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ORIGINAL ARTICLE

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Outcome of patients with rheumatoid arthritis treated by step-wise administration of disease-modifying antirheumatic drugs over a 10-year period

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Abstract Disease-modifying antirheumatic drugs (DMARDs) are expected to relieve polyarthritis, and thereby improve the patient's quality of life and eventually alter the prognosis of rheumatoid arthritis (RA) or the progressive joint destruction caused by it. DMARDs may cause adverse reactions and become less effective over time in some patients. Using changes in disease activity and X-ray findings as indicators, we retrospectively evaluated the long-term results of the step-wise administration of DMARDs in 200 patients with RA. The patients had been treated with gold compounds, SH compounds, and methotrexate, in this order, over a total of 10 years since initially being diagnosed with the disease in its relatively early stages. The step-wise administration of DMARDs had decreased and controlled RA activity and inflammatory response over the 10 years. Although X-ray findings for the wrists worsened over time in most of the patients, no knee or hip joint destruction was observed in patients in whom disease activity had been controlled well for a long period of time. The progression of destruction of major joints can be prevented in cases in which the Lansbury activity index and C-reactive protein are maintained at levels not more than 30% and 1.5 mg/dl, respectively. Since no drugs are now available which specifically prevent the progression of joint destruction, it is important to control RA activity for as long as possible.

Key words Disease activity · Disease-modifying antirheumatic drug (DMARDs) · Long-term outcome · Step-wise administration · X-ray finding

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Introduction

Rheumatoid arthritis (RA) is a chronic disease, inevitably requiring long-term treatment, in which disease-modifying antirheumatic drugs (DMARDs) play an important role. DMARDs can be expected to decrease RA activity, and thereby relieve polyarthritis and improve the quality of life (QOL), and eventually alter the prognosis of RA, or more specifically the prognosis of progressive joint destruction due to RA. They can induce complete remission of RA in patients who are remarkably responsive to them, but they can lead to problems, including a high incidence of adverse drug reactions (ADRs). There are many patients who are not responsive to DMARDs, and some who become less responsive to them.

We have therefore been using gold compounds, SH compounds, and immunosuppressive drugs, step-wise in this order, to achieve good therapeutic responses for as long as possible. In the present study, we retrospectively evaluated the long-term outcome of RA and the usefulness of DMARDs in treating RA, as well as the result of step-wise administration of DMARDs (step-wise DMARD therapy) as a standard strategy for DMARD treatment. Using changes in disease activity and X-ray findings as indicators, we assessed patients with RA who had been treated for over 10 years since the relatively earlier stages of the disease.

Subjects and methods

In principle, step-wise DMARD therapy is long-term treatment with low doses of DMARDs[1,2] (Fig. 1). The treatment of early or nontreated RA is initiated with a gold compound, a drug which has been used as a DMARD for more than 30 years[3] and whose efficacy and adverse reactions are well known. When the first choice of treatment proves ineffective, is discontinued because of ADRs, or becomes less effective, it is replaced by D-penicillamine (DP),which has

been used clinically for more than 20 years,[4] then bucillamine (BCL), and finally methotrexate (MTX). Sulfasalazine (SASP) is indicated for monotherapy in cases in which the use of SH compounds is discontinued because of ADRs. For patients who have started treatment since April 1988, auranofin (AF), a gold compound that has recently become available and has a lower risk of ADRs, has been the first choice for treatment. Gold sodium thiomalate (GST) has been used to replace AF for patients with gastrointestinal symptoms due to the use of AF, and has been added to AF for patients responding insufficiently to AF but presenting with no allergic reactions to this gold compound.[5] Since April 1995, BCL has been used in combinations with other DMARDs which have different mechanisms of action (BCL + SASP, BCL + MTX, and BCL + SASP + MTX), or replaced by a combination of such DMARDs (SASP + MTX) for some patients who respond insufficiently but present with no ADRs to the previous medication.[6]

We considered 317 patients diagnosed with RA in its relatively earlier stages and expected to progress to joint destruction (not more than 3 years' disease duration, radiological Larsen grade II or less in wrists and grade I or less in knees), and who were treated with step-wise administration of DMARDs from April 1980 to March 1990. Of these 317 patients, 37 had died of pneumonia or renal failure, 29 had become asymptomatic and discontinued treatment at the patient's request, and 51 had discontinued treatment due to a change of address or for other reasons. This retrospective study was conducted on the remaining 200 subjects who could be treated with DMARDs for 10 years or longer. The subject population comprised 31 male patients and 169 female patients, whose mean age at the start of treatment was 50.9 years (17–69 years); the mean follow-up period was 11 years and 6 months (10–20 years).

