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**Megumi Aso · Yoshiya Tanaka · Kazuyoshi Saito
Koichi Fujii · Akiko Takazawa · Toshiyuki Ota
Sumiya Eto**

Additive combination of actarit and methotrexate in the treatment of refractory rheumatoid arthritis

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Abstract The objective of this study was to evaluate the efficacy and safety of an additive combination of a disease-modifying antirheumatic drug (DMARD) actarit and low-dose methotrexate (MTX) in patients with active rheumatoid arthritis (RA) unresponsive to MTX. Thirty-four patients with active RA, who had been unsuccessfully treated with MTX for at least 3 months were enrolled on a 24-week course of actarit (300 mg/day) and MTX (2.5–10 mg/week). Disease activity was evaluated by physical global assessments using conventional measures (Japan Rheumatism Association), and the American College of Rheumatology (ACR) criteria of improvements in RA. Thirty-two patients completed this study. No severe adverse drug reactions were seen. Patients whose RA did not respond to MTX alone responded to the combination therapy, with a significant improvement in the duration of morning stiffness, grip strength, swollen joint counts, patient's articular pain score, modified health assessment questionnaire (M-HAQ) score, score of both patient's and physician's global assessments, and C-reactive proteins (CRP). Sixteen patients (50.0%) and 9 patients (31.0%) showed a significant improvement in overall conventional measures, and ACR response criteria, respectively, and 60.0% of RA patients who received MTX for more than 1 year showed improvement in ACR definition. Patients who responded to the combination treatment within the first 12 weeks showed persistent improvement for the remaining part of the 24 week period. Our results indicate that the additive combination of actarit and MTX is safe, and without serious adverse effects, and has an excellent efficacy in patients with active and refractory RA.

M. Aso · Y. Tanaka (✉) · K. Saito · K. Fujii · A. Takazawa · S. Eto
First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan
Tel. +81-93-603-1611 (ext. 2426); Fax +81-93-691-9334
e-mail: tanaka@med.uoeh-u.ac.jp

T. Ota
Clinical Laboratory, University Hospital of Occupational and Environmental Health, Kitakyushu, Japan

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology and is characterized by erosive synovitis as well as systemic organ involvement. Most patients exhibit chronic synovitis and progressive joint destruction, which result in irreversible deformities, significant work disability, and a diminished life span by 5–7 years.[1,2] The current therapy for RA generally consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and second-line agents, and disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX). That progression of RA can occur in the first 2 years has led to the recent recommendation of early DMARD use during the course of the disease.[3,4] DMARDs can potentially reduce or prevent joint damage, and preserve joint integrity and function in RA patients.[3] Among a variety of available DMARDs, MTX was initially selected particularly for those patients with severe disease, and produced significant benefits.[5] Low-dose MTX is considered to have a more rapid onset of action compared with other drugs, resulting in a greater amelioration of synovitis, and to have minimal toxicity.[6,7] With regard to the long-term use of DMARD therapy, Weinblatt et al.[8] reported that while 64% of their patients were able to continue MTX therapy after 5 years, only 35% showed 50% improvement criteria. Thus, MTX therapy for RA might show unsatisfactory results or only partial improvement, and many patients discontinue therapy because of drug toxicity and/or reduced efficacy.

In the present study, we examined the effects of MTX combined with another DMARD, actarit, which has been available on the Japanese market for the last 5 years. Only patients with active, refractory RA were studied. These patients did not show a satisfactory response to MTX treatment despite continued therapy for more than 3 months, but showed a significant improvement in disease activity

