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Usefulness of actarit in elderly rheumatoid arthritis

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Abstract Many elderly patients with rheumatoid arthritis (RA) who have decreased physiological functions due to aging may also have symptoms of other complications. Therefore, attention must be paid not only to the efficacy, but also to any possible adverse reactions, when selecting disease-modifying antirheumatic drugs (DMARDs). In this study, we examined the efficacy and safety of actarit for elderly patients with mildly to moderately active rheumatism. Twenty patients with elderly rheumatoid arthritis were enrolled on a 48-week course of actarit (300 mg/day). In the overall evaluation, 14 out of 20 patients (70%) met the criteria for a 20% improvement in the American College of Rheumatology (ACR) core set, and seven out of 20 patients (35%) met the criteria for a 50% improvement. In the evaluation parameters, a significant improvement was shown in the number of swollen joints, the patient's evaluation of pain, the patient's evaluation of chronic arthritis activity, the doctor's evaluation of chronic arthritis activity, erythrocyte sedimentation rate, C-reactive protein (CRP), and Lansbury's activity index after 48 weeks. A particularly remarkable improvement was shown in tender and swollen joints in the small joint category in elderly onset RA. No adverse reactions and no aggravation of complications were observed in this study. From these results, it was concluded that actarit was a safe and highly effective drug for use with elderly patients.

Key words Actarit · Elderly rheumatoid arthritis · Small joint category

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Introduction

With an aging society, the ratio of the elderly among patients with rheumatoid arthritis (RA) is increasing. In fact, the ratio of RA patients aged 60 years and over was given as 43.7% in the white paper on rheumatism published by the Japan Rheumatism Friendship Association in 1990,[1] whereas it was given as 54.3% in their 2000 publication.[2] Moreover, the ratio of patients aged 70 years and over had almost doubled from 9.9% to 19.6%, and the ratio of patients with so-called elderly onset RA had increased from 7.5% in 1990 to 10.6% in 2000, setting an age boundary of 60 years.

With aging, life-style diseases such as hypertension, diabetes mellitus, and hyperlipemia begin to occur, and a decrease in physiological functions induces renal, hematopoietic, and endocrine disorders. Consequently, various complications are found in elderly patients with RA. Furthermore, the prolonged period of sickness with RA may be complicated with extraarticular diseases such as hypothyroidism and amyloidosis in some patients, and treatment is often difficult.

Meanwhile, disease-modifying antirheumatic drugs (DMARDs) and nonsteroidal anti-inflammatory drugs are generally used as therapies for RA, although steroids and immunosuppressive drugs are sometimes used depending on the patient's pathological condition. Thus, elderly patients with RA need closer attention than young patients in order to prevent the occurrence of adverse reactions, since not only are there many treatments, but there are also many interactions with the drugs prescribed for complications, as well as delayed drug elimination due to lower renal function.

Among DMARDs, actarit belongs to group b (mild effect and relatively low incidence of adverse reactions), and is similar to auranofin by Uchida's classification.[3] Urano and Suzuki[4] and Mizutani[5] have reported the usefulness of actarit for elderly onset RA, and have suggested that actarit may be the drug of first choice for patients with elderly onset RA. However, in Mizutani's report, adverse reactions occurred in all patients aged 60 years and over, and thus the

influence of age on the safety and complications must be studied further.

In this study, we examine the efficacy and safety of actarit in elderly patients with mildly to moderately active rheumatism using the American College of Rheumatology (ACR) core set.

Materials and methods

Subjects

The subjects of this study were outpatients with RA who were treated in our hospital, who satisfied the classification criteria of ACR,[6] and who showed a partial response to the administration of nonsteroid anti-inflammatory drugs (NSAIDs) or DMARDs. A partial response was defined as when at least three out of the following four criteria were present: (1) three or more swollen joints; (2) four or more active joints (swollen and tender joints); (3) erythrocyte sedimentation rate (ESR) of 40 mm/h or higher; (4) C-reactive protein (CRP) of 1.0 mg/dl or higher.

RA that developed in patients of 65 years or older was defined as elderly onset RA (E-RA), and that in patients of less than 65 years as younger-onset RA (Y-RA). All the patients received a full explanation about the symptoms of RA, the expected effect of actarit on the symptoms, and the possible adverse reactions of the drug, and those who provided informed consent were included in the study.

Drugs examined and administration methods

An actarit tablet (containing 100 mg actarit per tablet) was administered orally, one tablet at a time, three times a day. The study period was 48 weeks. All increases in the doses of NSAIDs, steroids, and DMARDs, including immunosuppressive drugs or any new combination of these drugs, were prohibited during the study period.

Examination parameters

In accordance with the ACR core set,[7] the number of tender joints, the number of swollen joints, the patient's evaluation of tenderness (rated by a visual analog scale (VAS) entered by the patient), the patient's evaluation of rheumatic activity (systemic) (rated by a VAS entered by the patient), the doctor's evaluation of rheumatic activity (rated by a VAS related to the activity of rheumatoid arthritis on the examination day entered by the doctor), the patient's evaluation of functions (rated by a modified health assessment questionnaire (MHAQ)), ESR, serum CRP concentration, duration of morning stiffness, grasping power, joint score, and Lansbury's index (LAI) were all determined at the start and at the end (after 48 weeks) of drug administration.

Tender and swollen joints were analyzed by defining finger (metacarpophalangeal (MCP), proximal interphalangeal (PIP)), hand, toe, and foot joints as small joints, and the rest as large joints.

