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Combination Therapies in Spondyloarthropathies

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OBJECTIVES **To compare the efficacy and tolerability of single-agent sulfasalazine (SSZ) with combination therapies composed of SSZ and methotrexate (MTX) and SSZ, MTX and hydroxychloroquine (HCQ) in active spondyloarthropathy (SpA) patients with peripheral arthritis.**

METHODS **One hundred and fifty SpA patients with peripheral arthritis (male/ female: 92/58) who were treated in our clinic between 1994 and 1998 were enrolled in this trial. Patients treated with SSZ alone (1-3 gr/day) were included in Group I, patients treated with combination of SSZ (1-3 gr/day) and MTX (7.5-15 mg/week) in Group II, and patients treated with combination of SSZ (1-3 gr/day), MTX (7.5-15 mg/week) and HCQ (200 mg/day) in Group III. Forty-eight patients in Group I, 45 patients in Group II and III were eligible for statistical analysis at the end of study.**

RESULTS **The combination of MTX, SSZ, and HCQ, and the combination of MTX and SSZ were more effective regarding the clinical and laboratory parameters than SSZ alone ($p<0.05$). Moreover, the combination of MTX, SSZ, and HCQ was more effective than the combination of MTX and SSZ ($p<0.05$).**

CONCLUSION **Combination therapies seem to be more effective and no more toxic than monotherapy in SpA patients with peripheral arthritis.**

Spondylarthropathies (SpA) include a broad spectrum of diseases including ankylosing spondylitis (AS), Reiters' syndrome, reactive arthritis, psoriatic arthritis (PsA), arthritis related to inflammatory bowel disease and some forms of juvenile chronic arthritis (JCA). SpAs mainly affect the axial skeleton, but can also be complicated with peripheral articular involvement (1). The etiopathogenesis of SpAs has not been fully determined. Although SpAs are known to be benign diseases which do not reduce the life expectancy, they can cause decreased functional capacity especially in cases with peripheral joint involvement (1). Conventional therapies for SpAs include physiotherapy and administration of antiinflamatory drugs followed by disease modifying antirheumatic drugs (DMARD). Sulfasalazine (SSZ) is the most widely used DMARD in SpA patients (1-5). Methotrexate (MTX) has also been given to SpA patients especially with peripheral joint involvement (3, 6, 7). Antimalarial drugs are rarely preferred in those patients (3, 8). There are limited data with combination of DMARDs, and to our knowledge the combination of SSZ and MTX has not been previously investigated in SpAs. In this trial, we aimed to compare the efficacy and toxicity of combination therapies and monotherapy in patients with SpA.

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PATIENTS AND METHODS

Patients were selected among SpA patients who were treated in Hacettepe University School of Medicine Department of Rheumatology between the years 1994 and 1998. One hundred and fifty new patients who met the European Study Group Criteria for SpA with peripheral arthritis (9) were included in the study. Seventy-nine patients fulfilled modified New York classification criteria for AS (9). Thirty-seven patients had oligo-arthritis and sacroiliitis with dermatological lesions of psoriatic arthritis. Thirty-four SpA patients with peripheral arthritis were accepted as unclassified SpA.

Inclusion criteria were age over 18 years, duration of signs and symptoms more than 3 months, presence of active disease defined by elevated erythrocyte sedimentation rate (ESR) ≥ 20 mm/hr for male and ≥ 30 mm/hr for female, presence of morning stiffness lasting more than 30 minutes, and presence of at least one joint with active arthritis (defined as the presence of swelling or limitation of motion, with either pain on movement or tenderness). Exclusion criteria were history of hypersensitivity to any of the drugs given during the study, presence of hepatic, renal, hematological, pulmonary or cardiovascular disease, and presence of active peptic ulcer. Patients who were administered DMARDs before admission to our clinic were also excluded from the study. One hundred fifty patients who fullfilled the above-mentioned criteria were enrolled in the trial. However, 12 patients (2, 5, and 5 patients in Group I, Group II, and Group III, respectively) were not included in statistical analysis because of low degree of cooperation and incomplete data.