The subject population was surveyed for changes in the DMARDs used, and changes in the Lansbury activity index (LAI)[7] calculated from four RA activity parameters (duration of morning stiffness, tender joint score, hand grip, and erythrocyte sedimentation rate per hour), the inflammatory reaction marker C-reactive protein (CRP), and rheumatoid factor (RF). The subjects had undergone an X-ray examination once a year, and yearly changes in their radiological Larsen grade were also examined retrospectively not only for the wrists, but also the knee and hip joints. These are all changes which directly affect the activities of daily living (ADL) and lead to difficulty in walking with severe RA. The subjects were classified into three groups by their degree of disease activity determined from RA activity and CRP level, and the groups were compared for progression of disease observed radiologically. All statistical analyses were conducted using Student's *t*-test.

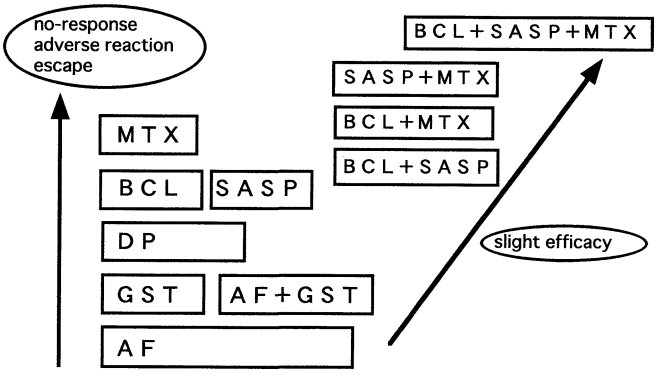

Fig. 1. Step-wise administration of DMARDs with additional combinations. *AF*, auranofin; *GST*, gold sodium thiomalate; *DP*, D-penicillamine; *BCL*, bucillamine; *SASP*, sulfasalazine; *MTX*, methotrexate

Results

Methods of DMARD administration and changes in use of DMARDs

The number of DMARDs used for treatment, their doses, and the main adverse reactions are shown in Table 1. The use of multiple drugs was required during the course of treatment over 10 years. All of these drugs were used in low doses. When there was no distinct decrease in LAI or CRP after 3–6 months from the start of treatment with a drug, that drug was judged to be ineffective (with the duration of efficacy of the drug being taken into consideration), and was replaced by another DMARD after obtaining informed

Table 1. Total number of drugs used in treatment, their mean doses, and main adverse reactions

	Total number of drugs used	Mean dose	Major adverse reactions (*n*)					
			Abdominal pain, nausea and/or diarrhea	Liver injury	Rash, itching	Stomatitis and/or taste abnormality	Proteinuria	Bone marrow suppression
AF	126	5.3 ± 0.8 mg/day	21	0	5	1	0	0
GST	81	9.3 ± 2.4 mg/week	0	0	12	1	1	0
DP	42	74 ± 23 mg/day	0	2	4	4	0	2
BCL	51	148 ± 41 mg/day	1	0	8	3	3	1
SASP	34	720 ± 230 mg/day	6	0	3	2	0	1
MTX	43	5.4 ± 2.1 mg/week	1	9	0	1	0	0

AF, auranofin; GST, gold sodium thiomalate; DP, D-penicillamine; BCL, bucillamine; SASP, sulfasalazine; MTX, methotrexate

consent from the patient. In cases of an adverse reaction, the use of the drug was stopped immediately, and the drug was changed to the next drug as a general rule, although in some cases treatment was restarted using the same drug at a reduced dose after resolution of the symptoms in patients who presented with mild adverse reactions such as diarrhea, itching, or liver injury. The most frequently observed adverse reactions were gastrointestinal symptoms for AF and SASP, mucocutaneous symptoms for GST, DP, and BCL, and liver injury for MTX. Serious adverse reactions were proteinuria in one patient receiving GST and three patients receiving BCL, and bone marrow suppression in two patients receiving DP and one patient receiving BCL, but the symptoms subsided with treatment. No renal dysfunction or drug-induced pulmonary disorder was observed in the patients studied.

