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Additive triple DMARD combination therapy of a low dose of sulfhydryl compounds, sulfasalazine and methotrexate in the treatment of rheumatoid arthritis: a clinical trial.*

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Abstract

To evaluate the efficacy and safety of additive triple disease modifying anti-rheumatic drug (DMARD) combination therapy of a low dose of sulfhydryl compounds inverted question markD-penicillamine, bucillamine or tiopronin inverted question mark, sulfasalazine (SSZ) and methotrexate (MTX) as a treatment for rheumatoid arthritis (RA) patients, we studied a total of 33 Japanese RA patients (6 males, 27 females). At 1 or 2 months after simultaneous administration of the 3 above-mentioned DMARDs was begun, significant improvements were seen in markers of joint inflammation, i.e., erythrocyte sedimentation rate and C-reactive protein in sera. At 6 months, clinical improvement judged by the physicians' overall assessment of joint symptoms and laboratory data was observed in 29 (88%) of the 33 RA patients. No marked effect was observed in the other 4 (12%) patients, however. We observed no significant adverse reaction to this therapy. This suggests that additive triple DMARD combination therapy of a low dose of sulfhydryl compounds, SSZ and MTX could be a useful drug therapy for the treatment of RA patients, even those who are refractory.

KEYWORDS: rheumatoid arthritis, joint inflammation, disease modifying anti-rheumatic drug, combination therapy

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Brief Note

Additive Triple DMARD Combination Therapy of a Low Dose of Sulfhydryl Compounds, Sulfasalazine and Methotrexate in the Treatment of Rheumatoid Arthritis: A Clinical Trial

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To evaluate the efficacy and safety of additive triple disease modifying anti-rheumatic drug (DMARD) combination therapy of a low dose of sulfhydryl compounds {D-penicillamine, bucillamine or tiopronin}, sulfasalazine (SSZ) and methotrexate (MTX) as a treatment for rheumatoid arthritis (RA) patients, we studied a total of 33 Japanese RA patients (6 males, 27 females). At 1 or 2 months after simultaneous administration of the 3 above-mentioned DMARDs was begun, significant improvements were seen in markers of joint inflammation, *i.e.*, erythrocyte sedimentation rate and C-reactive protein in sera. At 6 months, clinical improvement judged by the physicians' overall assessment of joint symptoms and laboratory data was observed in 29 (88%) of the 33 RA patients. No marked effect was observed in the other 4 (12%) patients, however. We observed no significant adverse reaction to this therapy. This suggests that additive triple DMARD combination therapy of a low dose of sulfhydryl compounds, SSZ and MTX could be a useful drug therapy for the treatment of RA patients, even those who are refractory.

Key words: rheumatoid arthritis, joint inflammation, disease modifying anti-rheumatic drug, combination therapy

Single disease-modifying anti-rheumatic drugs (DMARDs) have been used as a treatment for rheumatoid arthritis (RA) patients, and have yielded reductions in long-term disability (1) countered by limited efficiency (2). When a DMARD is effective for the management of a RA patient and when the action of the drug is sustained, the same regimen of medication is maintained for a long period (*e.g.*, several years) unless an adverse effect or a relapse of joint inflammation appears. There are, however, many RA patients who do not show satisfactory results with the administration of a single DMARD. In such cases, until the 1980's, rheumatologists designed therapeutic plans according to the "therapeutic pyramid" proposed by Smyth (3). Currently, based on the recent epidemiological data of long-term outcomes of RA, the perspectives in the treatment of RA are changing (4). The "step-down bridge" treatment for RA was proposed by Wilske and Healey (5) with the idea of starting combination therapy even in the early phase of disease onset. Fries (6) recently proposed a new therapeutic philosophy, the "sawtooth strategy". The effectiveness of a particular DMARD lasts for a period of time, perhaps 2 or 3 years. When the effectiveness of the DMARD begins to decline, another DMARD is administered in its place. Alternatively, in "additive DMARD therapy" (7, 8), another DMARD can be added to the present medication, when the effectiveness of a DMARD observed for a certain period of time starts to fade but retains some effectiveness. Yasuda *et al.* (9) reported

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that the addition of the DMARD bucillamine to a maintenance dose of gold sodium thiomalate showed additive efficacy in RA treatment. O'Dell *et al.* (10) recently showed that the efficacy of triple DMARD therapy (MTX, sulfasalazine, hydroxychloroquine) in RA patients was greater than that of the combination of 2 DMARDs.

In the present study, we examined the efficacy and safety of triple additive DMARD combination therapy of a low dose of sulfhydryl compounds {D-penicillamine (D-Pc), bucillamine (Buc) or tiopronin}, sulfasalazine (SSZ) and methotrexate (MTX) in the treatment of RA.

