

TREATMENT OF RHEUMATOID ARTHRITIS WITH METHOTREXATE ALONE, SULFASALAZINE AND HYDROXYCHLOROQUINE, OR A COMBINATION OF ALL THREE MEDICATIONS

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Abstract Background. Rheumatoid arthritis is a common disease that causes substantial morbidity and mortality. The responses of patients with rheumatoid arthritis to treatment with a single so-called disease-modifying drug, such as methotrexate, are often suboptimal. Despite limited data, many patients are treated with combinations of these drugs.

Methods. We enrolled 102 patients with rheumatoid arthritis and poor responses to at least one disease-modifying drug in a two-year, double-blind, randomized study of treatment with methotrexate alone (7.5 to 17.5 mg per week), the combination of sulfasalazine (500 mg twice daily) and hydroxychloroquine (200 mg twice daily), or all three drugs. The dose of methotrexate was adjusted in an attempt to achieve remission in all patients. The primary end point of the study was the successful completion of two years of treatment with 50 percent improvement in composite symptoms of arthritis and no evidence of drug toxicity.

Results. Fifty of the 102 patients had 50 percent improvement at nine months and maintained at least that degree of improvement for two years without evidence of major drug toxicity. Among them were 24 of 31 patients treated with all three drugs (77 percent), 12 of 36 patients treated with methotrexate alone (33 percent, $P < 0.001$ for the comparison with the three-drug group), and 14 of 35 patients treated with sulfasalazine and hydroxychloroquine (40 percent, $P = 0.003$ for the comparison with the three-drug group). Seven patients in the methotrexate group and three patients in each of the other two groups discontinued treatment because of drug toxicity.

Conclusions. In patients with rheumatoid arthritis, combination therapy with methotrexate, sulfasalazine, and hydroxychloroquine is more effective than either methotrexate alone or a combination of sulfasalazine and hydroxychloroquine. (N Engl J Med 1996;334:1287-91.)

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RHEUMATOID arthritis is a common disease¹ that causes substantial morbidity in most patients² and premature mortality in many.²⁻⁴ Conventional therapy for rheumatoid arthritis includes the administration of antiinflammatory drugs, followed by disease-modifying antirheumatic drugs such as methotrexate, hydroxychloroquine, sulfasalazine, and gold in patients with persistent active disease. Short-term studies⁵⁻¹⁴ and meta-analyses^{15,16} have repeatedly proved the efficacy of disease-modifying drugs, but their long-term effectiveness is less than optimal; therefore, most patients do not take them for more than two to five years,^{17,18} because of either lack of efficacy or toxic effects. Patients treated with methotrexate have the highest rate of continued long-term therapy,¹⁹⁻²¹ and therefore most rheumatologists consider it the drug of choice.²² We designed a study to determine whether disease-modifying drugs were effective as combination therapy for rheumatoid arthritis and whether the combinations studied had better efficacy than methotrexate alone.

METHODS

This study was conducted by the Rheumatoid Arthritis Investigational Network (RAIN), which brings rheumatologists at the University of Nebraska together with rheumatologists in Nebraska, Iowa, South Dakota, Minnesota, and Illinois who are interested in clinical studies of rheumatoid arthritis. All the participating physicians were

involved not only in enrolling patients and collecting data, but also in developing the study protocols.

Selection of Patients

We asked patients followed in the rheumatology clinics at the University of Nebraska Medical Center, the Omaha Veterans Affairs Medical Center, or the private offices of physicians in the network who met the criteria for this study to participate. The protocol was approved by the Food and Drug Administration and the institutional review board at the University of Nebraska, and all the patients gave informed written consent.

