Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis

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Abstract

Objective

The response to single disease modifying antirheumatic drug (DMARD) is often suboptimal in patients with rheumatoid arthritis (RA). Thus, despite the limited data on the therapeutic efficacy of combination therapies, many patients are currently treated with a combination of DMARDs.

Methods

We studied prospectively the efficacy of combination therapy with DMARDs. The study was designed as a randomized trial and a single DMARD or two or three DMARD combinations were adminstered to 180 consecutive, age- and sex-matched patients with active RA, each of whom was followed up for a period of 2 years under treatment. Patients were divided into 3 groups which did not differ with regard to demographic, clinical and laboratory parameters. Patients in group I were treated with a single DMARD [methotrexate (MTX) 7.5 - 15 mg/week or sulfasalazine (SSZ) 1 - 2 g/day or hydroxychloroquine (HCQ) 200 mg/day], group II with MTX + SSZ or MTX + HCQ, and group III with a combination of all three drugs. Patients were re-evaluated at regular intervals by means of clinical and biochemical tests designed to detect specific rheumatic activity. Radiological assessments were also performed and scored according to Larsen by the same radiologist who was blinded to the treatment groups.

Results

At the end of the trial there were significant improvements in the clinical and laboratory parameters in all 3 groups. However, improvements were greater and much more significant in the patients who were given combination therapies. The combination of MTX + SSZ + HCQ was more effective than both monotherapy and the two-drug combinations.

Conclusion

In conclusion, we suggest that patients with RA should be treated with combinations of DMARDs.

Key words

Rheumatoid arthritis, combination therapy, methotrexate, hydroxychloroquine, sulfasalazine.

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Introduction

Rheumatoid arthritis (RA) is a chronic, recurrent inflammatory disease that leads to substantial disability, loss of productivity, and increased mortality (1). The ideal treatment for RA should quickly control the inflammatory process, prevent articular lesions, preserve functioning, minimize toxic effects, and be economically accessible to the majority of patients. The therapeutic pyramid model had been accepted for years as the conventional therapy for RA, but in the past decade clinicians have been re-evaluating the situation because the outcome of patients treated with a single agent based on conventional pyramid has been disappointing.

New paradigms for the treatment of RA have been developed (2-5), and the use of combinations of disease modifying antirheumatic drugs (DMARDs) is being explored. It is suggested that combination therapy with two or three drugs may be more effective than single drug therapy. In this prospective, randomized trial, we sought to compare the efficacy of combination therapy and monotherapy in patients with RA.

Patients and methods

Patient selection

Patients were selected from among RA patients who were admitted to the Rheumatology Department of Hacettepe University Medical Faculty from 1993 to 1997. Three hundred and fifteen new patients were evaluated. Patients who were not receiving regular DMARD therapy were enrolled in the trial. Certain criteria were also used to select the participants, including: age ≥ 18 years; diagnosis of RA based on the criteria of the American Collage of Rheumatology (ACR); duration of disease > 6 months; and active disease with at least 3 of the following findings: erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr, morning stiffness lasting 45 minutes or more, 6 or more tender joints, and 3 or more swollen joints.

Excluded from the study were those patients with stage 4 disease; a history of allergy to any of the study drugs; hepatic, renal, hematologic, pulmonary or cardiovascular disease; or active peptic ulcer disease. A total of 180 consecutive patients were enrolled in the trial and 171 completed the trial. Each patient was followed up for a period of 2 years under treatment.

Study design

The study was designed as a two-year, prospective randomized trial. Patients were divided into 3 groups according to the treatment protocols. Each group consisted of 60 patients.

The patients in group I (monotherapy) were treated with either methotrexate (MTX) 7.5 - 15 mg/week orally, sulfasalazine (SSZ) 1 - 3 g/day, or hydroxychloroquine (HCQ) 200 mg/day. The patients were randomly assigned to one of the 3 drugs. At the end of the study 26, 17 and 14 patients had been treated with MTX, SSZ and HCQ, respectively.

Two different combinations (MTX + SSZ or MTX + HCQ) were given to the patients in group II, in the absence of any contraindications. Twenty-seven patients were treated with MTX + HCQ, and 29 patients with MTX + SSZ.