Patients and Methods

Patients. Thirty-three RA patients who satisfied the criteria for RA as set forth in 1987 by American Rheumatism Association (11) were treated with additive triple DMARD combination therapy. Six patients were males and 27 were females. Their average age was 57.2 years old (range: 29–77), and the average disease duration was 8.6 years (range: 0.5–20). Three patients were stage I, 6 were stage II, 4 were stage III and 20 were stage IV. The functional classes according to the criteria of Steinbrocker *et al.* (12) were as follows: class I, no patients; II, 27 patients; III, 6 patients; IV, 0 patients. Twelve of the 33 RA patients had been refractory to the full dosis of single DMARD therapy. Nineteen of the 33 patients were not being treated with gold sodium thiomalate (GST) because of its ineffectiveness or adverse effects. All of the patients were taking single non-steroidal anti-inflammatory drug (NSAIDs) at the same time as DMARDs. Twenty-one of the 33 patients were taking the oral steroid hormone prednisolone at less than 5 mg per day. The clinical profile of patients before entry in the study is shown in Table 1.

Table 1 Clinical profile of rheumatoid arthritis patients studied

Number of patients	33
Sex (M/F)	6/27
Age	57.2 (range: 29–77)
Disease duration (year)	8.6 (range: 0.5–20)
Stage I	3
II	6
III	4
IV	20
Class I	0
II	27
III	6
IV	0
ESR (mm/h)	69.6 ± 5.7 (mean ± SEM)
CRP (mg/dl)	5.8 ± 0.6 (mean ± SEM)

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

The erythrocyte sedimentation rate (ESR) was examined by the Westerngren method. Circulating blood cell counts, C-reactive protein (CRP) and biochemistry tests were performed by routine laboratory examinations.

Trial design. The 3 DMARDs at low doses, *i.e.*, sulfhydryl compounds (D-Pc 50–200 mg/day, Buc 100–200 mg/day or tiopronin 100 mg/day), SSZ (0.5–1.0 g/day) and MTX (2.5–5.0 mg/week) were given to the RA patients as the first, second or third choice for DMARDs. The first DMARD was replaced with another DMARD when the first DMARD failed to produce a 20 % reduction in the values of ESR, CRP, the number of painful joints and the number of swollen joints. For example, a patient was first treated with a single DMARD "A". When a satisfactory effect with DMARD "A" was not obtained after at least 4 weeks, another DMARD "B" was added to the regimen. The third DMARD "C" was added to the existing regimen when the prior combination therapy was not showing a satisfactory effect after at least 4 weeks. Thus, all of RA patients studied failed on either single or double DMARD therapy at the doses described above. No priority was given to any particular DMARD as the DMARD of first choice. However, most (82%) of the patients received the sulfhydryl compounds or SSZ as the first- or second-choice DMARD and MTX as the third-choice DMARD because MTX has not been accepted as DMARD in Japan. For sulfhydryl compounds, 1 patient had tiopronin, 12 had D-Pc and 20 had Buc. The average period of time from first DMARD given to triple DMARD therapy was 10 months, ranging 2 to 36 months. The disease activity of RA was evaluated by assessing joint symptoms and laboratory test results monthly after the time point when all three DMARDs were administered together. The clinical improvement in a physician's global assessment with a horizontal visual analog scale was judged in consideration of joint symptoms and laboratory test findings.

Statistical analysis. The values of ESR and CRP between before and after combination therapy were analyzed by paired Student's t test.

Results

Twenty-nine (88%) of the 33 RA patients showed clinical improvement in response to the additive triple DMARD therapy, as assessed by a physician's global assessment of disease activity at 6 months after all 3 DMARDs were administered together. There was no remarkable effect in the other four (12%) RA patients, however. The changes of ESR and CRP values during the 6 months of treatment are shown in Figs. 1 and 2. Significant decreases in the values of ESR and CRP were observed after 1 or 2 months. This tendency continued at 6 months. The improvement of joint symptoms was obtained almost in parallel to the decreases in these markers of joint inflammation.

The only side effect of the triple DMARD treatment observed was liver dysfunction in 1 patient who had been taking 5 mg/week of MTX. This liver dysfunction disappeared when the dosage was decreased to 2.5 mg/week.

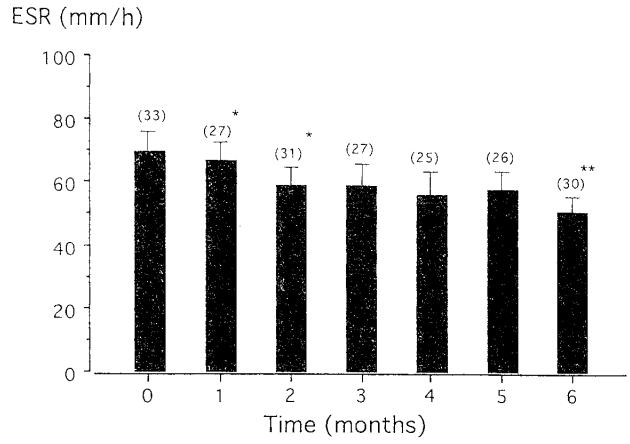

Fig. 1 Sequential changes of erythrocyte sedimentation rate (ESR) in 33 rheumatoid arthritis pateints treated with additive triple disease modifying anti-rheumatic drug therapy. Data are mean ± SEM. ( ) = number of patients. $*P < 0.05$; $**$ $P < 0.01$ *vs* before therapy.