A survey of the shift or addition of individual DMARDs showed that discontinuation owing to an insufficient effect accounted for 28%–31% of all changes, and discontinuation owing to an adverse reaction accounted for 15%–20%. One year after the start of administration, attenuated efficacy was observed in 42% and 31% of patients receiving DP and GST, respectively, and the addition of other DMARDs owing to insufficient efficacy was required for 28% and 27% of patients receiving AF and SASP, respectively.

The changes in the use of DMARDs are shown in Fig. 2. The additional drug, except for AF and GST, are shown by the name of the newly added DMARD. For all patients, treatment was initiated with AF or GST or a combination of the two. Five and 10 years after the start of treatment, gold compounds remained useful in controlling inflammation in 50% and 25% of patients, respectively, but had to be replaced by, or used in combination with, an SH compound, SASP, or MTX for the other patients. The administration of MTX was required in 15% and 23% of patients 5 and 10 years after the start of treatment, respectively, including four patients who required MTX administration within 1 year. In many patients who exhibited multiple drug resistance, additional combinations of DMARDs with different mechanisms of action were eventually used. Ten years after the start of treatment, SASP was used in combination with BCL in 19 of the 29 patients receiving SASP, and MTX was used in combination with BCL or SASP or both in 32 of the 45 patients receiving it.

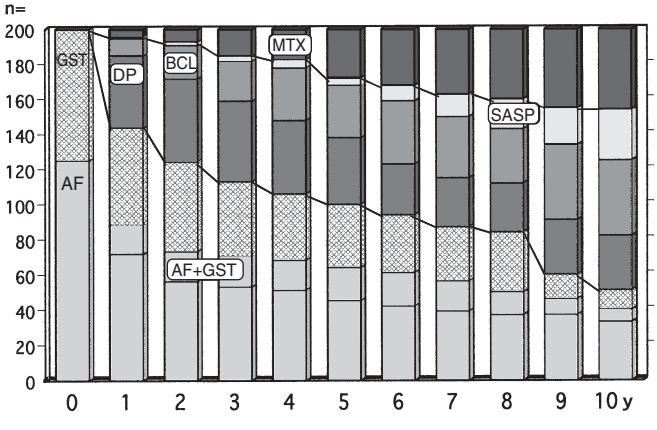

Fig. 2. Changes in the DMARDs used. Additional combinations are represented by the DMARD newly added

The reason for the replacement or addition of DMARDs was inefficacy in 28%–31% and ADRs in 15%–20% of cases. DP and GST became insufficiently effective in 42% and 31% of patients, respectively, after use for 1 year or longer. AF and SASP were used in combination with other DMARDs in 28% and 27% of patients, respectively, owing to insufficient efficacy.

Changes in disease activity

Although there were many patients in whom inflammation relapsed within 1 year and subsided with replacement DMARDs during the course of long-term treatment, clinical parameters obtained at the time when the inflammation was best controlled each year were used to observe changes in disease activity over the years. The duration of morning stiffness decreased significantly from a mean of 140 min (±80 min) at the start of treatment to a mean of 15 min (±15 min) the following year($P < 0.01$), and this decrease was maintained for 10 years. The tender joint score and erythrocyte sedimentation rate also decreased significantly ($P < 0.01$) from a mean of 49 points (±16 points) to a mean of 11 points (±10 points) and from a mean of 86 mm/h (±21 mm/h) to a mean of 38 mm/h (±13 mm/h), respectively, 1 year after the start of treatment, and these decreases were maintained for 10 years. Grip strength increased from a mean of 120 mmHg (±70 mm Hg) at the start of treatment to a mean of 260 mmHg (±40 mm Hg) the following year. Although grip strength decreased gradually in many patients with the progression of joint destruction, it was still significantly better ($P < 0.01$) after 10 years of treatment, with a mean of 240 mm Hg (±60 mm Hg).

Figure 3 shows changes in LAI calculated from the four RA activity parameters. LAI improved significantly from a mean of 63.1% at the start of treatment to a mean of 15.5% the following year, and the improvement remained significant 10 years after the start of treatment, with a mean of 16.0%. Although the number of patients followed for more than 10 years decreased, the improvement in LAI remained significant until 12 years after the start of treatment, and remained in most of the patients followed for 20 years. The inflammatory marker CRP decreased significantly from a mean of 4.8 mg/dl to a mean of 1.2 mg/dl in the year after the start of treatment, and decreases in CRP remained significant until 13 years after the start of treatment. Significant decreases were observed in RF for only a limited period of time because of large individual variations, but RF did decrease in many patients (Fig. 4).