within 12 weeks after commencing actarit/MTX combination therapy. Previous studies showed that actarit inhibited the development of arthritis in an experimental mouse model of arthritis,[9,10] and the mechanisms of action were studied using an experimental model of arthritis.[11–14] Actarit was originally designed to activate suppressor T cells in RA patients, and is also currently known to reduce the production of immunoglobulin (Ig) M, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and matrix metalloproteinase (MMP-1) by RA synovial macrophages and/or activated fibroblasts, and to reduce the adhesion of T cells to synovial cells.[15] Actarit is also known to exhibit fewer adverse effects compared with known DMARDs, making it appropriate for combination therapy with another DMARD. Recent reports indicate that combination therapy using actarit with parenteral gold (GST) or mizoribine is useful and safe for patients with active RA who were refractory to a single course of DMARD treatment.[16,17] The objectives of the present clinical trial were to evaluate the efficacy and safety of combination therapy using actarit and pulsed low-dose MTX for RA patients with refractory active disease who showed resistance to MTX alone.

Patients and methods

Patient selection and study design

Patients who met the revised criteria of the American Rheumatism Association 1987 for RA were initially treated with MTX once a week at a regular dose of 5–7.5 mg/week for a minimum of 12 weeks, in addition to corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) (see below). One unusual patient with refractory RA took 5 mg/week MTX for more than 1 year, and then a slight elevation of transaminase resulted in the dose of MTX being reduced from 5 to 2.5 mg/week. This dosage of MTX was determined by the clinician in charge, and was maintained throughout the course of treatment. If the physician was convinced at the end of the 12-week period that MTX was ineffective and the disease was still in an active form based on clinical characteristics, the patient was informed about the clinical trial and allowed to participate in the study on a voluntary basis. After a 12-week stabilization period, patients were screened to determine if they were eligible for entry into the trial. They were included in the trial if, on the day of screening, they had ≥6 tender/painful joints (of the 49 counted), ≥3 swollen joints (of the 46 counted), and an erythrocyte sedimentation rate (ESR) of ≥28 mm/h (Westergren). Patients were considered not eligible for entry and were excluded if they were severely or physically incapacitated. Female patients who were pregnant were also excluded. All patients gave written informed consent for the trial and the study was approved by the local ethics committees. Thirty-four patients were enrolled in the trial conducted in our hospital.

DMARDs other than MTX, if any, were withdrawn before screening for trial eligibility and were not permitted during the 24 weeks of the study. For 12 weeks prior to screening for study entry and during the 24-week study, patients taking oral corticosteroids (≤10 mg/day prednisolone) were maintained on the same dose during the study or permitted to use a lower dosage when a significant improvement was noted. The dose of any NSAIDs was maintained throughout the study. Patients received 100 mg of actarit three times per day, together with a fixed weekly dosage of MTX (2.5–10 mg/week).

Evaluation of treatment efficacy and safety

Prior to the study, repeat baseline measurements of clinical and laboratory parameters were made. Patients visited the hospital for follow-up assessments every 4 weeks for 24 weeks. The following measures were evaluated for changes from baseline (day 0) at weeks 4, 8, 12, 16, and 24: duration of morning stiffness, grip strength, swollen joint count, tender joint count, patient's and physician's global assessments, patient's articular pain score (on 10-cm VAS), disability as assessed by a modified Health Assessment Questionnaire (M-HAQ) score, ESR, and serum C-reactive proteins (CRP) level. The data set collected during the study was analyzed by physical global assessments using conventional measures (Japan Rheumatism Association) and the American College of Rheumatology (ACR) definition of improvement.[18] In physical global assessments (Japan Rheumatism Association), the changes in clinical and laboratory parameters at 24 weeks compared with baseline are evaluated by seven improvement items.

Safety was monitored continuously until the end of the 24-week clinical trial, whether or not the patient continued to use the trial medication. Adverse effects were either recorded by the clinician in charge, reported by the patient at follow-up visits, or elicited from the patient by questioning at each visit.

Laboratory tests

The following conventional measures and ACR improvement criteria were examined at day 0 (before the trial) and at weeks 4, 8, 12, 16, and 24. Rheumatoid arthritis hemagglutination (RAPA), IgG-rheumatoid factor (IgG-RF), complement value (CH50, by Mayer), and immunoglobulins (IgG, IgA, IgM). Laboratory tests included a complete blood cell count, measurement of serum bilirubin, total protein, transaminases, alkaline phosphatase, lactic dehydrogenase, blood urea nitrogen, creatinine, components of serum total protein, ESR, CRP, and urinalysis.