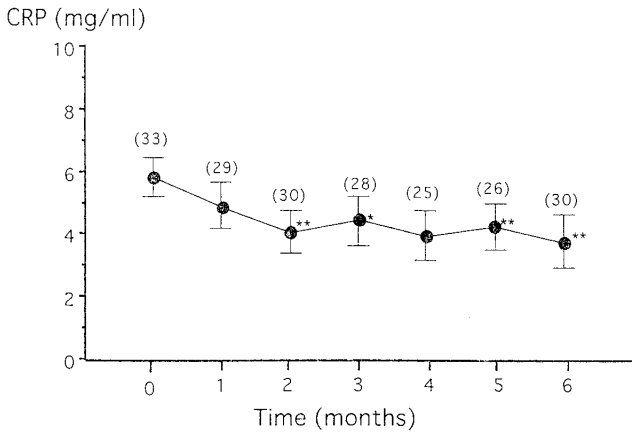

Fig. 2 Sequential changes of C-reactive protein (CRP) levels in sera from 33 rheumatoid arthritis patients treated with additive triple disease modifying anti-rheumatic drug therapy. Data are mean ± SEM. ( ) = number of patients. $*P < 0.05$; $**$ $P < 0.01$ *vs* before therapy.

Discussion

The strategy for RA treatment has changed from the pyramidal plan to the "step-down bridge" concept or "sawtooth" therapy (3, 5, 6). On the basis of evidence that RA patients have significant morbidity and increased mortality (13), the idea of combination therapy has been developed learning from the results obtained in the field of oncology (14). Many trials of combination therapy have demonstrated the additive synergistic effects of DMARDs on RA to some extent (14–16). Considering the DMARD mechanisms of action, kinetics and toxicities, suitable combinations of DMARDs could be elucidated (17). A meta-analysis of combination therapy has, however, not offered a substantial improvement in efficacy, but had higher toxicity than a single drug therapy (18).

We chose sulfhydryl compounds, SSZ and MTX for DMARD combination therapy based on their different mechanisms. The sulfhydryl compounds were tiopronin, D-Pc and Buc. The immunologic actions of D-Pc such as the induction of autoantibodies and decreased humoral and cellular immunity are reviewed in Dawkins *et al.* (19). Bucillamine, which was developed in Japan, has the ability to increase suppressor T-cell function and suppress the level of rheumatoid factor (20). The mechanism(s) of action of MTX in RA are not well understood. MTX might act as an anti-inflammatory agent rather than as an immunosuppressive agent by inhibiting pro-inflammatory cytokine production by immune cells (21), or by inducing anti-inflammatory cytokine gene expression (22). MTX inhibits methylation reactions and promotes adenosine release (23). The action of SSZ is also unclear at this time. SSZ might inhibit thromboxane synthetase and lipoxygenase pathways, leukocyte motility, proteolytic

enzyme activity, and/or IgE-mediated mast cell degranulation (24).

The full doses of D-Pc and Buc used in RA are 400-600 mg/day and 300 mg/day, respectively (19, 20); those of SSZ and MTX are 2 g/day and 10-15 mg/week (24, 25). We used a low dose of each DMARD to minimize the risk of adverse effects of the drugs. In addition, each DMARD was added following the evaluation of the efficacy and toxicity of the previously administered DMARD. We found no adverse effect by this combination therapy except in 1 patient who developed liver dysfunction when administered 5 mg/week of MTX. Twenty-nine of the 33 patients showed clinical and laboratory improvement without side effects. There was, however, no effect of this therapy on the 4 remaining patients.

Most of reports in combination therapy employed only 2 DMARDs. O'Dell *et al.* showed the efficacy of triple DMARDs of MTX, SSZ and hydroxylchloroquine in a double blind, placebo-controlled study (10). Instead of hydroxylchloroquine, which is not used in Japan because of retinal toxicity (2), sulfhydryl compounds were chosen in our prospective study. Our report and O'Dell's report could not be compared because of differences in the number of patients studied, the DMARD regimens used and the experimental methodologies employed.

Recent clinical studies have reflected the good long-term efficacy and tolerability of MTX (2). Weinblatt *et al.* reported marked improvement of joint pain and swelling index in 76-80% of 123 RA patients treated with MTX at a maximum dose of 20 mg/week after a mean of 26 months (26). We used a relatively small dose of MTX (2.5-5 mg/week) in combination with 2 other DMARDs and observed a clinical improvement in 88% of 33 RA patients after 6 months. Thus, the results in this study indicate the possibility that a low dose of additive triple DMARD combination therapy is effective for early RA patients and even for some refractory RA patients, with no adverse effects. However, long-term and large-scale trials are necessary to elucidate the effectiveness of this therapy for RA patients.

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