The remaining patients (group III) received all 3 of these drugs in combination. Two patients suffered side effects, one from SSZ and one from HCQ, and in each case the offending drug was replaced by azathioprine (AZA) 2 mg/kg/day. Therefore, 56 patients completed the study with MTX + SSZ + HCQ, one patient with MTX + HCQ + AZA and one patient with MTX + SSZ + AZA in this group.

In addition to the DMARD therapy, we allowed to all patients to take non-steroidal antiinflammatory drugs (NSAIDs) if they felt the need (diclofenac sodium 100 mg/day, in suppository form). The weekly dose of NSAIDs was recorded by the patients. We also prescribed to all patients 1 or 2 mg/day peroral methylprednisolone.

The study design summarized in Fig. 1.

Evaluation criteria

The clinical and laboratory findings of the patients were re-evaluated at 3-month intervals, and the radiological findings at 6-month intervals. At the end of the first 6 months, if the clinical and laboratory improvements were not > 50% according to the modified Paulus Criteria (6), the patients in groups I and II were

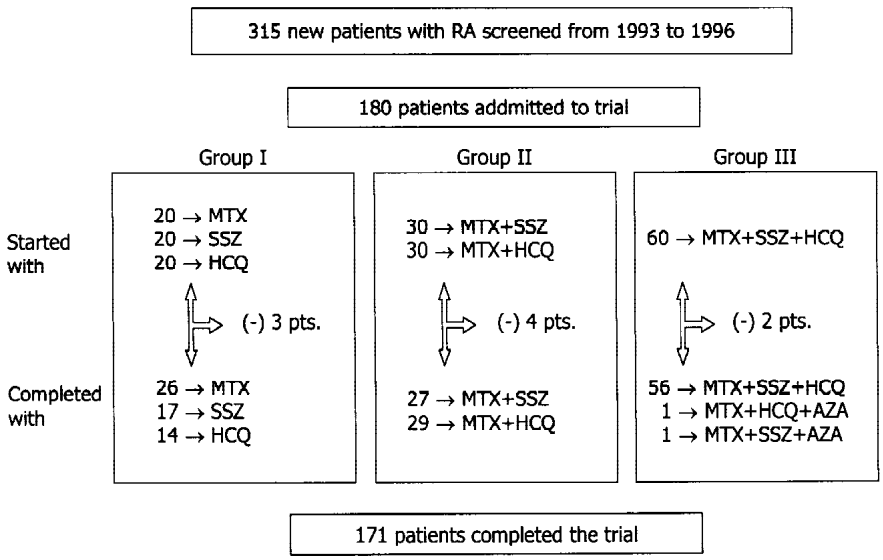

Fig. 1. The study design.

switched to another drug or drug combination.

Patients meeting at least 3 of the following criteria were accepted as showing 50% improvement: morning stiffness < 30 minutes or a 50% reduction in this complaint; 50% reduction in both the tender and swollen joint counts and scores; ESR < 30 mm/hr in females and < 20 mm/hr in males.

The patients were also evaluated every 6 months on the basis of ACR remission criteria, including (7): duration of morning stiffness ≤ 15 minutes; no fatigue; no joint pain (by history); no joint tenderness or pain on motion; no soft tissue swelling in the joints or tendon sheaths; ESR <30 mm/hr in women and < 20 mm/hr in men. For remission, 5 or more of these criteria had to be fulfilled for at least 2 consecutive months.

Additional parameters for the clinical evaluation were used: estimated duration of morning stiffness; weekly NSAID requirement; the tender and swollen joint counts; and scoring the tender and swollen joints according to the modified Ritchie articular index (scoring 36 joints 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 (VAS; 0 = normal and 10 = severe problems) (8, 9). An ophthalmologist examined all patients every six months for the potentially toxic effects of HCQ.

The laboratory evaluation of the patients included ESR, C-reactive protein (CRP), a complete blood count (CBC), total protein, albumin, urea, creatinine, serum aspartate and alanine aminotransferase (AST,ALT), alkaline phosphatase (ALP), and gamma glutamyl transpeptidase (GGT) concentrations. These parameters were monitored every 3 months. In patients receiving MTX, the CBC was measured weekly and liver function tests were performed every six weeks. Plain radiographs of the hands and feet were taken every 6 months and scored according to the modified Larsen's method (10) by a single radiologist who was blinded to the treatment groups. Joint space narrowing, erosion, pseudocysts and malalignment of the small joints of the hand and foot were scored from 0 (normal) to 4 (severe).