Statistical analysis

All patients were included in the efficacy analysis. Changes in morning stiffness, grip strength, swollen joint count, tender joint count, patient's and physician's global assessments, pain score, M-HAQ, ESR, and CRP at various

intervals during actarit/MTX therapy were compared with their respective values at baseline using Student's *t*-test. For determining the individual ACR end points, if a patient withdrew from treatment at any time during the study, the last available value was used as the 24-week value. *P* values are reported without adjustments for multiple comparisons. *P* values <0.05 were considered significant. Data were expressed as the mean ± SEM. Patients were divided according to the MTX dose, corticosteroid dose, and period of MTX use, and the percentages of those showing improvement in conventional measures and ACR criteria during treatment were compared.

Table 1. Patient characteristics at baseline[a]

Age (years)	
Mean	57.9
Range	24–80
Sex	
Male	3 (9)
Female	29 (91)
Disease duration (years)	
Mean	8.6
Range	1–28
Prior DMARDs	31 (96.9)
Pathological stage	
I	3 (9)
II	10 (31)
III	9 (28)
IV	10 (31)
Functional class	
1	5 (16)
2	20 (62)
3	7 (22)
Taking corticosteroids (equivalent to prednisolone, mg/day)	
None	15 (47)
0–5	13 (41)
5–10	4 (12)
Taking MTX (mg/week)	
2.5	1 (3)
5	21 (66)
7.5	8 (25)
10	2 (6.3)

[a] All 32 patients were taking NSAIDs during the study. Except where otherwise indicated, values are number (%)
DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate

Results

Patient characteristics

Of the 34 patients enrolled in the study, data from 32 patients were analyzed. One patient decided to quit a medicine shortly after commencement of the study owing to adverse effects, and another did not visit the hospital later in the study. Thirty-two patients completed the study. Table 1 shows the characteristics of our patients at baseline. Ninety-one percent were females, and the mean age of the patients was 57.9 years. The mean disease duration was 8.6 years. All patients were at functional classes 1, 2, and 3, and 20 patients (62%) were class 2. Seventeen patients (53%) had been treated with corticosteroid. Twenty-one patients (66%) and 10 patients (31%) had previously received MTX at 5 mg/week and 7.5–10 mg/week, respectively, for at least 12 weeks before enrolling in the present study. Only one patient had taken the reduced dosage of MTX (2.5 mg/week) for 16 weeks because of slight elevation of transaminase.

All enrolled patients had active RA, ≥6 tender/painful joints (of the 49 counted), ≥3 swollen joints (of the 46 counted), and an ESR of ≥28 mm/h (Westergren) on entry to the actarit/MTX study, although they had received 5–10 mg/week MTX treatments for at least 12 continuous weeks, except for the one patient mentioned above. Table 2 shows the results of clinical and laboratory assessments of RA. These results indicated the presence of an active disease state in all patients on entry to the actarit trial after more than 12 weeks of MTX treatment.

Table 2. Changes in clinical and laboratory variables indicative of disease activity at baseline, and in weeks 12 and 24 of additive combination therapy ($n = 32$)

	Baseline	Weeks after commencement of combined therapy	
		12	24
Morning stiffness (min)	143 ± 40	87 ± 25*	82 ± 29
Grip strength (mmHg)	93 ± 11	106 ± 13**	116 ± 16**
Swollen joint count	10 ± 1	7 ± 2*	7 ± 2
Tender joint count	16 ± 2	14 ± 2	14 ± 3
Pain score (scale 0–10)	5.8 ± 0.4	5.0 ± 0.4*	5.2 ± 0.5
M-HAQ (range 0–24)	8.2 ± 1.0	7.0 ± 0.9	6.6 ± 1.0*
Patient's global assessment (scale 0–10)	6.1 ± 0.4	5.1 ± 0.3**	5.0 ± 0.4*
Physician's global assessment (scale 0–10)	6.3 ± 0.3	4.9 ± 0.4*	4.3 ± 0.4**
CRP (mg/dl, normal <0.7)	3.0 ± 0.6	2.4 ± 0.4*	2.5 ± 0.6
ESR (mm/h)	43 ± 5	39 ± 4	40 ± 5