The criteria for entry into the study were an age of 19 to 70 years; rheumatoid arthritis fulfilling the criteria of the American Rheumatism Association²³; disease lasting more than six months; and active disease with at least three of the following: erythrocyte sedimentation rate ≥ 28 mm per hour, morning stiffness lasting 45 minutes or more, eight or more tender joints, and three or more swollen joints. In addition, the patients must have had poor responses to treatment with at least one of the following: gold, hydroxychloroquine, penicillamine, sulfasalazine, and methotrexate. Patients were not eligible for the study if they had received combination therapy with two of these drugs; if they had stage IV disease²⁴ or were allergic to any of the study drugs; if they were women of childbearing age who were not using contraception; if they had liver, renal, hematologic, pulmonary, or cardiovascular disease; if they had visual difficulties, including a recent decrease in visual acuity, retinal disease, or macular degeneration; or if they had active peptic ulcer disease.

Study Design

We enrolled 102 patients in this two-year, double-blind, randomized, controlled study. The pharmacy performed the randomization; equal numbers of cards with each group assignment were mixed, drawn, and placed in sequentially numbered envelopes that were opened as the patients were enrolled. The patients were treated with methotrexate alone, the combination of hydroxychloroquine and sulfasalazine, or all three drugs. They received methotrexate (Rheumatrex, Lederle, Pearl River, N.Y.) or placebo in one bottle, sulfasalazine (Azulfidine, Pharmacia, Columbus, Ohio) or placebo in another bot-

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tle, and hydroxychloroquine (Plaquenil, Sanofi Winthrop, New York) or placebo in a third bottle. The doses of sulfasalazine and hydroxychloroquine were 500 and 200 mg twice daily, respectively, and the initial dose of methotrexate was 7.5 mg per week.

The patients were evaluated three months after enrollment by physicians who were unaware of the treatment-group assignments. If a patient did not meet the criteria for remission,²⁵ we increased the dose of methotrexate (or placebo) to 12.5 mg per week. The patient was then evaluated at six months. If he or she was not in remission, the dose of methotrexate (or placebo) was increased to 17.5 mg per week. Since most patients did not meet the criteria for remission while taking lower doses, over 90 percent received 17.5 mg of methotrexate or placebo per week. We evaluated the patients again after nine months of therapy (i.e., after three months of maximal therapy), and if their condition had not improved by 50 percent we considered the treatment ineffective. If they had improved by 50 percent or more, we followed them every three months for the remainder of the two-year study period.

Evaluation Criteria

The main end point was whether the patient's condition improved by at least 50 percent, as determined by whether three of the following requirements had been fulfilled (the modified Paulus composite criteria²⁶): morning stiffness of less than 30 minutes' duration, or decreased by 50 percent; joint tenderness decreased by 50 percent; joint swelling decreased by 50 percent; and an erythrocyte sedimentation rate of less than 30 mm per hour in women and less than 20 mm per hour in men. Patients who did not have this degree of improvement at any of the three-month evaluations after receiving maximal therapy were considered to have had treatment failures.

Additional measures of evaluation included estimates of the duration of morning stiffness and scores on a modified Ritchie articular index,²⁷ in which 38 joints in each patient were scored on a scale of 0 to 3 with regard to tenderness and swelling. The patient's global status and level of overall pain (as scored by the patient) and the physician's global assessment were scored on a visual-analogue scale on which 0 indicated normal and 10 indicated severe problems.²⁸

Monitoring of Toxicity

An ophthalmologist examined all the patients every six months for potentially toxic effects of hydroxychloroquine. All the patients had complete blood counts and measurements of serum aspartate aminotransferase, albumin, and creatinine concentrations monthly during the study. Erythrocyte sedimentation rates were measured every three months. Patients were excluded from the study if their serum aspartate aminotransferase values were more than twice the upper limit of the normal range on two successive occasions.

Concurrent Therapy

We permitted concurrent therapy with systemic corticosteroids if the dose remained stable throughout the study period and the patient took no more than 10 mg of prednisone (or its equivalent) per day. We also permitted the use of nonsteroidal antiinflammatory medications, both as regular therapy and on an as-needed basis.

Statistical Analysis

The primary end point was successful completion of the two-year study. Differences among the three treatment groups in the number of patients who completed the study and the number who had treatment failures were analyzed by both the chi-square test and the log-rank test.²⁹ We developed a Kaplan-Meier curve for the patients who completed the study, with all those who did not do so considered to have had treatment failures. The log-rank test was used to compare these groups.²⁹ Cox proportional-hazards regression analysis was used to adjust for differences among the groups at study entry.