Statistical analysis

Data were analyzed using a statistical software package (SPSS for Windows ver. 7.5). The Chi-square test was used to compare the non-parametric values of the groups. The pre-treatment and post-treatment parametric values for each group were compared using a paired samples t-test. Between group comparisons were performed using an independent samples t-test. One-way analysis of variance (ANOVA) was used to compare the differences between the clinical and laboratory parameters for the groups. A p value < 0.05 was considered statistically significant.

Results

The demographic features and clinical characteristics of the 180 patients who participated in the study are presented in Table I.

The pre-treatment and post-treatment clinical and laboratory parameters were first compared within each group. Then the groups were compared to each other. The pre-treatment and the post-treatment alterations in laboratory and clinical parameters were statistically significant in each group, except for the hemoglobin and hemotocrit values in group I. The pre-treatment and post-treatment radiological scores were also compared within each group, and were found to be significantly changed only in group I. The comparison of the pre- and post-treatment values by group are shown in Tables II and III.

At the end of the study, > 50% improvement in the clinical and laboratory parameters (based on the modified Paulus criteria) was observed in 28 patients in group I (49.1%), 41 patients in group II (73.2%), and 51 patients in group III

Table I. Demographic features and clinical characteristics of the patients in the study.

	Group I	Group II	Group III
Age (years)	48.62 ± 12.31	49.43 ± 4.14	48.17 ± 9.84
Sex (female/male)	52 / 8	53 / 7	51 / 9
RF (% of patients)	73.3	61.7	78.3
RN (% of patients)	21	23	23
Duration of disease (years)	2.25 ± 2.27	2.48 ± 2.34	2.23 ± 2.95

RF: rheumatoid factor; RN: rheumatoid nodule.

Table II. Comparison of pre-treatment and post-treatment laboratory parameters among the groups.

Variables	Group I		Group II		I vs II		Group III		I vs III		II vs III	
	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
ESR	54.05±20.50	37.25±24.63	56.95±19.85	30.25±21.69	NS	NS	59.55±24.39	21.1±22.95	NS	0.006	NS	0.020
CRP	39.86±20.30	27.40±22.84	38.35±20.12	15.46±16.54	NS	0.001	43.91±27.94	10.08±16.55	NS	<0.001	NS	0.040
PLT	369±101	321±84	360±94	296±73	NS	NS	355±119	278±90	NS	0.007	NS	NS
Albumin	3.82±0.44	4.06±0.44	3.97±0.36	4.28±0.35	NS	0.003	4±0.34	4.56±0.44	NS	<0.001	NS	<0.001
RS	32.76±18.29	43.04±21.02	33.6±20.32	36.88±18.54	NS	0.012	33.36±19.13	35.92±14.85	NS	0.050	NS	NS

HTC: hemotocrit; HB: hemoglobin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PLT: platelets.; RS: radiological score; NS: not significant.

Table III. Comparison of pre-treatment and post-treatment clinical parameters between the groups.

Variables	Group I		Group II		I vs II		Group III		I vs III		II vs III	
	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
MS BT (min.)	124.75±82.9	60.50±58.71	110±81.06	33.66±48.28	NS	0.007	129.33±70.6	23.25±43.61	NS	<0.001	NS	NS
NSAID req	9.23±3.12	4.65±1.18	10.03±2.14	3.73±2.14	NS	0.003	11.65±2.69	1.29±2.67	NS	0.0001	NS	0.001
TJC BT	8.96±3.17	4.61±4.11	9.55±3.96	3.31±4.62	NS	NS	10.36±3.99	1.43±4.31	NS	0.005	NS	0.028
TJS BT	21.65±5.49	5.38±5.74	22.46±7.39	3.75±5.70	NS	NS	23.38±6.52	1.53±4.59	NS	0.003	NS	0.020
SJC BT	4.66±2.02	0.71±1.66	5.50±1.64	0.43±1.45	NS	NS	5.86±2.03	0.16±0.66	NS	0.019	NS	NS
SJS BT	13.90±6.49	2±5.09	15.28±3.85	1.21±4.29	NS	NS	14.53±5.82	0.46±2.58	NS	NS	NS	NS
PGA BT	6.61±1.96	4.76±2.91	7.56±1.90	3.56±2.66	NS	0.020	6.75±1.92	2.45±2.1	NS	<0.001	NS	0.012
PhGA BT	6.21±2.16	4.65±2.89	7.2±2.19	3.43±2.44	NS	0.014	6.6±1.94	2.53±2.16	NS	<0.001	NS	0.035

MS: morning stiffness; NSAID req: dose of NSAID per week; TJC: tender joint count; TJS: tender joint score; SJC: swollen joint count; SJS: swollen joint score; PGA: patient's global assessment; PhGA: physician's global assessment; NS: not significant.