Data are mean ± SEM
M-HAQ, modified health assessment questionnaire; CRP, C-reactive proteins; ESR, erythrocyte sedimentation rate (Westergren)
* $P < 0.05$, ** $P < 0.01$, compared with baseline (Student's *t*-test)

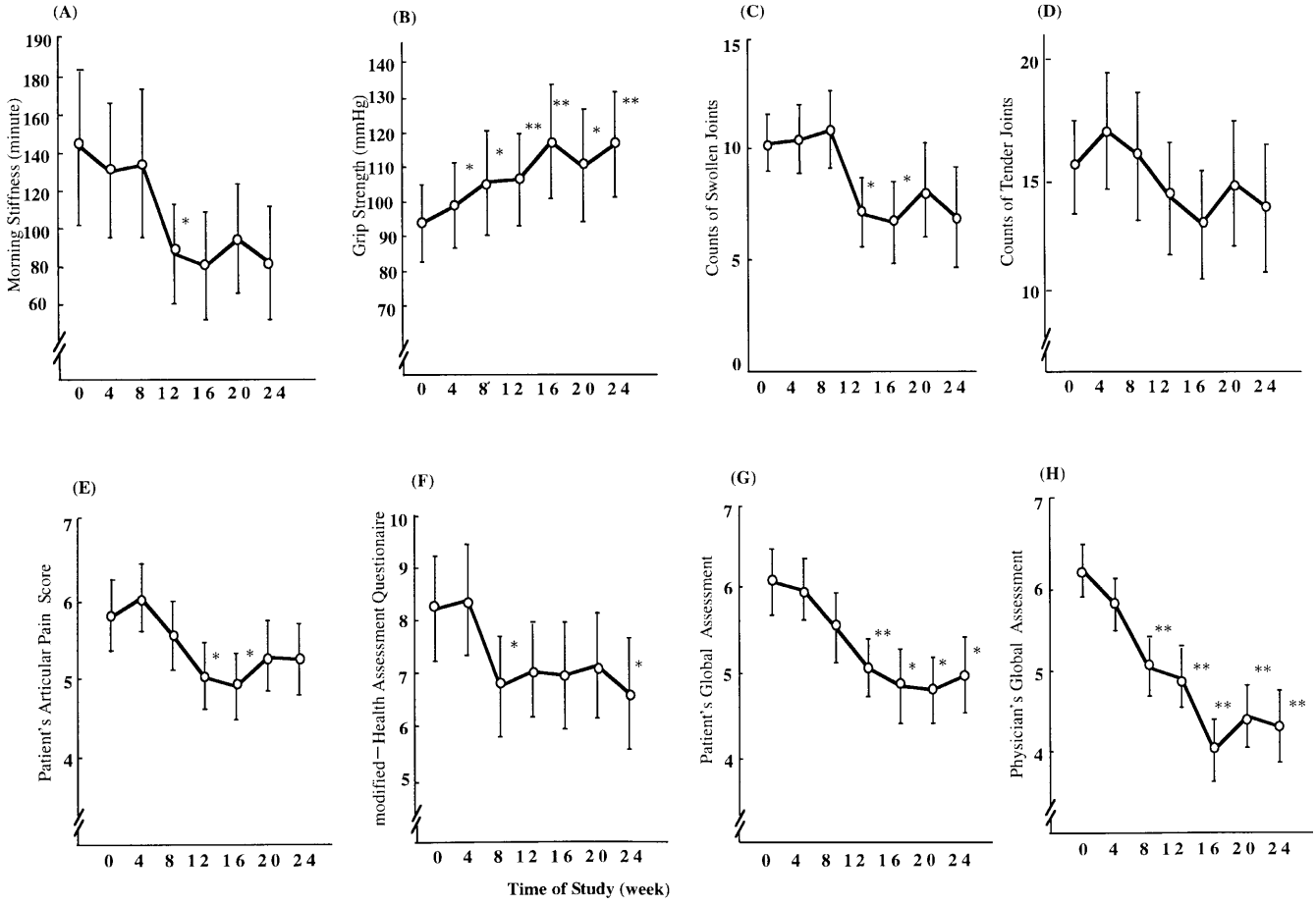

Fig. 1. Serial changes in various parameters of arthritis during actarit/MTX combination treatment. **A** Duration of morning stiffness; **B** grip strength; **C** counts of swollen joints; **D** counts of tender joints; **E** patient's articular pain/severity score; **F** score of M-HAQ; **G** score of patient's global assessments; **H** score of physician's global assessments. Data are mean ± SEM. $*P < 0.05$, $**P < 0.01$, compared with week 0 (baseline assessments, by Student's *t*-test)

Efficacy

Table 2 shows changes in clinical and laboratory variables at weeks 12 and 24. A significant improvement in various parameters was noted at week 12 or week 24 after combining MTX with actarit relative to baseline data. However, no significant changes were noted in the number of tender joints, ESR (Table 2), RAPA (data not shown), IgG-RF (data not shown), and CH50 (data not shown). Figure 1 shows serial changes in each parameter during the 24-week course of actarit/MTX therapy. Although no change was noted within the first 8 weeks of additive combination therapy (with the exception of grip strength, M-HAQ score, and physician's global assessments), significant improvements in the duration of morning stiffness, counts of swollen joints, patient's articular pain/severity score, and other parameters were observed at week 12. These changes persisted throughout the remaining part of the treatment course. Interestingly, grip strength increased within 4 weeks after commencement of the actarit trial and persisted throughout the study. It is noteworthy that the scores of patient's global health assessment and physician's global assessments improved within 8 or 12 weeks, and such improvement continued up to 24 weeks after the start of combination therapy but a lower level of scores was maintained thereafter.