Differences in the mean values of other outcome variables were evaluated by two-tailed Student's *t*-tests, assuming unequal vari-

ance.²⁹ Analysis of covariance was used to adjust for base-line differences in the severity of disease among the treatment groups.²⁹

RESULTS

We randomly assigned 36 patients to receive methotrexate, 35 patients to receive sulfasalazine and hydroxychloroquine, and 31 patients to receive all three drugs. There were no significant differences among the groups at study entry (Table 1). Thirteen patients discontinued the study because of drug toxicity, and 37 patients did so because of lack of efficacy. Two patients were withdrawn from the study for protocol violations (failure to have laboratory studies done). The remaining 50 patients completed the two years of the study successfully, having 50 percent or greater improvement at nine months and maintaining at least 50 percent improvement for the duration of the study.

Toxicity

Treatment with all three drugs did not produce more toxic effects than did methotrexate therapy alone. Seven patients in the methotrexate group discontinued treatment because of toxic effects: two patients had pneumonia; one patient each had stomatitis, diarrhea, nausea, and vertigo; and one patient had sepsis and subsequently died. Three patients assigned to sulfasalazine and hydroxychloroquine discontinued treatment because of pneumonia, diarrhea, and Crohn's disease, respectively; and three patients in the three-drug group discontinued treatment because of nausea, cervical cancer, and weight gain, respectively.

No patient had serum aspartate aminotransferase values more than twice the upper limit of the normal range during the study. The patients in the three-drug group had higher serum creatinine values than those in the other two groups at nine months ($P=0.03$), but this difference was not apparent at two years.

Treatment Outcomes

The 50 patients who had at least 50 percent improvement at nine months and maintained that degree of improvement to the end of the two-year treatment period included 24 of the 31 patients receiving all three drugs (77 percent), 14 of the 35 patients receiving sulfasalazine and hydroxychloroquine (40 percent), and 12 of the 36 patients receiving methotrexate alone (33 percent) ($P=0.003$ and $P<0.001$ for the respective comparisons between the three-drug group and the other two groups). Three patients in the three-drug group, 18 in the sulfasalazine-hydroxychloroquine group, and 16 in the methotrexate group were considered to have had treatment failures. The remaining patients in each group discontinued the study because of toxic effects or protocol violations.

The proportions of patients who completed the two-year treatment period successfully are shown in Figure 1. In the figure, all the patients who did not complete the study are counted as having had treatment failures,

Table 1. Base-Line Characteristics of Patients with Rheumatoid Arthritis, According to Study Group.*

CHARACTERISTIC	METHOTREXATE (N = 36)	SULFASALAZINE AND HYDROXY- CHLOROQUINE (N = 35)	ALL THREE DRUGS (N = 31)
Age (yr)			
Mean	50	49	50
Range	21–69	36–63	27–67
Sex (F/M)	25/11	26/9	20/11
Duration of disease (yr)	10±8	6±6	10±10
Rheumatoid factor present (% of patients)	89	85	84
Current prednisone therapy (% of patients)	53	46	52
Prednisone dose (mg/day)	6±3	5±3	6±3
Disease-modifying antirheu- matic drugs previously used (no. of drugs)	1.6±0.8	1.6±0.8	1.5±0.8
Prior methotrexate therapy (no. of patients)	3	4	4
Erythrocyte sedimentation rate (mm/hr)	39±29	45±27	36±26
Duration of morning stiffness (min)	190±109	156±96	135±98
Scores on assessment scales†			
Tender joints	31±18	32±14	29±13
Swollen joints	31±19	31±20	27±12
All joints	63±33	62±31	56±19
Patient's global status and pain	6±2	6±2	6±2
Physician's global assessment	6±2	6±2	6±1
Hemoglobin (g/dl)	13±2	13±2	13±2
Platelets (×10 ³ /mm ³)	376±118	357±100	340±123
Serum aspartate aminotrans- ferase (U/liter)	22±10	19±6	20±10
Serum creatinine (mg/dl)‡	0.84±0.21	0.79±0.16	0.89±0.20

*Plus–minus values are means ±SD.