Laboratory examinations

For the laboratory examinations, we measured the leukocyte count, erythrocyte count, hemoglobin, hematocrit, platelet count, total protein, GOT, GPT, Al-P, blood urea nitrogen (BUN), creatinine, serum electrolytes (Na, K, Cl), urinary protein, and urinary sediment.

Adverse reactions

For the adverse reactions, any aggravation of complications and abnormal laboratory values, including the type, severity, treatment, and outcome as well as the causal relationship, were recorded.

Overall evaluation

Based on the criteria for an improvement in the ACR score set, the patients who showed improvement were examined.

The criteria for an improvement in the ACR core set were an improvement in the number of tender joints by 20% (or 50%) or higher, an improvement in the number of swollen joints by 20% (or 50%) or higher, as well as an improvement by 20% (or 50%) or higher in three out of the following five parameters: (1) patient's evaluation of tenderness; (2) patient's evaluation of rheumatic activity (systemic); (3) doctor's evaluation of rheumatic activity; (4) patient's evaluation of functions; (5) acute-phase reactive substances (ESR or CRP). The subjects who met these criteria were judged to be ACR 20 (or ACR 50).

Statistical analysis

Student's *t*-test was performed on the parametric data, while Fisher's direct probability test was performed on the nonparametric data, and the significance level was set at 5% in both cases.

Results

Patient background

In this study, the drug being studied was administered to 20 patients to whom administration was possible for the whole 48 weeks. Tables 1 and 2 show their background data. The subjects were 5 men and 15 women, and their mean age was 73.3 years. Their mean period of sickness was 9.4 years, and the age of onset was less than 65 years in 8 subjects and at 65 years or over in 12 subjects. According to Steinblocker's classification, 1, 5, 2, and 12 subjects belonged to Stages I, II, III, and IV, respectively, indicating that destruction of the joints was relatively advanced in many cases. According to class classification, 13 subjects belonged to class 2 and 7 belonged to class 3.

All patients had some complications, and hyperlipidemia and diabetes, which were observed in 4 subjects, were the

Table 1. Patient characteristics

	Mean ± SD	Range	Complications	20/0
Sex (%female, $n = 20$)	75%		Hyperlipidemia	4
Age (years)	73.3 ± 4.0	70–83	Diabetes mellitus	4
Disease duration (years)	9.4 ± 10.6	0.25–22	Interstitial pneumonia	3
Stage (%I + II, $n = 20$)	30%		Cerebral infarction	3
Class (%1 + 2, $n = 20$)	65%		Hypertension	2
Tender joint count	4.5 ± 3.3	1–15	Pulmonary emphysema	2
Swollen joint count	5.9 ± 3.7	2–17	Pulmonary fibrosis	2
Patient's articular pain score (mm)	56.8 ± 24.2	2–10	Chronic nephritis	2
Patient's global assessment (mm)	54.9 ± 23.6	1.3–10	Alcoholic hepatitis	1
Physician's global assessment (mm)	55.9 ± 12.2	3.5–10	Bronchiectasis	1
MHAQ (range 0–24)	7.0 ± 5.3	0–17	Bronchial asthma	1
ESR (mm/h)	85.4 ± 34.9	30–138	Osteoporosis	1
CRP (mg/dl)	3.06 ± 2.50	0.13–7.75	Sjögren's syndrome	1
Morning stiffiness (min)	153.0 ± 178.5	0–480	Carcinoma of the colon and rectum + lung metastasis	1
Grip strength (mmHg)	143.6 ± 66.1	48–270	Diabetic nephropathy	1
Active joint score	71.2 ± 36.4	22–144	Breast cancer, postoperative 2 years	1
Lansbury index (%)	68.3 ± 34.3	20–142	Chronic hepatitis	1

Except where otherwise indicated, values are mean ± SD
MHAQ, modified health assessment questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate (Westergren)

Table 2. Patient's medication

Patient No	Sex	Age (years)	Also taking a NSAID	Also taking a steroid	Also taking a DMARD	DMARD used previously
1	Male	77	Etodolac	–	MTX 5.0 mg/week, 5 years	–
2	Female	70	Zaltoprofen	–	–	–
3	Female	70	Oxaprozin	–	–	–
4	Female	71	–	–	Mizoribine, 6 months	GST, GST, Bucillamine,
5	Female	70	Diclofenac sodium	–	MTX 2.5 mg/week, 15 months	Lobenzarit disodium
6	Male	83	Etodolac	–	–	–
7	Female	77	Oxaprozin	–	–	–
8	Female	71	Ampiroxicam	–	Mizoribine, 9 months	GST, Bucillamine, MTX
9	Female	70	Loxoprofen sodium	–	MTX 5.0 mg/week, 6 months	Mizoribine
10	Female	70	Oxaprozin	–	–	–
11	Female	74	Ampiroxicam	–	–	–
12	Male	71	Loxoprofen sodium	–	–	GST, Bucillamine, CCA
13	Female	70	Oxaprozin	–	–	–
14	Male	71	Loxoprofen sodium	–	–	–
15	Female	75	Loxoprofen sodium	–	–	–
16	Male	71	Zaltoprofen	–	–	–
17	Female	77	Loxoprofen sodium	–	–	–
18	Female	76	Zaltoprofen	–	–	–
19	Female	81	Oxaprozin	5 mg/day, 15 months	MTX 2.5 mg/week	–
20	Female	70	Ampiroxicam		–	–