The patients were classified into three groups according to the DMARDs used. One group consisted of 99 patients in whom inflammation was controlled for 5 years or longer with the use of one or two gold compounds. Only four patients (4%) in this group required concomitant treatment with prednisolone (PSL) continuously for 1 year or longer. Another group contained 55 patients who required treat-

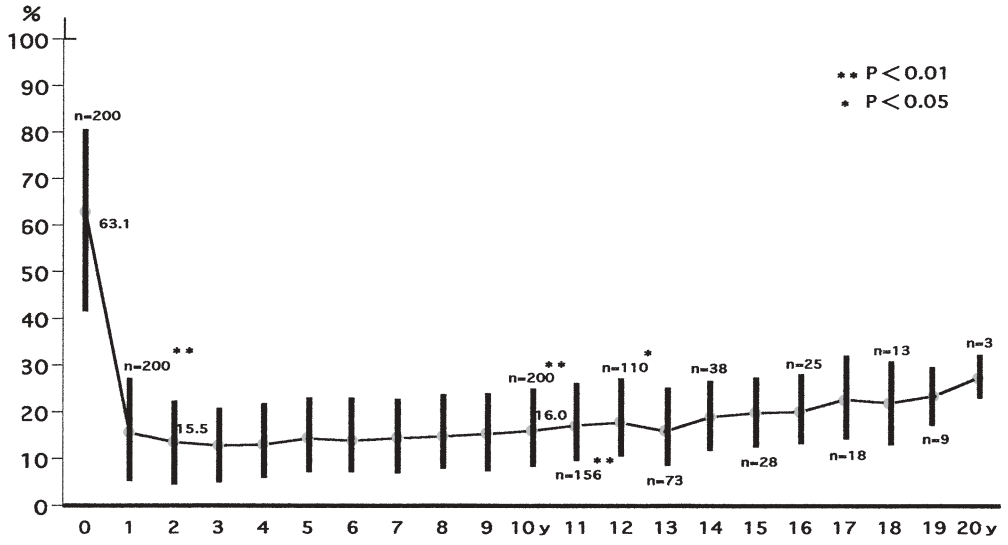

Fig. 3. Changes in disease activity indicated by the Lansbury activity index calculated from four RA activity parameters. Disease activity was significantly decreased in the year after the start of treatment, and remained significantly decreased until 12 years after the start of treatment