Patients were consecutively treated with single agent SSZ (1-3 g/day) between the years 1994 and 1995 (Group I, n=48, m/f=29/19), with SSZ (1-3) g/day plus MTX (7,5-15 mg/week) between 1995 and 1996 (Group II, n=45, m/f=28/17), and with the combination of SSZ (1-3 g/day), MTX (7,5-15 mg/week), and HCQ (200 mg/day) between 1997 and 1998 (Group III, n=45, m/f=26/19). In addition to the DMARD therapy, all patients were allowed to take non-steroidal antiinflammatory drugs (NSAIDs) for symptomatic relief (diclofenac sodium 100 mg/day, in suppository form). The weekly dose of NSAIDs was recorded by the patients. Clinical, biochemical and radiological parameters were recorded for each patient after a 2-year follow-up period.

EVALUATION CRITERIA

The clinical and laboratory findings of the patients were re-evaluated with 3-months intervals. In each visit the duration of morning stiffness, NSAID consumption per week, tender joint count, swollen joint count, patient's global assessment, physician's global assessment and Schober test (anterior flexion) were noted. ESR, C-reactive protein (CRP), complete blood count (CBC), total protein, albumin, urea, creatinine, serum aspartate and alanine aminotransferases (AST, ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) concentrations and urine analysis were also obtained in each visit. The patient's global status, the 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 100 mm: severe problems). Anterior flexion was measured as described by Mc Rae (10). Clinical assessments were performed by the same physician (by Dr. M. Çalgüneri). An ophthalmological examination for HCQ retinopathy was performed in every 6 months.

Direct roentgenograms of the sacroiliac joints were taken in every 6 months and were scored according to New York criteria. Grade 0, 1, 2, 3, and 4 were accepted as normal, suspicious, mild sacroiliitis, moderate sacroiliitis and ankylosis respectively (1). Radiological evaluation was again performed by the same physician for each patient (by Dr. M. Çalgüneri).

Clinical, biochemical and radiological parameters of the patients after 2-year follow-up period were used for statistical analysis. Data were analyzed using a statistical software package (SPSS for Windows version 10.0). One-way analysis of variance (ANOVA) was used to compare the differences between the clinical and laboratory parameters for the groups. Statistically significant differences obtained from one-way ANOVA analysis were further tested by Tukey test for post hoc pairwise comparisons. A p value below 0.05 was considered as statistically significant.

RESULTS

The distribution of patients according the type of SpA in each group is given in Table I, and the demographic features and clinical characteristics of the patients are presented in Table II. The groups were found be comparable regarding age, gender, disease duration, and clinical and laboratory parameters (one-way ANOVA, $p>0.05$). At the end of the 2-year follow-up, the duration of morning stiffness was shorter, NSAID consumption per week, tender joint count and swollen joint count were less, patient's global assessment and physician's global assessment were superior, and ESR and CRP values were lower in combination therapy groups (Group 2 and Group 3) ($p<0.05$). Results of Schober test were also significantly better in combination therapies. Moreover, all of those clinical and laboratory parameters were superior in Group 3 (SSZ+MTX+HCQ group) compared to Group 2 (SSZ+MTX group) ($p<0.05$). However, the degree of sacroiliitis was not statistically different among the groups ($p>0.05$) (Table III).

The frequencies of adverse drug reactions were comparable in all groups. Although elevated levels of serum ALT and AST were observed in 4 patients in Group II and in 2 patients in Group III those elevations were transient and less than two times of the upper limit. No elevation of liver enzymes was observed in patients in Group I. Gastrointestinal intolerance occurred in one patient in Group I and in 3 patients both in Group II and III. Retinal toxicity of HCQ was not observed in any patient. Transient decrease in leukocyte count below 4000 were detected in 1, 3, and 2 patients in Group I, II, and III, respectively. Two patients in Group II and 3 patients in Group III could not take MTX due to stomatitis for 1-2 weeks. Stomatitis regressed after 5 mg folic acid replacement.