The overall efficacy of additive combination therapy in 32 RA patients was estimated by percentage improvement in conventional measures (Japan Rheumatism Association) and ACR response criteria (Table 3). Sixteen patients (50.0%) showed a significant improvement in conventional measures, while 9 patients (31.0%) showed a significant improvement in ACR criteria. A better improvement in conventional measures was observed in patients treated with a lower dose of MTX (2.5–5 mg/week) (59.1%) than in those with a higher dose of MTX (7.5–10 mg/week) (30.0%), whereas the dosage of MTX did not show any differences in degree of improvement based on evaluation using the ACR criteria. The percentage improvement estimated by both conventional measures and ACR criteria was comparable in patients treated with or without corticosteroids. It is noteworthy that the best improvement estimated by conventional measures and ACR criteria was observed in patients who received MTX for more than 1 year. In particular, 60.0% of patients who were treated with MTX for more than 1 year showed improvement in ACR,

whereas only approximately 16% of patients receiving MTX for less than 1 year improved by ACR criteria.

Figure 2 shows the effects of dosage of MTX, adjuvant corticosteroid treatment, and duration of MTX therapy on the serial changes in the score of physician's global assessments during treatment with actarit/MTX. The score of physician's global assessments started to improve within 4 or 8 weeks and continued up to 12 or 16 weeks after starting combination therapy, and a lower score was persistently recorded throughout the remaining part of the study by all classifications. There was no significant effect for the dosage of MTX or the additional use of corticosteroids. However, patients treated with MTX for >1 year showed a better improvement in the score from week 8 to week 24 compared with patients treated for <6 months and 6–12 months (Fig. 2C).