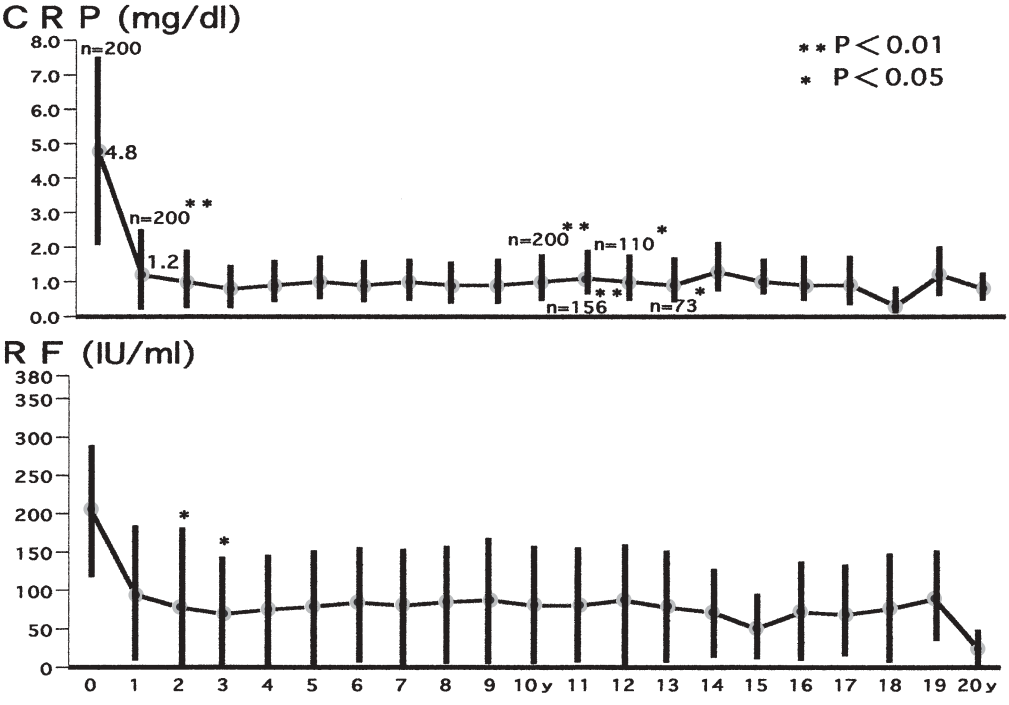

Fig. 4. Changes in C-reactive protein (*CRP*) and rheumatoid factor (*RF*). CRP remained significantly decreased until 13 years after the start of treatment. No significant decrease was observed in RF, but many patients had decreased levels of RF

ment with a SH compound to replace a gold compound, or required further treatment with SASP to replace the SH compound within 10 years after the start of treatment. Eleven patients (20%) in this group required concomitant use of PSL. The remaining group consisted of 44 patients who required treatment with MTX to replace, or in addition to, their preceding medication or medications. Nineteen patients (41.3%) in this group required concomitant use of PSL. A significant therapeutic improvement was observed in all three groups. A gold compound or a combination of gold compounds achieved a good therapeutic improvement in many patients with high levels of RA activity and inflammatory parameters at the start of treatment.

Changes in X-ray findings

Figure 5 shows changes in radiological Larsen grades in the wrist, knee, and hip joins. Most patients exhibited bilateral disease progression on X-rays, with Larsen grades which did not differ by more than one grade in 173 patients (86.5%) and in 136 patients (68%). When the Larsen grade differed between the right and left joints, the higher grade was used as the grade for determining joint destruction. Patients who had undergone artificial joint replacement were evaluated as grade V. Despite treatment with DMARDs, X-ray findings for the wrist deteriorated over time in most of the patients to a Larsen grade III or higher,

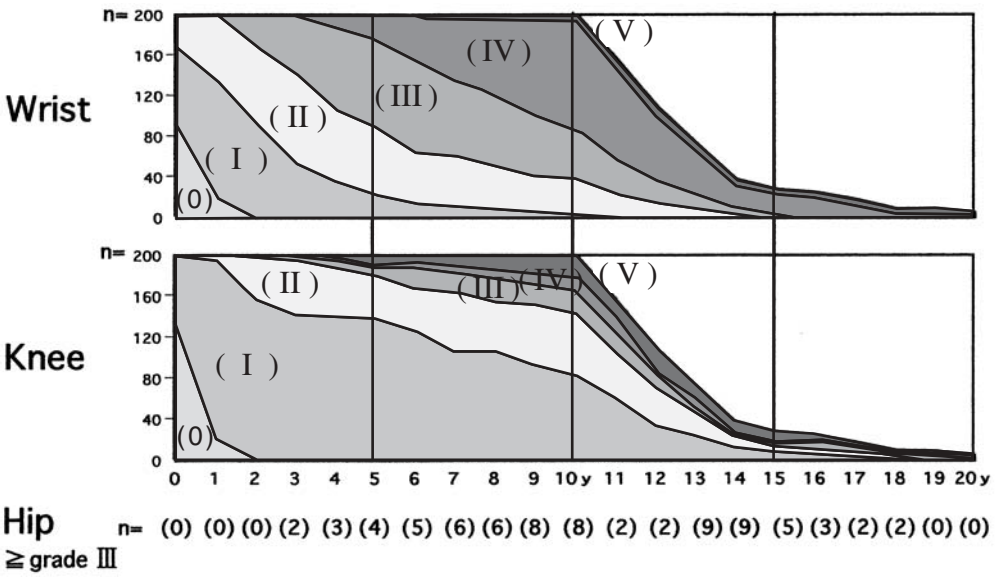

Fig. 5. Changes in X-ray findings for the wrist, knee, and hip joints. The Roman numerals in parentheses represent the Larsen grade for the wrist or knee, or the number of patients whose Larsen grade for the hip joint was III or higher. The incidence of joint destruction with Larsen grade III or higher was 80% for the wrist, 20% for the knee, and only 4% (8 cases) for the hip joint 10 years after the start of treatment