Table I. Distribution of patients according to sex and type of spondyloarthropathy

	AS	**PsA**	**UspA**	**Total**
Group-I (m/f)	16/10	7/5	6/4	29/19
Group-II (m/f)	17/7	5/5	6/5	28/17
Group III (m/f)	18/9	5/6	3/4	26/19
Total (m/f)	51/26	17/16	15/13	83/55

Abbreviations: AS: ankylosing spondylitis, PsA: psoriatic arthritis, USpA: unclassified spondyloarthropathy, m: male, f: female.

Table Ⅱ. Baseline measurements among patients with spondyloarthropaties

	Group 1 (single-agent SSZ)	**Group 2** (SSZ+MTX)	**Group 3** (SSZ+MTX+HCQ)
Age (years)	32.5±8.3	32.8±6.4	30.5±8.3
Disease duration (mo)	89.4±27.6	86.2±38.8	84.2±38.2
ESR (mm/hr)	529±19.7	51.9±21.6	53.5±22.8
CRP (mg/dl)	3.18±1.4	3.22±1.3	3.25±1.3
MS (min)	70.9±20.2	70.4±13.8	70.6±20.4
SJC	1.67±0.81	1.69±0.9	1.71±1.06
TJS	2.69±0.9	2.69±0.97	2.64±0.96
Schober (cm)	3.25±0.55	3.30±0.62	3.26±0.42
PGA (mm)	66.3±15.5	66.3±14.7	67.8±15.9
PhGA (mm)	70.8±15.4	70.9±14.2	71.5±12.6
SI	2.59±0.9	2.56±0.45	2.60±0.44
AC (per week)	6.4±0.8	6.5±0.6	6.7±0.6

Abbreviations: SSZ: sulfasalazine, MTX: methotrexate, HCQ: hydroxychloroquine, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, MS: Morning stiffness, SJC: swallen joint count, TJC: Tender joint count, PGA: Patient's global assessment (VAS), PhGA: Physician's global assessment (VAS), SI: Degree of sacroiliitis, AC: analgesic consumption

Table III. The comparison of clinical, biochemical and radiological parameters of different treatment groups the end of 2-year follow-up

	Group 1 (single-agent SSZ)	**Group 2** (SSZ+MTX)	**Group 3** (SSZ+MTX+HCQ)
ESR (mm/hr)	32.6±14.0 [a, b]	22.0±14.2 [c]	13.8±9.1
CRP (mg/dl)	1.15±0.93 [a, b]	0.74±0.78 [c]	0.39±0.52
MS (min)	44.8±16.6 [a, b]	28.3±16.6 [c]	20.4±14.2
SJC	0,92±0,68 [a, b]	0,51±0,73 [c]	0,24±0,43
TJC	1.06±0.78 [a, b]	0.56±0.8 [c]	0.26±0.4
Schober (cm)	3.45±0.63 [a, b]	3.84±0.9 [c]	4.38±0.9
PGA	32.5±13.1 [a, b]	24.3±15.1 [c]	17.2±11.6
PhGA	31.8±15.0 [a, b]	25.4±13.7 [c]	18.2±16
Sİ	2.75±0.6	2.72±0.7	2.62±0.7
AC (per week)	4.57±3.9 [a, b]	2.5±1.7 [c]	0.97±0.9

Abbreviations: SSZ: sulfasalazine, MTX: methotrexate, HCQ: hydroxychloroquine, ESR: Erythrocyte sedimentation rate, C-reactive protein, MS: Morning stiffness, SJC: swallen joint count, TJC: Tender joint count, PGA: Patient's global assessment (VAS), PhGA: Physician's global assessment (VAS), SI: Degree of sacroiliitis, AC: Analgesic consumption