Table 3. Percentage of patients showing improvement evaluated by conventional measures and ACR improvement criteria, after additive combination therapy

Classification	% improvement by	
	Conventional measures	ACR criteria
Overall change	50	31
Dosage of MTX		
2.5–5 mg/week (n = 22)	59	32
7.5–10 mg/week (n = 10)	30	30
Corticosteroid treatment		
With (n = 15)	53	29
Without (n = 17)	47	33
Duration of MTX treatment		
<6 months (n = 13)	46	17
0.5–1 year (n = 9)	44	14
>1 year (n = 10)	60	60

Adverse effects

Thirty-two of 34 patients completed the present study. Two patients withdrew owing to adverse effects. Table 4 lists the adverse effects encountered during the additive combination therapy and which occurred in 10 patients (29.4%). One patient withdrew 3 days after the start of therapy owing to nausea and epigastralgia, while the other patient withdrew at day 81 owing to the development of amenor-

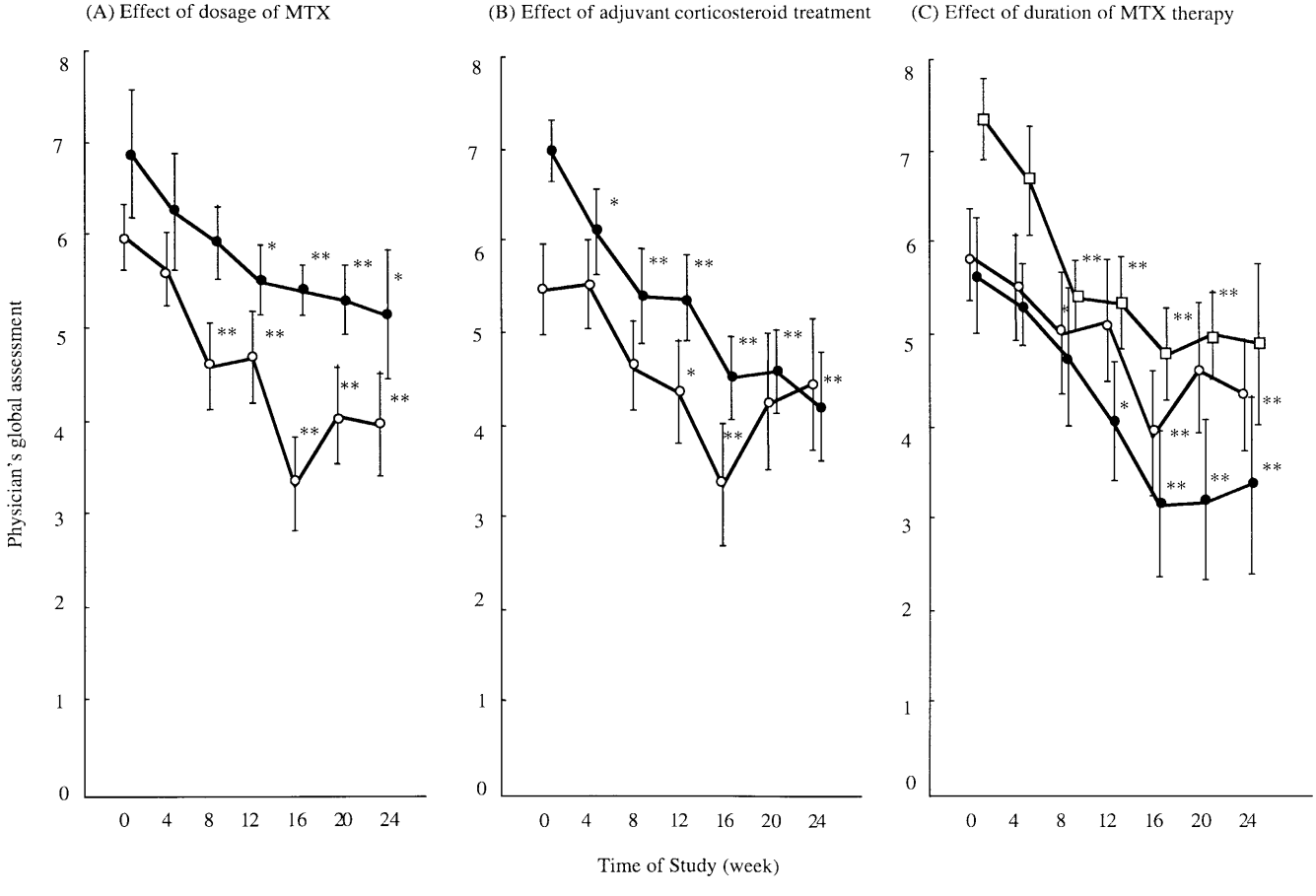

Fig. 2. Serial changes in the score of physician's global assessment by visual analog scale during actarit/MTX combination treatment. **A** Effect of dosage of MTX: *solid circles*, MTX at 2.5–5 mg/week; *open circles*, MTX at 7.5–10 mg/week. **B** Effects of adjuvant corticosteroid treatment: *solid circles*, no corticosteroid; *open circles*, with corticosteroid. **C** Effects of duration of MTX therapy: *open squares*, <6 months; *open circles*, 0.5–1 year; *solid circles*, >1 year. Data are mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, compared with week 0 (baseline assessment, by Student's t-test)

Table 4. Adverse effects reported during study weeks 0–24 ($n = 34$)

Adverse effects	No. (%)
Nausea or epigastralgia	3 (9)
Increase in AST or ALT	3 (9)
Increase in LDH	2 (6)
Breast tenderness	1 (3)
Amenorrhea	1 (3)
Glaucoma	1 (3)
Herpes zoster	1 (3)
Total number of patients	10 (29)

In some patients, more than one adverse effect was noted
AST, aspartic acid transferase; ALT, alanine transferase; LDH, lactic dehydrogenase

rhea. The most frequent adverse effects were nausea, epigastralgia, and increase in serum AST or ALT. However, all adverse effects were mild, and gradually disappeared even though the treatment was continued.

Discussion