GST, gold sodium thiomalate; MTX, methotrexate; CCA, lobenzarit disodium

most frequent. Table 2 shows the medication of individual patients. NSAIDs had been administered to 19 out of 20 patients, and a steroid had been administered to 1 patient (case 19) at 5 mg/day. In 6 out of 20 patients (cases 1, 3, 4, 8, 9, and 19), actarit had been administered in addition to methotrexate (MTX) or mizoribine. DMARDs had been administered to 5 patients (cases 4, 5, 8, 9, and 12), gold sodium thiomalate (GST) to 4 patients, bucillamine to 3 patients, lobenzarit disodium (CCA) to 2 patients, mizoribine to 1 patient, and MTX to 1 patient. No histories of DMARDs were given by the remaining 15 patients.

At the start of the study, the mean number of tender joints was 4.5, that of swollen joints was 5.9, mean ESR was 85.4 mm/h, and mean CRP was 3.06 mg/dl, indicating that the majority of the patients had mild to moderate rheumatic activity.

Adverse reactions and laboratory values

In this study, there were no adverse reactions or any aggravation of complications. Concerning changes in the laboratory values, the normal values at the start of administration changed to abnormal values after 48 weeks as 10 events in 8 subjects. These were an increased erythrocyte count in one event, an increased leukocyte count in one event, an increased platelet count in one event, decreased hematocrit in one event, decreased creatinine in one event, increased

Table 3. Changes in laboratory values during the study ($n = 20$)

Patient No.	Age	Sex		Start of study	End of study
2	70	Female	RBC ($\times 10^4/\mu l$)	474	551
4	71	Female	Creatinine (mg/dl)	1.0	1.3
5	70	Female	WBC (μl)	8900	9300
6	83	Male	Creatinine (mg/dl)	0.8	0.6
12	71	Male	RBC ($\times 10^4/\mu l$)	525	370
			Ht (%)	41.5	32.5
			Cl (mEq/l)	102.4	110.7
17	77	Female	BUN (mg/dl)	17.0	27.5
18	76	Female	RBC ($\times 10^4/\mu l$)	398	377
20	70	Female	PLT ($\times 10^4/\mu l$)	33.9	34.6

RBC, red blood cells; WBC, white blood cells; Ht, hematocrit; BUN, blood urea nitrogen; PLT, platelets

creatinine in one event, increased BUN in one event, increased serum chromium in one event, and erythropenia in two even to (Table 3). However, these changes were all mild, and it was not known whether they were related to aging, rheumatic activity, or actarit.

Profiles of examination parameters

Numbers of tender and swollen joints

The mean number of tender joints, which was 4.5 at the start of drug administration, improved significantly to 1.5 after 48 weeks, and the value reached 0 in 9 out of 20 subjects. The number of tender joints improved by 20% or higher in 16 out of 20 subjects (80%). Out of 20 subjects, 15 (75%) showed a 50% or higher improvement in the number of tender joints. The number of swollen joints also showed a significant improvement from the mean value of 5.9 at the start of drug administration to 2.4 after 48 weeks, and it reached 0 in 5 out of 20 subjects. The number of swollen joints was improved by 20% or higher in 16 out of 20 subjects (80%). Out of 20 subjects, 14 (70%) showed a 50% or higher improvement (Figs. 1, 2).

Patient's evaluation of pain, and patient's and doctor's evaluations of rheumatic activity

The patients' evaluation of pain improved significantly from a mean scale of 56.8 mm at the start of administration to 31.5 mm after 48 weeks. Out of 20 subjects, 15 (75%) showed a 20% or higher improvement in self-evaluated pain. Out of 20 subjects, 8 (40%) showed a 50% or higher improvement.

The patients' evaluations of rheumatic activity improved significantly from a mean scale of 54.9 mm at the start of administration to 29.3 mm after 48 weeks. Out of 20 subjects, 16 (80%) showed a 20% or higher improvement in self-evaluated pain. Out of 20 subjects, 10 (50%) showed a 50% or higher improvement. The doctor's evaluations of rheumatic activity also improved significantly from a mean scale of 55.9 mm at the start of administration to 36.6 mm after 48 weeks. Out of 20 subjects, 11 (55%) showed a 20% or higher improvement in self-evaluated rheumatic activity. An improvement of 50% or higher was shown by 4 out of 20 subjects (20%) (Figs. 1, 3).

Patient's evaluation of functions (MHAQ)

The patients' evaluations of functions improved significantly from a mean score of 7.0 points at the start of administration to 4.9 points after 48 weeks. Out of 20 subjects, 12 (60%) showed a 20% or higher improvement in self-evaluated functions, while 6 out of 20 subjects (30%) showed a 50% or higher improvement (Figs. 1, 3).

Erythrocyte sedimentation rate and C-reactive protein

ESR improved significantly from a mean value of 85.4 mm/h at the start of administration to 59.3 mm after 48 weeks. Out of 20 subjects, 14 (70%) showed a 20% or higher improvement in ESR, while 5 out of 20 (25%) showed a 50% or higher improvement. CRP improved significantly from a mean value of 3.06 mg/dl at the start of administration to 1.61 mg/dl after 48 weeks. Out of 20 subjects, 15 (75%) showed a 20% or higher improvement in CRP, while 11 out of 20 (55%) showed a 50% or higher improvement (see Figs. 1, 2).