[a]: $p<0.05$, for Group 1 vs Group 2

[b]: $p<0.05$, for Group 1 vs Group 3

[c]: $p<0.05$, for Group 2 vs Group 3

DISCUSSION

In this trial, we compared the therapeutic efficiencies and the toxicities of combination therapies composed of SSZ, MTX, and HCQ, and SSZ plus MTX with SSZ alone in SpA patients complicated with peripheral arthritis. We demonstrated that the combination of MTX, SSZ, and HCQ, and the combination of MTX and SSZ were more effective regarding the clinical (duration of morning stiffness, NSAID consumption per week, tender joint count, swollen joint count, patient's global assessment, physician's global assessment, Schober test) and laboratory (ESR, CRP) parameters than SSZ alone ($p<0.05$), and moreover they are not more toxic. Furthermore, the combination of MTX, SSZ, and HCQ was superior to the combination of MTX and SSZ concerning the above-mentioned criteria ($p<0.05$).

SpAs are traditionally treated with NSAIDs. However, this therapeutic approach is considered to only address the symptoms. Accordingly, a significant number of patients develop chronic disease of peripheral joints or axial skeleton, demonstrating insufficient response to the classical NSAID therapy. Better understanding of the etiopathogenic mechanisms and increasing recognition of the natural course of the SpAs have been leading to more rational therapeutic approaches to this large group of arthritides. A more aggressive therapeutic regimen is being advocated in a manner not too much different from that advocated for the treatment of rheumatoid arthritis (RA). Second-line drugs have been given to those patients with progressive disease over the last three decades (3). Placebo-controlled double-blind studies demonstrated that SSZ is a safe and effective drug in SpAs (2-5). MTX is another therapeutic option for SpA treatment (3, 6, 7). In a recent 3-year open trial, MTX improved clinical and laboratory parameters and reduced daily dose of indomethacine in SpA patients, and moreover radiographs of the spine and sacroiliac joints did not show any sign of disease progression (7). In another one-year open prospective study, MTX was effective especially in patients with peripheral arthritis (6). However, its efficacy in this disease remains to be established in controlled studies (11). On the other hand, there are anecdotal reports regarding the therapeutical effects of antimalarials in SpAs (8, 12-14). However, combination of DMARDs in SpAs is not in routine practice. To our knowledge only two uncontrolled studies investigated the efficiency of combination therapies composed of MTX and cyclosporine A in patients with PsA (15, 16). Although the results were promising, the number of patients was very small (8 and 10 patients). Moreover those studies did not include SSZ, which is the most efficient and most widely used DMARD in SpA patients (1-5).

Each of those DMARDs has different pathways in controlling the inflammation. SSZ have been shown to scavenge reactive oxygen species, inhibit the production of various prostanoids, reduce the circulating activated lymphocytes, and reduce the proinflammatory cytokines interleukin (IL)-1α, IL-1β, and tumor necrosis factor-α, and IL-6 (5, 17). MTX inhibits dihydrofolatereductase (DHFR) and other folate dependent enzymes, and hence interferes with de novo purine biosynthesis (18). Antimalarial drugs are weak bases that enter the lysosome, are protonated, raise the pH, and interfere with enzyme activity that depends on an acid milieu (12). Hence, combinations of second-line agents could theoretically enhance the overall efficacy in controlling the inflammation due to the different mechanisms of action. A theoretical disadvantage of combination drug therapy might be increased toxicity, since both SSZ and MTX exhibit antifolate activity. However, there are studies suggesting the efficacy of MTX and SSZ combination without additional adverse effects. Moreover, HCQ can decrease the hepatotoxicity of MTX by increasing the number and size of lysosomes as well as stabilizing the lysosomal membranes (19, 20). We along with others have previously demonstrated that combination of SSZ, MTX and HCQ was

therapeutically more advantageous than any of those drugs given alone in RA (21, 22). In the present study we observed that a similar therapeutical advantage has also been achieved in controlling the symptoms and the ongoing inflammation without increased toxicity in SpA patients with the same combination.

In conclusion, combination therapies are effective and well tolerable regiments for the treatment of SpA patients. However, double blind placebo-controlled prospective randomized clinical trials are needed to draw more dependable conclusions.

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