Table IV. Global comparison of clinical and radiological results of patients.

Variables	Group I	Group II	Group III	I vs II	I vs III	II vs III
Improvement more than 50% (%)	49.1	73.2	87.9	< 0.001	< 0.001	< 0.001
ACR remission (%)	31.5	44.6	60.3	0.007	0.007	0.007
Non-radiological progression (%)	24.5	64.2	68.9	0.001	0.001	0.210

Table V. Adverse drug reactions (no. of pts.).

	Group I	Group II	Group III
GI intolerace	-	2*	1*
HCQ toxicity	1*	-	1*
Neutropenia	1*	1*	-
Raised ALT / AST	4	6	5
Oral aphthosis	1	-	1
Rashes	1	1	-

GI: Gastrointestinal
*These toxicities led to a change in the treatment protocol.

(87.9%). Eighteen patients in group I (31.5 %), 25 patients in group II (44.6%), and 35 patients in group III (60.3%) were in clinical remission according to the ACR remission criteria. The improvement seen in the 3 groups, using either the criterion of > 50% improvement or of ACR clinical remission, was statistically significant. Radiological scores were found to be unchanged or decreased in 14 patients in group I (24.5%), 36 patients in group II (64.2%), and 40 patients in group III (68.9 %) at the end of the 2-year trial. The differences of patients who had no radiological progress between group I and II, and group I and III were statistically significant. Radiological differences were insignificant between groups II and III (Table IV).

The frequency of adverse drug reactions was similar in all 3 groups. The treatment protocol was changed for 2 patients in group I, 3 patients in group II, and 2 patients in group III, due to drug toxicity. These differences were statistically insignificant.

Although elevated levels of serum ALT and AST were observed in 4 patients in group I, 6 patients in group II and 5 patients in group III, these elevations were transient and less than two times the upper limit (Table V). The data on 9 patients (3 in group I, 4 in group II and 2 in group III) were excluded from the final study analysis because of the patients' low degree of cooperation and incomplete control examinations.

Discussion

The inflammatory process is both the central feature of the RA and the focus of antirheumatic therapy. The optimal approach to the treatment of RA remains controversial. The reasons for the move away from traditional management approaches are manifold and include the realization that RA is a debilitating condition associated with increased mortality and morbidity (1), the finding that disability progresses rapidly in the first few years after disease onset (11), and the demonstration that the majority of the patients have radiographic abnormalities within 2 years of the disease's presentation (12, 13). Given the high proportion of therapeutic failures reported with monotherapy based on the conventional pyramid approach, various more aggressive therapeutic modalities such as the step down bridge (2), the sawtooth strategy (3), the graduated step strategy (4), and therapeutic targeting (5) have been proposed.

Another new strategy under consideration is the use of drug combinations. The theoretical advantage of multiple second-line agents is an enhancement of overall efficacy due to the different mechanisms of action and the lower doses of the individual drugs and the concomitantly lower frequency of adverse effects.

The first report of combined DMARD therapy for RA was published by Sievers *et al.* in 1963 (14). In that study, the combination of antimalarial drug and gold salts was compared with the antimalarial alone, and it was found that combination therapy was more effective. However, in 1966 Lockie *et al*. advised against using chloroquine with gold salts, because the hazards of toxicity appeared to be increased by the concomitant use of two potentially toxic agents (15). Due to concern about increasing toxicity, there was little interest in combination therapy between 1966 and 1982.

In 1982, McCarty *et al*. reported that combined cyclophosphamide (CYC), AZA and HCQ therapy was effective in patients with intractable RA (16). This report encouraged other researchers to perform trials on other combinations. To date a number of studies on various combinations have produced different results. Some have suggested improved efficacy with combination therapy (17-31). However, others reported no improvement in efficacy (32-39) or increased toxicity (16, 17, 19, 22, 31, 32, 35).