In this study, we evaluated the efficacy and safety of an additive combination of actarit and low-dose MTX in the treatment of active RA patients. The major findings of our study are detailed below. First, 32 patients with RA who failed to respond to a regular dosage of MTX alone showed a clinical response to an additive combination therapy of actarit and MTX, including a significant improvement in the duration of morning stiffness, grip strength, counts of swollen joints, patient's articular pain/severity score, M-HAQ score, score of patient's global health assessments, score of physician's global assessments, and CRP levels. Sixteen (50.0%) and 9 (31.0%) patients showed a significant improvement in conventional measures and ACR response criteria, respectively. Second, 60.0% of RA patients receiving MTX for more than 1 year showed improvement in ACR criteria, whereas only approximately 16% of patients receiving MTX for less than 1 year had improved by ACR criteria. Third, patients with active, refractory RA who responded to the combination treatment within the first 12 weeks showed a persistent response for at least a 24 week period. Fourth, combination therapy is safe and had no serious adverse effects in patients with RA.

RA synovitis is characterized by chronic inflammatory processes with proliferation and activation of synovial cells, and marked infiltration of the synovium by T cells. Joint inflammation is caused by both cellular components and soluble mediators (cytokines). We and other authors[19–24] have previously reported that T cells infiltrating the rheumatoid synovium play an important role as both regulatory and effector cells in the initiation and perpetuation of the inflammatory process of RA synovitis. It is also known that T cell-activated B lymphocytes lead to the production of rheumatoid factor and other autoantibodies, while macrophages may be more important for the effector mechanisms leading to joint destruction. Furthermore, various adhesion molecules as well as cytokines are thought to contribute to the inflammatory processes.[19–24] DMARDs can potentially reduce or prevent joint damage, and preserve joint integrity and function in RA patients.[3] Because progression of RA can occur in the first 2 years, any new patient with RA should be treated with DMARD as promptly as possible to prevent or slow further damage.[3,25] However, treatment of RA patients with a single DMARD is often unsatisfactory in that it only produces a partial response, and many patients discontinue therapy because of drug toxicity and/or reduction of efficacy.