Lansbury's activity index (LAI)

LAI improved significantly from 68.3% at the start of administration to 45.9% after 48 weeks. Similarly, the duration of morning stiffness, grasping power, and active joint score all improved significantly (Fig. 4).

Immunoglobulin

Figure 5 shows the profiles of IgG, IgA, IgM, and rheumatoid factor; a significant decrease was shown in IgG compared with the baseline value.

Stratification analysis

Patients with E-RA had more tender and swollen joints than those with Y-RA, although there was no difference in

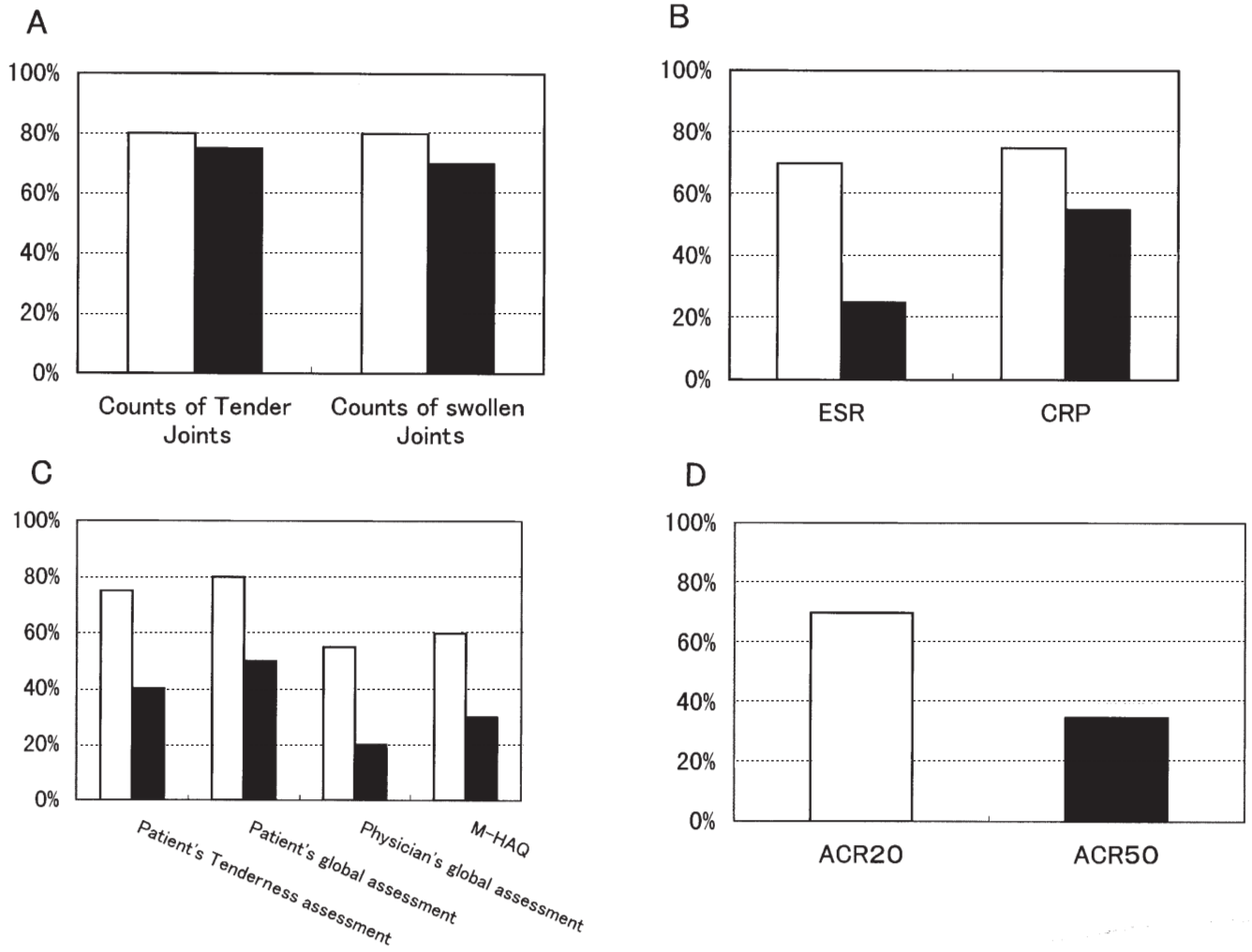

Fig. 1. Percentage of patients showing an improvement as evaluated by the American College of Rheumatology (ACR) improvement criteria. **A** Counts of tender and swollen joints. **B** Erythrocyte sedimentation rate (*ESR*) and C-reactive protein (*CRP*). **C** Patient's tenderness assessment, patient's and physician's global assessment, modified health assessment questionnaire (*MHAQ*). **D** ACR core set 20% and 50%. *Open blocks*, ACR20%; *solid blocks*, ACR50%

ESR or LAI (Table 4). Examination by disease stage showed that the joints of patients with E-RA were significantly larger than those of patients with Y-RA in stages I and II. The joints of patients with E-RA were also larger than those of patients with Y-RA in patients with RA in the small joints alone. The improvement in tenderness and swelling in both large and small joints after actarit treatment was examined by dividing the patients into those with E-RA and those with Y-RA (Table 5). The results showed that tenderness and swelling in the small joints were markedly improved in patients with E-RA, but that symptoms in the large joints were not significantly improved in patients in either group.