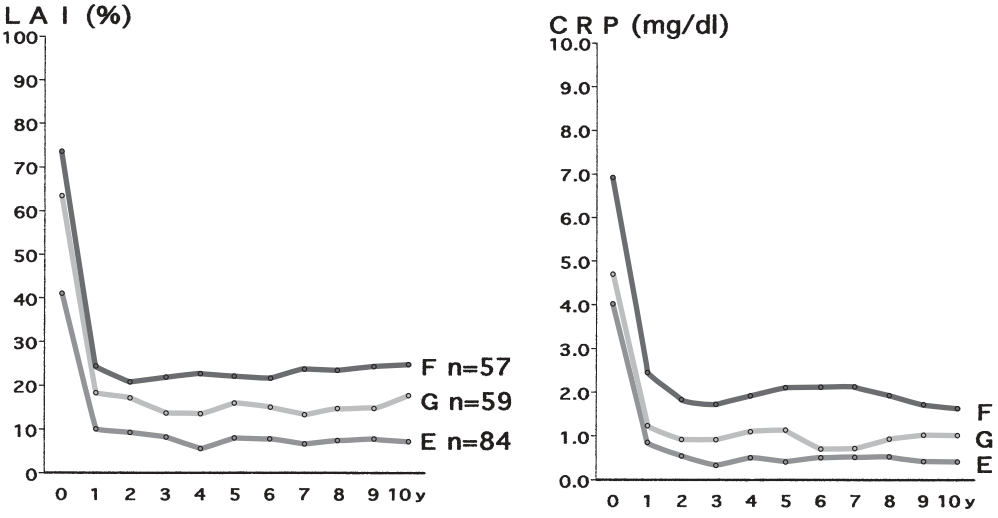

Fig. 6. Changes in mean Lansbury activity index (*LAI*) and mean CRP In group E ($n = 84$), group G ($n = 59$), and group F ($n = 57$), classified by disease activity control over 10 years. There were significant differences in baseline values among the groups (see Table 2), but no significant difference was observed in rate of improvement among the groups

indicating joint destruction in 50% and 80% of the patients 5 years and 10 years after the start of treatment, respectively. However, the progression of joint destruction was slower in larger joints, with the knee Larsen grade being III or higher in 8% and 20% of patients 5 years and 10 years after the start of treatment, respectively, and with hip joint destruction being observed in only eight patients (4%) 10 years after the start of treatment.

Comparison of disease activity and changes in X-ray findings

The patients were divided into three groups according to the control of disease activity over 10 years (Fig. 6). One of the three groups contained 84 patients, in whom excellent control of disease activity, or a condition close to complete remission, was achieved, with LAI and CRP values not more than 20% and 1.0 mg/dl, respectively, and with little or no arthritis or problems in ADL (group E). Another group contained 59 patients in whom good disease activity control was achieved, with LAI and CRP values not more than 30% and 1.5 mg/dl, respectively (group G), with few problems in ADL but with slight arthritis. The remaining group contained 57 patients whose disease activity was controlled to a fair extent, but with more active inflammation (group F). The background factors of patients in each group are shown in Table 2. There were no major differences in the distribution of gender, age, or duration of disease among the groups. Disease activity at the start of treatment was significantly higher in patients in groups G and F, who also had higher RF values. In group E, 64 patients (76%) did not require treatment with any DMARDs other than gold compounds for 5 years or longer, and only five patients (5.9%) required concomitant use of PSL. In group G, one-third of the pa-

Table 2. Patient background factors by group

	Group E (n = 84)	Group G (n = 59)	Group F (n = 57)
Females No. (%)	70 (83.3)	51 (86.4)	47 (82.5)
Age, mean ± SD years	51.5 ± 8.1	49.8 ± 8.1	51.0 ± 9.2
Disease duration, mean ± SD years	1.9 ± 1.1	1.6 ± 0.9	1.8 ± 1.3
LAI at baseline, mean ± SD %	41.3 ± 21.2	63.5 ± 17.1*	75.3 ± 16.9*
CRP at baseline, mean ± SD mg/dl	4.0 ± 2.2	4.7 ± 2.7	6.9 ± 3.2*
RF at baseline, mean ± SD IU/ml	162 ± 111	177 ± 115	306 ± 256*
Receiving concomitant prednisolone, No. (%)	5 (5.9)	7 (11.9)	22 (38.6)