Based on the complex pathological process of RA, it is therefore appropriate to initiate RA therapy using a combination DMARD therapy. Since each DMARD has a different mechanism of action, such drugs are likely to attack more than one pathway and/or pathological process.[26] In particular, the use of combination DMARD therapy is recommended for patients with a very active disease process and refractory arthritis.[3] It is very important to know which DMARDs should be selected for the combination therapy, and to know the mechanisms of action of each drug, the pharmacokinetics, and the toxicity, in order to develop a rational and synergistic DMARD combination with little overlap in order to control disease activity with improved efficacy and minimal toxicity.[26,27] Among many studies that have used DMARD combination therapy, MTX has been the most frequently used drug.[1,28] For example, MTX and parenteral gold were the most effective DMARDs, followed by azathioprine and penicillamine.[29] The combination of MTX with sulfasalazine or hydroxychloroquine was more effective than either MTX alone or a combination of sulfasalazine and hydroxychloroquine, and MTX with cyclosporine was also more efficacious than MTX alone.[30,31]

The rationale for the combination of actarit with MTX appears to be appropriate based on their different mechanisms of action, pharmacokinetics, and toxicity. MTX is known to reduce neutrophil chemotaxis, monocyte activation, B cell activation, production of dihydrofolate reductase, lipoxygenase, IL-1, and Th1 cytokines.[2,32] On the other hand, actarit is reported to inhibit the development of arthritis in experimental mouse models, activate suppressor T cells[9–14], and reduce the production of IgM, TNF-α, IL-1β, and MMP-1 from RA synovial macrophages and/or activated fibroblasts, and to reduce adhesion of T cells with synovial cells.[15] MTX is metabolized mainly in the liver, and shows multiple organ toxicity such as hepatic failure, life-threatening pulmonary toxicity, gingivitis, stomatitis, and bone marrow suppression.[1,2] On the other hand, actarit is excreted in urine in the unchanged form from the kidney and has much less severe adverse effects. It is therefore appropriate for combination therapy.

Based on these properties, we selected the combination of MTX and actarit. Our study is the first to report the efficacy of additive combination therapy with actarit and MTX in patients with active RA. Our results demonstrate that RA patients who did not respond to a regular dosage of MTX alone had a significant improvement following treatment with actarit and MTX. Sixteen patients (50.0%) in the

current study showed a significant improvement in conventional measures, which is better than that for patients treated with actarit alone (36.8% improvement), as reported by Shiokawa et al.[33] Furthermore, our results demonstrated that 60.0% of RA patients receiving MTX for more than 1 year showed improvement in the ACR criteria which were proposed by ACR in 1995, and which reflect clinically important changes in the "real life" of patients with RA.[18,34] These results also suggest that the efficacy was due to the additive combination rather than the direct effects of MTX, and that there might be unknown synergistic effects between actarit and MTX affecting differential mechanisms in the pathogenesis of RA. Moreover, serious adverse effects were not observed in the present study. Only two patients of 34 withdrew owing to adverse effects, and the overall safety of the therapy was estimated to be 94.1%, which was comparable to the safety levels for patients treated with actarit alone (92.2% safety) reported by Shiokawa et al.[33] However, further analyses are required for laboratory parameters including ESR, RAPA, IgG-RF, and CH50 (data for the last three are not shown), in which no significant changes were noted at weeks 12 and 24 after the additive therapy.

In conclusion, this study indicates that additive combination therapy with actarit and MTX is safe and has no serious adverse effects, and has an excellent efficacy sating in patients with active and refractory RA.

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