Overall evaluation

Out of 20 subjects, 14 (70%) met the criteria for a 20% improvement in the ACR score set, and 7 out of 20 (35%) met the criteria for a 50% improvement (see Fig. 1). In the stratified analysis with respect to stage, significantly more ACR 20% and ACR 50% patients were found in the stage I + II group than in the stage III + IV group. However, no significant difference was shown in either onset age or sick period (see Table 3). Although the data are not shown, stratified analysis with respect to ESR, CRP, and LAI did not show any distinct differences.

Discussion

In RA in elderly patients who have decreased physiological functions due to aging, many patients have complications such as renal, hematopoeitic, or endocrine disorders as extraarticular symptoms accompanying RA and as a result of long-term chemotherapy. Therefore, attention must be paid not only to their efficacy, but also to any possible adverse reactions, when selecting DMARDs.[8]

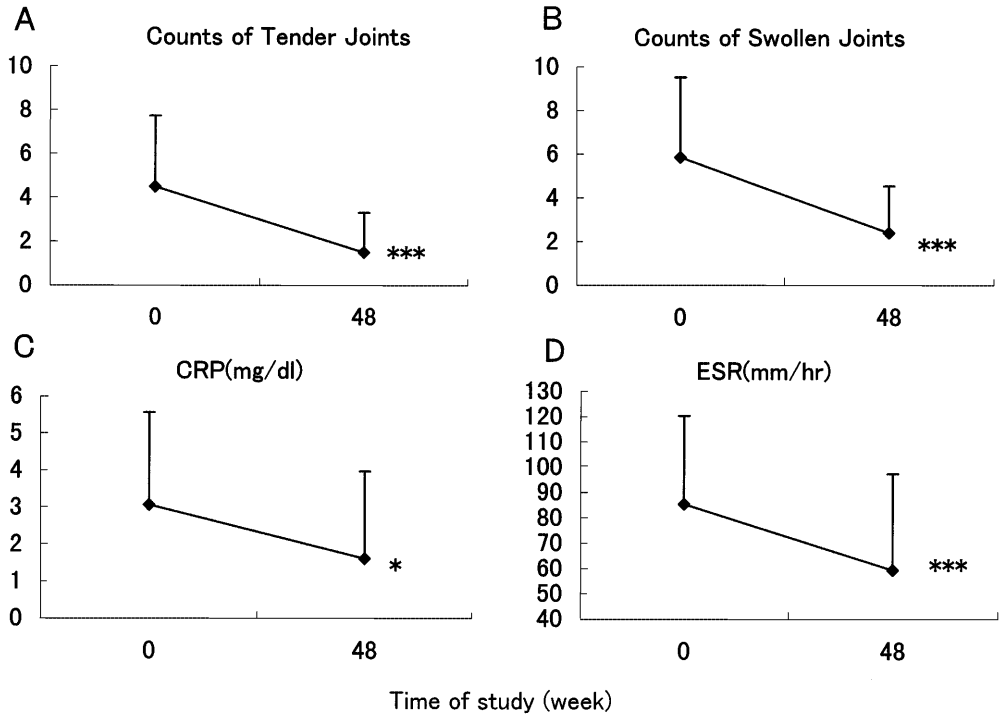

Fig. 2. Serial changes in arthritis during actarit treatment in (**A**) counts of tender joints, (**B**) counts of swollen joints, (**C**) *CRP*, and (**D**) *ESR*. *Bars* are mean ± SD. * and ***, significant changes from baseline ($P < 0.05$ and 0.001, respectively)