In most published studies (17-26), combination therapy with two DMARDs provided improvement in efficacy, but the majority of these trials were open studies and included only a limited number of patients. However, they were of value because they tested drugs commonly used in rheumatological practice. In these trials, many potential combinations such as MTX + HCQ, gold salts + HCQ, gold salts + SSZ, MTX + SSZ, MTX + cyclosporine A (CyA), and HCQ + CyA were studied. We believe that these results will encourage authors to perform larger prospective, randomized, double-blind, placebo controlled trials of the new combinations.

In contrast to studies reporting the beneficial effects of combination therapy with two DMARDs, there have also been clinical trials that suggest no improved efficacy (32-39). Except for two, however, in which MTX was combined with AZA or auronafin, these studies did not include MTX which is considered to be the gold standard for the treatment of RA by most rheumatologists. Nor did they test the combination of MTX + SSZ, or MTX + HCQ. Deciding which drugs to use in combination therapy is difficult because the mode of action of most DMARDs is still uncertain. SSZ + MTX could have a greater toxicity profile since both drugs exhibit antifolate activity. However, there are studies and case reports suggesting the efficacy of MTX + SSZ without additional adverse effects (23, 24, 40).

Fries *et al*. have suggested that adding HCQ can decrease the hepatotoxicity of MTX. They hypothesized that this protective effect may occur through the action of HCQ by increasing the number and size of lysosomes as well as stabilizing the lysosomal membrane (41). For these reasons, we chose the combinations of MTX+SSZ and MTX+HCQ for our two-drug therapies.

To date there have been 4 published trials (27-31) of three-drug combinations, in which MTX + SSZ + HCQ (27, 28), AZA + MTX + HCQ (29, 30) and CYC + AZA + HCQ (16, 31) were tested. All of them reported an improvement in efficacy. However, only one of these trials was a randomized, double blind and placebo controlled study; others were open trials. Although the four studies suggested no increased toxicity, the trial including the combination of CYC + AZA + HCQ (16, 31) performed by McCarty *et al*. reported increased toxicity, especially malignancy. These authors suggested that CYC should be replaced with a non-alkylating agent. Therefore, CYC is not currently used in the treatment of RA except for special conditions such as rheumatoid vasculitis and interstitial lung disease.

Our study differs from the others with regard to its study design. Our aim was not to evaluate the effectiveness of individual drugs, but rather to compare the therapeutic efficacy of combination therapies versus monotherapy. Therefore, we compared 3 different monotherapies in group I and two 2-drug combinations in group II. The drugs used were changed if adverse reactions were observed or the response to therapy was inadequate.

The combinations of MTX + SSZ and MTX + antimalarial drugs have been reported to be effective treatments for RA in two open studies (23, 24), and in two randomized, double-blind placebo controlled studies (17, 18). The two-drug combinations were also more effective than monotherapy in our study.

The results of the three-drug combination treatment in our study are concordant with previously reported studies. O'Dell *et al.* reported that the combination of MTX+SSZ+HCQ was more effective than both SSZ+HCQ and MTX alone, without increased toxicity (27, 28). We also found the three-drug combination to be superior to both the single drug and the two-drug combinations. The frequency of adverse drug reactions did not increase with the number of drugs. In our study, the two-drug combination was also more effective than single-drug therapy, unlike O'Dell's study in which they did not detect any difference between SSZ+HCQ and monotherapy. A possible explanation of this discrepancy may be the combination, SSZ+HCQ, used in their study. SSZ+HCQ has been studied in other trials and although it seemed to be more effective

than monotherapy, the difference was statistically insignificant (39).

A small number of combination therapy studies have included radiologic comparisons (17, 19, 32, 33, 36, 37). Trnavsky *et al.* and Gibson *et al.* reported that combined therapy is superior to single drug therapy with respect to the prevention of radiologic progression ,while other authors did not reach the same conclusions. Our two-drug results are concordant with those of Trnavsky *et al.* and Gibson *et al.* There are no published data available for comparison with our triple therapy results, as none of the triple-drug studies included radiologic evaluations and comparison.

Since most of the studies to date except two (35-37) report combinations including MTX to be more effective, we considered that using MTX in our combinations was a reasonable choice.

In conclusion, we suggest that patients with RA, a disease with high mortality and morbidity, should be treated with combination DMARD therapy.

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