There were no major differences in gender, age, or disease duration among the groups. At the start of treatment, LAI was significantly higher in groups G and F than in group E (*$P < 0.05$), and CRP and RF were significantly higher in group F than in groups E and G (*$P < 0.05$). The proportion of patients treated concomitantly with prednisolone was the smallest in group F, followed by groups G and E in increasing order

LAI, Lansbury activity index; CRP, C-reactive protein; RF, rheumatoid factor

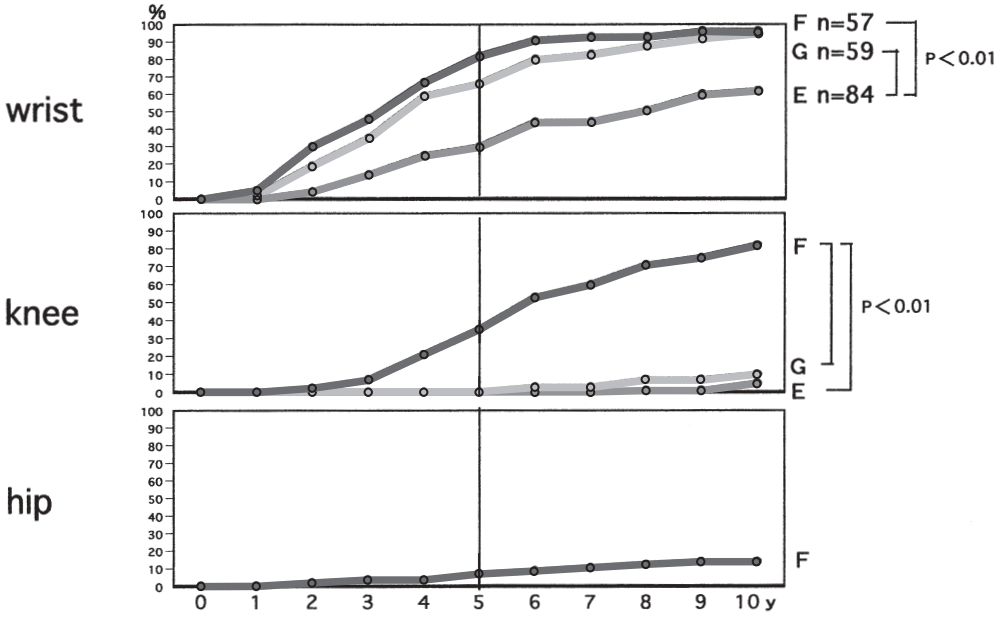

Fig. 7. Changes in the incidence of joint destruction with Larsen grade III or higher in the three groups (E, G, and F) classified by control of disease activity. The incidences of wrist joint destruction were 62%, 95%, and 95%, and those of knee joint destruction were 5%, 10%, and 82%, in groups E, G, and F, respectively, 10 years after the start of treatment. Hip joint destruction was observed in group F only

tients were treated with gold compounds only, and another one-third and the remaining one-third required treatment with an SH compound and MTX, respectively. In group F, 29 patients (50.9%) required treatment with MTX. Some patients in group G and the majority of patients in group F were unresponsive to multiple drugs and required treatment with MTX from an early stage of treatment in order to control inflammation, with many of them requiring concomitant treatment with PSL.

Figure 7 shows the incidence of joint destruction indicated radiologically with Larsen grade III or higher in each of the three groups classified by control of disease activity. The incidences of wrist joint destruction detected radiologically were 30%, 66%, and 82% in groups E, G, and F, respectively, 5 years after the start of treatment, and 62%, 95%, and 95%, respectively, 10 years after the start of treatment. The incidence of knee joint destruction detected radiologically remained zero 5 years after the start of treatment, and was still only 5% and 10% In groups E and G, respectively, after 10 years. In group F, however, it was 35% and 82% 5 years and 10 years after the start of treatment, respectively. Hip joint destruction was detected radiologically only In group F, with an incidence of 14% 10 years after the start of treatment.

Discussion

DMARDs play a major role in the treatment of RA and are considered indispensable in cases with a clear inflammatory response.[8] It is not unusual for the use of DMARDs to result in a disease-free condition in patients who are remarkably responsive to them. DMARD therapies have several problems, however. It is impossible to predict whether a patient will respond to a certain DMARD or not.