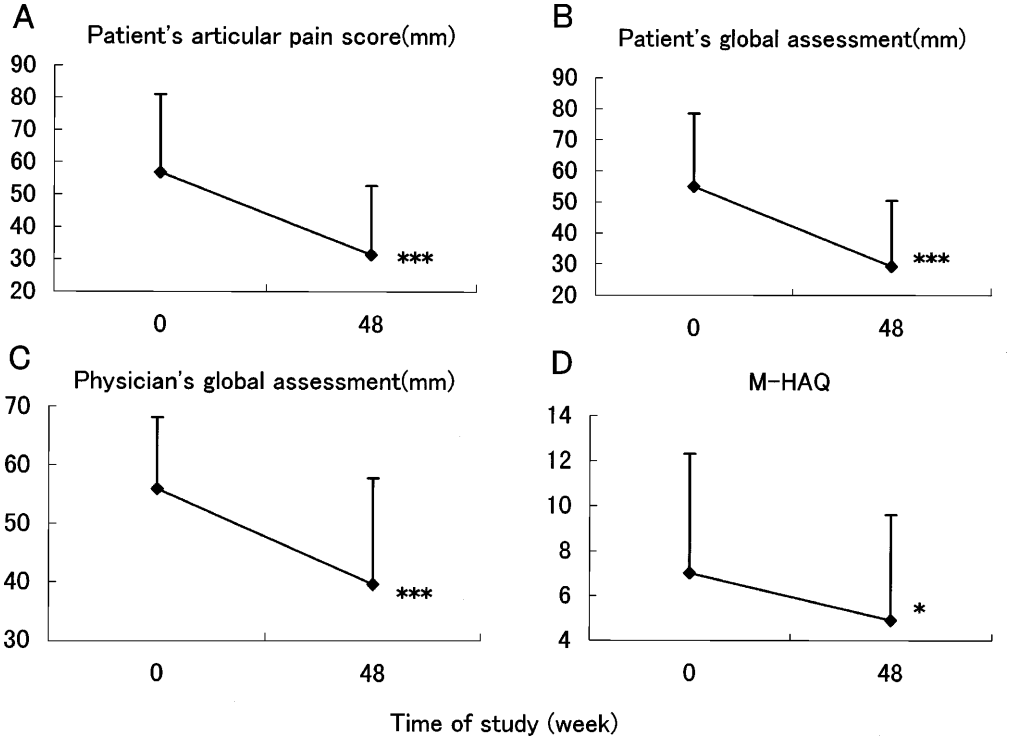

Fig. 3. Serial changes in arthritis during actarit treatment in (**A**) patient's articular pain score, (**B**) score of patient's global assessment, (**C**) score of physician's global assessment, and (**D**) score of *MHAQ*. *Bars* are mean ± SD. * and ***, significant changes from baseline ($P < 0.05$ and 0.001, respectively)

Actarit is known to have mild effects and relatively few adverse reactions. The incidence of adverse reactions associated with actarit during its development and after marketing was 9.5% (495/5199 cases), which was lower than that for other DMARDs, and most of the major adverse reactions were reported to be skin disorders or gastrointestinal disorders.[9]

Based on these findings, we administered actarit to elderly patients with RA with mildly to moderately active rheumatism, and examined both its efficacy and its safety.

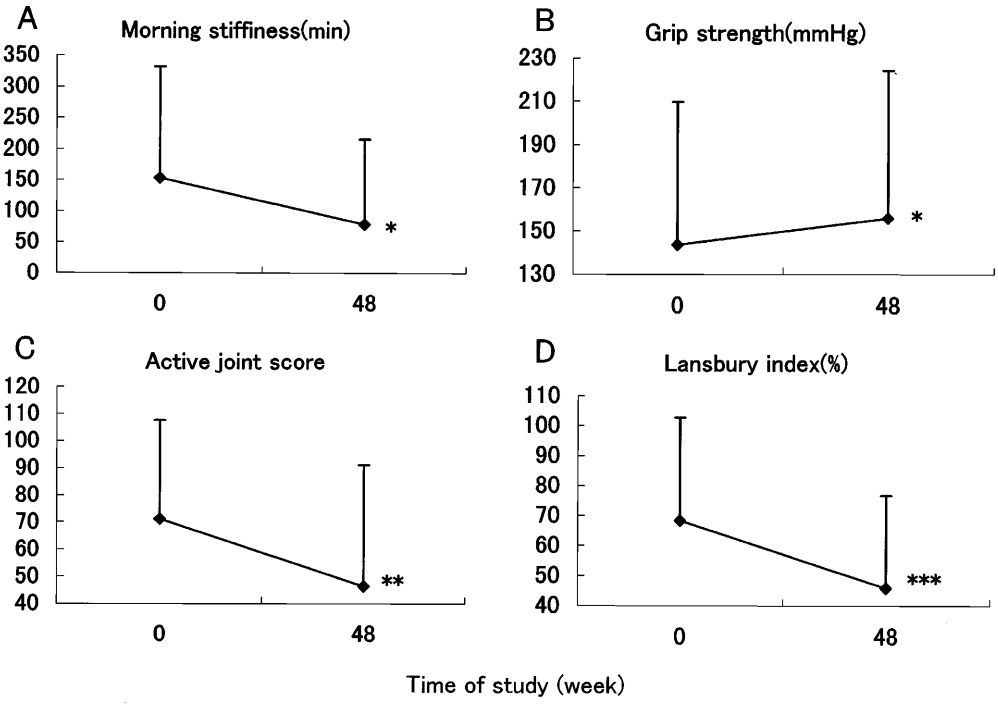

Fig. 4. Serial changes in arthritis during actarit treatment in (**A**) duration of morning stiffness, (**B**) grip strength, (**C**) active joint score, and (**D**) Lansbury index. *Bars* are mean ± SD. *, **, and ***, significant changes from baseline ($P < 0.05$, 0.01, and 0.001, respectively)

Table 4. Characteristics of patients with elderly or young-onset RA

	Elderly onset RA ($n = 12$)	Young-onset RA ($n = 8$)	P value
Sex (%female)	25%	25%	0.704
Age (years)	77.6 ± 4.4	71.3 ± 2.4	0.103
Stage (%I + II)	50%	0%	0.024
Disease duration (years)	3.3 ± 3.7	18.5 ± 11.3	0.000
Small joint type arthritis (%)	58.3%	12.5%	0.187
Swollen joint count	7.3 ± 3.9	3.9 ± 2.2	0.019
Tender joint count	5.6 ± 3.6	3.3 ± 2.3	0.048
Patient's articular pain score (scale 0–10)	52.6 ± 23.1	63.0 ± 25.9	0.359
Patient's global assessment (scale 0–10)	49.7 ± 23.1	62.6 ± 23.6	0.238
Physician's global assessment (scale 0–10)	55.6 ± 14.3	56.4 ± 8.8	0.891
MHAQ (range 0–24)	6.7 ± 5.2	7.4 ± 5.9	0.800
ESR (mm/h)	80.3 ± 35.0	93.0 ± 35.7	0.441
CRP (mg/dl)	2.79 ± 2.66	3.46 ± 2.35	0.574
Lansbury index (%)	69.0 ± 33.4	67.3 ± 37.9	0.915

Except where otherwise indicated, values are mean ± SD

The study included 20 subjects to whom administration was possible for 48 weeks; thus all the subjects were eligible for the statistical analysis of efficacy and safety. Concerning the overall evaluation, 70% of the subjects showed a 20% improvement (ACR20), while 35% showed a 50% improvement (ACR50). In the evaluation parameters, a significant improvement was shown in the number of swollen joints, the patient's evaluation of pain, the patient's evaluation of chronic arthritis activity, the doctor's evaluations of chronic arthritis activity, ESR, CRP, and LAI after 48 weeks. Although no adverse reactions or any aggravation of complications were observed in this study, abnormal laboratory values were detected as 10 events in 8 subjects. However, these changes were all mild, and no finding was considered to be abnormal.