†As described in the Methods section.

‡To convert values to micromoles per liter, multiply by 88.4.

including the 13 with toxic effects, the 37 with treatment failures, and the 2 who were withdrawn from the study because of protocol violations. The comparison between the three-drug group and each of the other groups with respect to good responses (Fig. 1) was statistically significant ($P=0.003$ by the log-rank test). To ensure that these divergent results were not caused by differences in the severity of disease at base line, we performed an adjusted analysis of the time to treatment failure, using the presence of rheumatoid factor, the erythrocyte sedimentation rate, the duration of disease, the number of previous disease-modifying drugs taken, the patient's global status, the physician's global assessment, and the total joint score as variables. The sedimentation rate, the patient's global status, and the total joint score all had weak but statistically significant effects on the time to treatment failure. However, the difference between the three-drug group and the methotrexate group remained significant after this adjustment ($P=0.009$).

Other Measures of Efficacy

Table 2 shows the other clinical measurements of arthritis activity at base line, after nine months, and after

two years of therapy. We chose nine months because that was the point at which the decision to retain the patient in the study (on the basis of at least 50 percent improvement) was made. There were trends toward clinical improvement in the three-drug group as compared with the other two groups on all measures of efficacy. The results at two years were particularly impressive, considering that all these patients had already been selected as those who were doing well (i.e., who had at least 50 percent improvement).

DISCUSSION

With the disease-modifying therapy currently available, complete remissions of rheumatoid arthritis are disappointingly rare.^{25,30} Therefore, most clinicians have resorted to using combinations of drugs to treat a substantial subgroup of patients.^{22,31} There are few data to suggest that combinations of drugs are better than therapy with single drugs, however. A recent meta-analysis of combination therapy in rheumatoid arthritis concluded that there is little evidence to support the use of combination therapy,³² but few studies have been done, and only two have included methotrexate.^{33,34} In one of these, the dose in the methotrexate-plus-azathioprine group was only half the dose in the methotrexate-alone group,³⁴ making comparison difficult or impossible. In the other study using methotrexate, the maximal dose was only 7.5 mg per week.³³ Three studies in the meta-analysis included oral gold or penicillamine,^{33,35,36} medications that are now seldom used by rheumatologists.²²

Our double-blind, controlled, randomized study demonstrates the tolerability and the benefit of combination therapy with methotrexate, hydroxychloroquine, and sulfasalazine as compared with methotrexate alone. This enhanced efficacy occurred with no increase in toxicity. We believe that our results are particularly pertinent to clinicians for several reasons. The study design includ-

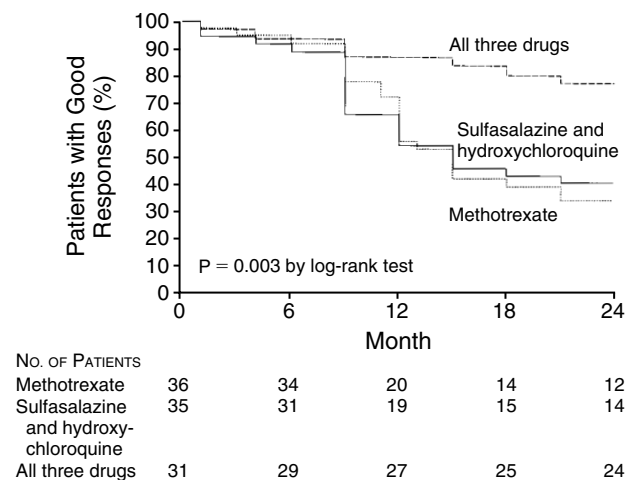


Figure 1. Patients with Good Responses to the Assigned Study Treatment.

