more frequently with etanercept–methotrexate therapy. A total of 17 participants discontinued the intervention owing to an adverse event. Gastrointestinal disorders ac-

counted for 7 of 12 discontinuations in the triple-therapy group, whereas infections accounted for 4 of the 5 discontinuations in the etanercept–methotrexate group.

Although the overall frequency of serious adverse events was similar in the two groups, there was a larger number of serious infections with etanercept–methotrexate therapy. A total of 12 serious infections occurred with etanercept–methotrexate therapy. One of these resulted in death due to pneumonia, and there was one case each of pulmonary aspergillosis and recurrent fungal sinusitis; in both cases, the patients recovered. Four serious infections occurred in the triple-therapy group; all resolved without sequelae.

DISCUSSION

Prior studies have shown that the addition of either a TNF inhibitor[10-20] or several different conventional DMARDs[21-25] to methotrexate in patients with rheumatoid arthritis who have active disease despite treatment with methotrexate results in substantial clinical benefit. Despite this knowledge and the considerable cost differences between these two approaches, few blinded studies have compared their effectiveness. This blinded trial compared the strategy of first adding conventional therapy to methotrexate with the strategy of first adding etanercept to methotrexate in patients with active disease despite treatment with methotrexate. In clinical practice, patients' therapies are escalated if their disease is not responding; therefore, in this trial, participants were switched at 24 weeks to the other therapy if they had not had a meaningful response. Because we were evaluating which therapy to start first, the primary outcome was the change in DAS28 from baseline to 48 weeks according to the initial treatment to which the participant had been randomly assigned. In this noninferiority trial, triple therapy was shown to be noninferior to etanercept–methotrexate. An important secondary outcome was radiographic progression at 48 weeks, and again there was no significant clinical or statistical difference between the two regimens.

Comparative-effectiveness trials in rheumatoid arthritis are challenging, given that the disease has been shown to progress when it is inadequately controlled. Randomly assigning participants to a fixed treatment regimen and then requiring them to continue that regimen for months or years, regardless of response, is ethically questionable[35] and does not provide meaningful clinical data past the point at which participants who have not had an adequate response should have switched to a different therapy. Trials that allowed for clinically indicated switches have all been open-label in design[8,9,36] and suffer from the potential biases of open studies. We mandated a blinded switch in therapy at 24 weeks unless participants had a clinically meaningful improvement. It was recognized when the trial was designed that if the rate of switching differed significantly between the two groups at 24 weeks, clinical interpretation of the trial results could be problematic. However, the observed rates of switching were nearly identical (27.0% in the triple-therapy group and 26.7% in the etanercept–methotrexate group), further validating the similarity of the regimens.

Two published trials, the Swedish Pharmacotherapy (Swefot) study[9] and the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) study,[6] have compared conventional therapy with TNF inhibitors in patients with active disease despite treatment with methotrexate. The Swefot study, which was not blinded and allowed frequent switches, showed no significant difference between infliximab therapy and therapy with sulfasalazine and hydroxychloroquine at 6 months but did show a benefit with infliximab at 12 months. The TEAR study, which involved patients with very early rheumatoid arthritis, included a subgroup of patients who had not had an adequate response to methotrexate and then received either etanercept or sulfasalazine and hydroxychloroquine; there was no significant difference in outcome between these two regimens, thus corroborating our finding in a different population.

Our study has several limitations. First, the target sample size was not reached. Despite this shortfall, the 95% confidence interval for noninferiority did not approach the conservatively defined threshold of 0.6. Since a DAS28 change of 1.2 or more is an accepted standard for clinically meaningful change,[29] a DAS28 change of 0.6 or less was thought to be clinically insignificant. Second, in our study, which included a large number of participants from Veteran Affairs hospitals, 54% of the participants were men, as compared with 20 to 30% of the participants in other studies. The literature suggests that men may have a better response to treatment than women,[6] but to our knowledge, there

Table 2. Change from Baseline in Outcome Measures.*

Measure	Triple Therapy		Etanercept–Methotrexate		P Value†
	No. of Participants Assessed	Mean Change	No. of Participants Assessed	Mean Change	
Continuous measures					
DAS28‡					
At 24 wk	157	−1.79±1.20	161	−2.06±1.35	0.06
At 48 wk	154	−2.12±1.28	155	−2.29±1.30	0.26
Health Assessment Questionnaire II score§					
At 24 wk	155	−0.44±0.77	160	−0.51±0.84	0.46
At 48 wk	155	−0.46±0.82	155	−0.64±0.78	0.06
Modified Sharp score					
At 24 wk	158	0.42±1.91	160	0.003±3.62	0.20
At 48 wk	151	0.54±1.93	153	0.29±3.32	0.43
Erosion¶					
At 24 wk	158	0.23±1.32	160	−0.03±1.44	0.10
At 48 wk	151	0.29±1.35	153	0.08±1.48	0.21
Joint-space narrowing‖					
At 24 wk	158	0.19±1.25	160	0.03±2.47	0.45
At 48 wk	151	0.25±1.18	153	0.21±2.09	0.83
Clinical Disease Activity Index					
At 24 wk	157	−17.53±13.07	160	−18.72±13.07	0.48
At 48 wk	154	−20.93±12.61	154	−21.56±11.25	0.64
Dichotomous measures — no. (%)					
DAS28 ≤3.2					
At 24 wk	157	39 (24.8)	161	56 (34.8)	0.05
At 48 wk	154	57 (37.0)	155	65 (41.9)	0.38
DAS28 ≤2.6					
At 24 wk	157	20 (12.7)	161	35 (21.7)	0.03
At 48 wk	154	32 (20.8)	155	39 (25.2)	0.36
ACR 20**					
At 24 wk	159	89 (56.0)	163	90 (55.2)	0.89
At 48 wk	155	89 (57.4)	155	102 (65.8)	0.13