In a double-blind placebo-controlled study of actarit,[10] it was reported that 36.8% of patients in the actarit group and 14.8% in the placebo group were evaluated as "Improved" or better in the final global improvement assessment in Week 16. Okano et al.[11] also conducted an evaluation of RA by the ACR core set of disease activity measures. They administered mizoribine for 24 weeks, and reported that 12 out of 42 patients (28.6%) satisfied the ACR20 criteria. In addition, a final global improvement was found in 10 patients in this study (23.8%). Shiokawa et al.[10] reported that the efficacy of actarit is hardly influenced by stratified factors such as the stage of the disease, or age. However, a long-term continuous study of actarit showed that the efficacy was higher in patients with a short illness duration or who were in the early stages.[12]

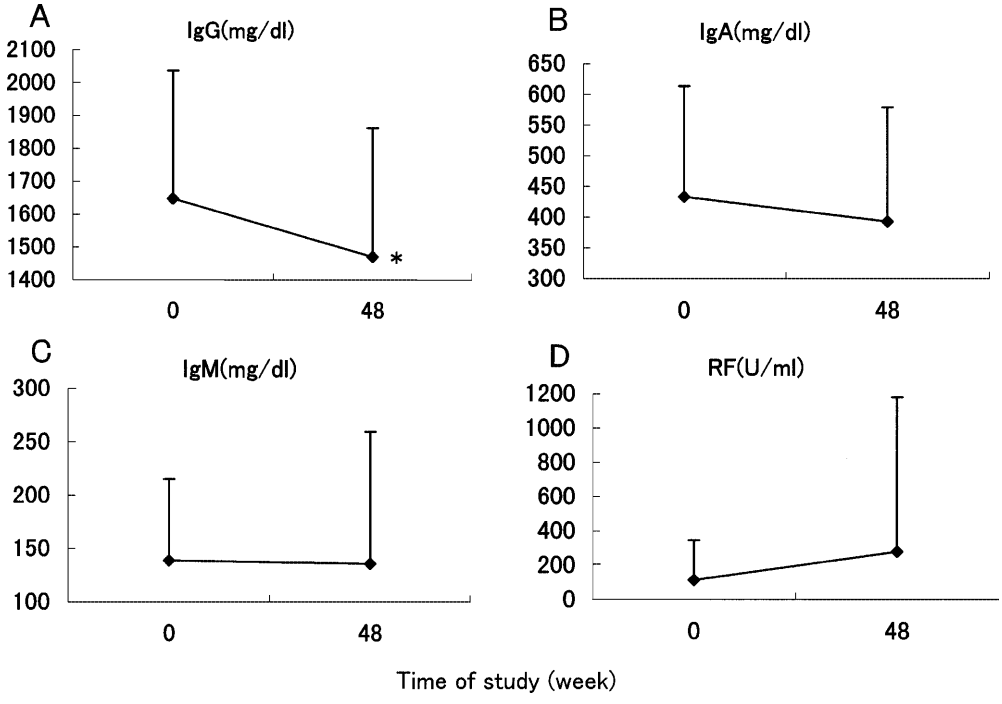

Fig. 5. Serial changes in arthritis during actarit treatment in (**A**) IgG, (**B**) IgA, (**C**) IgM, and (**D**) reumatoid factor (*RF*). *Bars* are mean ± SD. *, significant change from baseline ($P < 0.05$)

Table 5. Changes in active joints of elderly and young-onset RA

	Elderly onset RA ($n = 12$)			Young-onset RA ($n = 8$)		
	0	48 week	*P* value	0	48 week	*P* value
Tender joint count	5.6 ± 3.6	1.2 ± 1.3	0.001	3.3 ± 2.3	2.0 ± 2.4	0.335
			$P = 0.048$			
Large joint count	0.7 ± 1.9	0.3 ± 0.5	0.096	1.4 ± 0.9	1.0 ± 1.1	0.285
			$P = 0.171$			
Small joint count	4.9 ± 3.5	0.9 ± 1.1	0.002	1.9 ± 2.1	1.1 ± 1.8	0.442
			$P = 0.018$			
Swollen joint count	7.3 ± 3.9	2.2 ± 2.1	0.001	3.9 ± 2.2	2.8 ± 2.3	0.301
			$P = 0.019$			
Large joint count	0.8 ± 1.0	0.5 ± 0.8	0.191	1.5 ± 0.9	1.3 ± 1.0	0.351
			$P = 0.159$			
Small joint count	6.6 ± 3.8	1.7 ± 1.9	0.001	2.4 ± 2.3	1.5 ± 2.3	0.361
			$P = 0.008$			

Values are mean ± SD

Although the IL-10 production enhancement effect from CD8-positive cells,[13] VCAM-1 adhesion inhibition by the modifying effect of VLA-4,[14] and the inhibitory effect of the development of Flt-1, which is the VEGF-receptor,[15] have all been reported as being the pharmacologically effective points of actarit, its inhibitory effect on events observed during the early period of RA onset is believed to be the main one. In addition, there have been no reports of a direct inhibitory proliferation effect on the synovial membrane, or a direct anti-inflammatory effect[16] such as the adenosine production enhancement effect reported for MTX.