Table 2. Changes in Joint Symptoms and Measures of Activity in the Study Patients, According to Treatment Group.*

VARIABLE	METHOTREXATE	SULFASALAZINE AND HYDROXY- CHLOROQUINE	ALL THREE DRUGS	P VALUE†	
				METHOTREXATE VS. THREE DRUGS	SULFASALAZINE AND HYDROXY- CHLOROQUINE VS. THREE DRUGS
No. of patients					
Base line	36	35	31		
9 Mo	33	30	29		
24 Mo	12	14	24		
Erythrocyte sedimentation rate (mm/hr)					
Base line	39±29	45±27	36±26	0.63	0.19
9 Mo	19±16	36±29	14±12	0.22	0.001
24 Mo	16±13	16±12	10±9	0.12	0.11
Duration of morning stiffness (min)					
Base line	190±109	156±96	135±98	0.08	0.38
9 Mo	65±85	64±77	46±50	0.27	0.27
24 Mo	63±88	50±48	38±62	0.34	0.55
Tender joints (score)					
Base line	31±18	32±14	29±13	0.58	0.53
9 Mo	20±16	15±16	10±15	0.018	0.25
24 Mo	7±8	7±6	3±3	0.06	0.016
Swollen joints (score)					
Base line	31±19	31±20	27±12	0.25	0.35
9 Mo	16±14	17±17	8±7	0.004	0.008
24 Mo	5±4	7±6	2±2	0.006	0.001
Total joints (score)					
Base line	63±33	62±31	56±19	0.33	0.36
9 Mo	36±27	31±29	18±18	0.003	0.03
24 Mo	12±10	14±11	5±3	0.007	<0.001
Patient's global status and pain (score)					
Base line	6±2	6±2	6±2	0.59	0.92
9 Mo	3±2	4±3	3±2	0.47	0.36
24 Mo	3±2	3±3	2±2	0.02	0.07
Physician's global assess- ment (score)					
Base line	6±2	6±2	6±1	0.46	0.81
9 Mo	3±2	3±2	3±2	0.51	0.31
24 Mo	2±1	3±1	1±1	0.002	<0.001

*Plus-minus values are means ±SD. Joint scores and other assessment scores are described in the Methods section.

†P values shown are for individual comparisons. Seven comparisons of efficacy were made at each point; if the Bonferroni correction for multiple comparisons was applied, the P value would need to be less than 0.008 for significance at the 0.05 level to be retained.

ed a combination of the three most widely used disease-modifying drugs. We compared this combination therapy with methotrexate alone, currently the gold standard of treatment for rheumatoid arthritis. The goal of the study was to induce remission, and the dose of methotrexate was increased (to up to 17.5 mg per week) to try to achieve this goal. The dose of the other drugs remained the same in the two groups that received them, and therefore we can directly compare the treatment groups with respect to efficacy. Our study lasted two years, making it one of the longer controlled trials of any therapy, combination or otherwise, in patients with rheumatoid arthritis. Finally, the main end point was 50 percent or greater improvement rather than 20 percent improvement, as is frequently used. Fifty percent improvement is a clinically relevant end point because patients and treating physicians can readily observe this degree of improvement.

We sought to design and conduct a study that would reflect clinical practice and yield results applicable to

patients with rheumatoid arthritis and their physicians. Therefore, we allowed patients to continue taking nonsteroidal antiinflammatory drugs and prednisone if the dose was relatively low.

Some will question the fact that only a small percentage of patients in the methotrexate group completed the two-year study successfully. Most clinicians believe that methotrexate is more effective than our results suggest, and in open-label studies lasting three to five years 50 to 65 percent of patients were reported to have sustained improvement.¹⁹⁻²¹ Reconciling these seemingly disparate results requires acknowledging that the measure of efficacy we used (50 percent improvement) differs from the measures used in routine clinical practice and other longitudinal studies. In one clinic, for example, 64 percent of patients were still taking methotrexate after five years,^{19,37} but only 35 percent had at least 50 percent improvement.³⁷ The percentage of patients who dropped out of our study because of side effects was higher because of the double-blind nature of this study. These side effects would often not have precluded the continuation of methotrexate therapy if the patients had been followed in clinical practice or an open-label study.

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