ACR 50**					
At 24 wk	159	41 (25.8)	163	58 (35.6)	0.06
At 48 wk	155	55 (35.5)	155	66 (42.6)	0.20
ACR 70**					
At 24 wk	159	8 (5.0)	163	26 (16.0)	0.001
At 48 wk	155	28 (18.1)	155	41 (26.5)	0.08

* Plus–minus values are means ±SD.
† P values for the comparison between triple therapy and etanercept–methotrexate with respect to the change from baseline were calculated with the use of Student's t-test for continuous measures and the chi-square test for dichotomous measures.
‡ A change of 1.2 or more is considered to be a clinically meaningful change.[29]
§ A change of 0.22 or more is considered to be a clinically meaningful change.[34]
¶ Erosion was graded on a scale of 0 to 220, with higher scores indicating more extensive erosion.
‖ Joint-space narrowing was graded on a scale of 0 to 160, with higher numbers indicating increased narrowing of joint spaces.
** American College of Radiology (ACR) 20, 50, and 70 responses indicate 20%, 50%, and 70% reductions, respectively, in the number of both tender and swollen joints and equivalent improvement in at least three of five other criteria.[31]

are no data to suggest that sex is associated with a differential response to a particular therapy. Moreover, our study did not show a differential treatment response or a significant difference in improvement according to sex alone (data not shown). Third, the mean dose of methotrexate that the participants in our study were taking (19.6 mg per week) was significantly higher than the mean dose in most of the previous trials (13.5 to 17.0 mg per week).[14-20] The methotrexate dose in our study was higher by design, to ensure that the participants had adequate exposure to methotrexate. This design makes our findings more relevant to a patient population that requires intensification of therapy beyond methotrexate. Finally, our study showed a clear trend favoring a more rapid response in the etanercept–methotrexate group. Although ACR 20 responses were nearly identical in the two groups, the percentage of patients with ACR 70 responses at 24 weeks was higher with etanercept–methotrexate than with triple therapy. Whether a more rapid response earlier in treatment translates into a longer-term benefit is unknown.

In the majority of patients with rheumatoid arthritis who have active disease despite methotrexate therapy, treatment with methotrexate and either a TNF inhibitor or sulfasalazine and hydroxychloroquine does not result in low disease activity (DAS28 ≤3.2), and such patients are at least potential candidates for a change in therapy.[10-25] The proportions of participants in our trial who had a DAS28 of 3.2 or less at 24 weeks were similar to the proportions that have been reported with other therapies.[15-19] We assessed the responses of patients who did not have a meaningful response (defined as a decrease of at least 1.2 points on the DAS28) while receiving triple therapy and were then treated with etanercept–methotrexate, and, conversely, the responses of patients who did not have a meaningful response with etanercept–methotrexate and were then treated with triple therapy. Our secondary analysis of the responses showed significant clinical improvement in both groups.

In this blinded trial, we have compared conventional combination DMARD therapy with etanercept in patients with rheumatoid arthritis who had active disease despite treatment with methotrexate. Our findings suggest that a strategy of first administering triple therapy, with a switch to etanercept–methotrexate in patients who do not

Table 3. Most Frequently Reported Adverse Events.*

Variable	Triple Therapy (N=222)	Etanercept (N=219)
	no. of patients (%)	
Death	0	1 (0.5)
Discontinuation of treatment owing to adverse event	12 (5.4)	5 (2.3)
Any adverse event	170 (76.6)	165 (75.3)
Adverse events in ≥5% of patients†		
Eye disorder	21 (9.5)	17 (7.8)
Gastrointestinal disorder‡	66 (29.7)	47 (21.5)
General disorder or administration-site condition	38 (17.1)	41 (18.7)
Infection or infestation§	56 (25.2)	82 (37.4)
Injury, poisoning, or procedural complication	18 (8.1)	21 (9.6)
Laboratory abnormalities	29 (13.1)	26 (11.9)
Musculoskeletal or connective-tissue disorder	44 (19.8)	39 (17.8)
Nervous system disorder	33 (14.9)	41 (18.7)
Respiratory, thoracic, or mediastinal disorder	28 (12.6)	24 (11.0)
Skin or subcutaneous tissue disorder‡	22 (9.9)	36 (16.4)
Any serious adverse event	25 (11.3)	26 (11.9)
Serious adverse events in ≥1% of patients		
Gastrointestinal disorder	4 (1.8)	4 (1.8)
Infection or infestation	4 (1.8)	9 (4.1)
Renal or urinary disorder	0	3 (1.4)
Surgical or medical procedure	3 (1.4)	4 (1.8)
Vascular disorder	3 (1.4)	4 (1.8)
Cardiac disorder	4 (1.8)	0
Respiratory, thoracic, or mediastinal disorder	3 (1.4)	0
Other	6 (2.7)	3 (1.4)

* The adverse events are listed according to the therapy that the participant was receiving at the time of the event.
† A total of 561 adverse events were reported in 5% or more of the patients in the triple-therapy group, and 614 in the etanercept–methotrexate group.
‡ $P<0.05$ for the between-group comparison, assuming equal follow-up time and independent treatment groups.
§ $P=0.006$ for the between-group comparison, assuming equal follow-up time and independent treatment groups.

have an adequate response to triple therapy, will allow a substantial percentage of patients to be treated in a more cost-effective way without adversely affecting the clinical outcomes.

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