Thus, our result of 70.0% ACR20 in week 48 in this study of actarit in elderly patients, who were mainly at stage IV, is high compared with previous reports. One reason for this is considered to be that most patients had mildly to moderately active rheumatism when they were selected. Their mean LAI before the administration of actarit was 64.9% in the patients who satisfied ACR20, and 76.3% in the patients who did not, while it was 75.6% in the patients who satisfied ACR50. Thus, although no difference was significant, ACR improvement values were higher in patients with lower LAI values. Furthermore, the fact that there were many patients with RA of a facet is also considered to be a reason for our results.

Another reason is that all the patients completed the therapeutic course of actarit without any adverse reactions or laboratory value abnormalities because actarit is less likely to cause adverse reactions than other DMARDs. Other DMARDs have frequently caused adverse reactions in elderly patients, and such patients had to discontinue the treatment before they experienced any beneficial effect.

However, it has also been reported that there was no difference in the incidence of adverse events between elderly subjects aged 65 or older and nonelderly subjects in an investigation of the efficacy of MTX,[17] and that the efficacy was higher in elderly subjects. Further detailed investigation is required.

Elderly patients with RA are generally classified into two groups, one of patients with a young age of onset (young-onset RA), and the other of those with an elderly age of onset (at 60 years and older). Urano and Suzuki[4] examined the effects of elderly onset RA (at 60 years and older) in 9 patients, and reported that patients with relatively low rheumatic activity showed a greater tendency to improve. Mizutani[5] examined 9 patients with elderly onset RA (at 60 years and older) and reported that 44.4% of them showed an improvement. As for adverse reactions, skin symptoms occurred in 3 patients and all of them belonged to the elderly onset group, indicating the necessity of regular laboratory examinations in addition to lower doses being given to elderly patients.

By dividing our 20 patients into those with E-RA and those with Y-RA, it was shown that those with E-RA had significantly larger tender and swollen joints than those with Y-RA, that the two groups were significantly different in the stage of the disease, but that there was no difference between them in ESR and LAI. Since the joints of patients with E-RA were larger than those of patients with Y-RA when the disease was in the small joints only, it was suggested that there was some difference in the RA activity between the groups, although the relationship between the higher incidence of RA in the small joints and the duration of the disease could not be denied.

The improvement in tenderness and swelling after the administration of actarit was then examined by further dividing the patients by the size of the affected joints. The results showed that tenderness and swelling in the small joints were markedly improved in patients with E-RA, while the symptoms in the large joints were not significantly improved in either group. These results are consistent with those of Izumihara et al.[18] and Matsubara et al.,[19] in which actarit was reported to be more effective in the small joints than the large joints. Therefore, this drug is probably generally more effective for RA in small joints.

These results suggest that the improvement in active joints was greater in the elderly onset RA group than in the young-onset group, but the improvement based on ACR20 and ACR50 showed no significant difference between groups, as shown in Table 6. It is also known that the natural course of the disease differs slightly between elderly onset RA and young-onset RA.[20–22]

Generally, E-RA has the following clinical characteristics: higher sex ratio in favor of men, increased swollen joints and articular score, reduced grip and more serious disease class, and high values of inflammation markers such as ESR and CRP.

To clarify this contradiction, a further study with an increased number of subjects, examining the influence of the sick period in detail, will be required.

All 20 subjects in this study had some complications. Among the 31 complications, 10 were so-called life-style diseases such as hyperlipemia, diabetes mellitus, and hypertension. Since these diseases, as well as osteoporosis, might be closely associated with steroids, attention should be paid to the long-term steroid therapy given to patients with RA. Although no adverse reaction was observed in this study, abnormal laboratory values were found in 10 events in 8 subjects (see Table 3). Case 12 had an abnormal hematocrit level, probably because of the complications of a large

Table 6. Percentage of patients showing an improvement as evaluated by the American College of Rheumatology improvement criteria with stratified analysis

	n	ACR 20% criteria	*P* value	ACR 50% criteria	*P* value
Stage					
I + II	6	100.0%	0.077	66.7%	0.078
III + IV	14	57.1%		21.4%	
Onset age					
<65 years	8	62.5%	0.455	25.0%	0.392
≥65 years	12	75.0%		41.7%	
Duration period					
<5 years	9	77.8%	0.426	44.4%	0.370
≥5 years	11	63.6%		27.3%	

bowel cancer and lung metastasis. Case 17 showed an increase in BUN from 17.0 to 27.5, although it was not considered to be important because of a slight change in Cr from 0.8 to 1.0, and negative urinary protein. However, as elderly patients often show a sudden aggravation of symptoms, regular monitoring is necessary.

Since the above results suggest that actarit is useful for mildly to moderately active E-RA, especially in the small joints, it is considered reasonable to use it as a first-choice drug in suitable patients.

Although none of the subjects showed adverse reactions in this study, it is necessary to consider a reduction of the dose and to conduct regular laboratory examinations in elderly patients in order to deal with any possible adverse reactions.

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