Not infrequently, DMARDs induce adverse drug reactions (ADRs), including serious hematopathy, renal disorder, and respiratory disturbance.[9] Moreover, patients who respond to certain DMARDs may become less responsive over time.[10] With these advantages and disadvantages, the aim of DMARD therapy is to relieve polyarthritis by inhibiting RA inflammation, thereby improving the quality of life (QOL) and eventually altering the resulting prognosis of RA or progressive joint destruction.[11,12]

Because of the problems with DMARD therapy, we have used DMARDs step-wise to continuously control RA inflammation as long as possible.[1,2] To evaluate the long-term outcome of RA and the usefulness of DMARDs in treating RA, as well as the usefulness of our step-wise DMARD therapy as a type of DMARD treatment, we conducted the present retrospective study in patients whom we had treated for 10 years or longer since relatively early-stage RA which, even after the start of treatment, was expected to progress to joint destruction. Because this was a retrospective study over 10 years, we used the Lansbury activity index (LAI),[7] which reflects pain and swelling in major joints, and C-reactive protein (CRP) as indicators of disease activity, although other indicators and criteria, such as the American College of Rheumatology's core set,[13] have recently been used for the same purpose. The results of this study showed that the step-wise administration of DMARDs was useful for controlling RA activity and inflammatory response over 10 years. The progression of RA is often evaluated by joint destruction in the wrists, hands, and feet[12] using the Sharp score,[14] or other methods. Since activities of daily living (ADL) are affected more seriously by the destruction of larger joints, we examined changes in X-ray findings in the knees and hip joints as well as in the wrists. Despite the control of disease activity with the use of DMARDs, X-ray findings for the wrists showed deterioration, and revealed joint destruction in most patients over time. As a result of the use of DMARDs, however, destruction of the knee and hip joints was observed in only a small proportion of patients. There are patients, as we have also experienced, who have a monocyclic type disease which goes into remission at an early stage of onset without progression to joint destruction.[15] With the exception of the monocyclic-type disease, joint destruction progresses in RA despite currently available treatment.[16] If the inflammation subsides before affecting major joints such as the hip joints and knees, it does not result in difficulties in walking. Patients who have wrist contracture or ankylosis with radiologically confirmed progression of RA in the wrists do not necessarily have serious digital deformity or dysfunctional elbows, and often have satisfactorily functional upper extremities. From the natural course of the disease, Ochi et al.[17] classify cases of RA into the least erosive subset (LES), i.e., cases with joint destruction limited to peripheral joints, the more erosive subset (MES), i.e., cases with joint destruction not only in peripheral joints, but also in major joints, and a subset resulting in mutilating disease (MUD). The results of the present study showed that treatment with DMARDs may not always have changed the natural course that individual cases followed, but it did successfully alter the natural course of a certain proportion of patients with MES, which could eventually result in the destruction of major joints, to a course similar to the natural one for LES. DMARD therapy should ideally control RA inflammation to a level close to complete remission, with LAI and CRP being not more than 20% and 1.0 mg/dl, respectively. However, it is believed that the progression of destruction of major joints can be prevented in cases in which LAI and CRP are maintained for a long period of time at levels not more than 30% and 1.5 mg/dl, respectively.

Reports have been published on the use of treatment regimens consisting of multiple DMARD therapy and steroid therapy from the early stages of RA, such as the step-down bridge method.[18] However, because the course of RA is not always the same, it is difficult to determine the prognosis of each case until treatment has continued for a year or longer. Patients initially presenting with a strong inflammatory response often respond very well to gold therapy. Patients who are strongly responsive to gold compounds can be classified as having benign synovitis using Wilske's classification.[19] With maximal use of gold compounds or SH compounds, their inflammation can be controlled and their ADL and QOL can be maintained satisfactorily for a long period of time. There are patients who develop multiple DMARD resistance, and continue to have high RA activity during the course of treatment. Including those of mutilans-type RA,[20] these cases can be classified as having aggressive synovitis and can be expected to have rapidly progressive joint destruction. In the treatment of such patients, a DMARD will have to be replaced by, or used in combination with, another DMARD or DMRADs, and possibly with an immunodepressant such as MTX, from the early stages of disease, as was the case with some of our patients.

Since there is at present no drug that specifically inhibits joint destruction, it is very important to select DMARDs appropriately for individual cases in order to control RA inflammation. The step-wise administration of DMARDs allows us to predict the prognosis of each case during the course of treatment. Because it is difficult to inhibit the progression of joint destruction in RA with the use of currently available DMARDs alone, the development of effective new biological products or genetic therapy is anticipated.

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