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ORIGINAL ARTICLE

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Efficacy and safety of iguratimod compared with placebo and salazosulfapyridine in active rheumatoid arthritis: a controlled, multicenter, double-blind, parallel-group study

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Abstract We conducted a 28-week, randomized, double-blind, parallel-group study of iguratimod in 376 Japanese patients with active rheumatoid arthritis to compare the efficacy and safety of the drug with those of placebo and salazosulfapyridine. In the American College of Rheumatology (ACR) 20 response rate, iguratimod was superior to placebo (53.8% versus 17.2%; Fisher's exact test, $P < 0.001$) and was not inferior to salazosulfapyridine (63.1% versus 57.7%, 95% confidence interval for the rate difference, –7.9% to 18.7%). Iguratimod began exhibiting its therapeutic effect within 8 weeks after the initiation of treatment and was effective even in patients who had a poor response to previous treatment with disease-modifying antirheumatic drugs. No statistically significant difference was noted in the incidence of adverse reactions between iguratimod and salazosulfapyridine. The study results suggest that iguratimod could become a new option for the treatment of rheumatoid arthritis.

Key words Controlled study · Iguratimod · Rheumatoid arthritis · Salazosulfapyridine

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Introduction

Disease-modifying antirheumatic drugs (DMARDs) can control the activity of rheumatoid arthritis but have several disadvantages such as inter-patient differences in drug response, slow action, the escape phenomenon, and frequent adverse reactions. Although the treatment of rheumatoid arthritis has made progress (e.g., the recent approval of anticytokine therapy), currently available antirheumatic drugs are not effective in all patients. More effective antirheumatic drugs have been awaited to increase options for the treatment of rheumatoid arthritis. Iguratimod (*N*-[7-[(Methanesulfonyl)amino]-4-oxo-6-phenoxy-4*H*-1-benzopyran-3-yl]formamide) is a novel immunomodulator. The drug suppresses inflammatory cytokine production in cultured human synovial cells and human THP-1 cells.[1–3] It also reduces immunoglobulin (Ig) production by acting directly on B lymphocytes in both mice and humans despite no notable action on B-lymphocyte proliferation.[4] Iguratimod has anti-inflammatory effects and improves abnormal immunological findings in animal models with arthritis or autoimmune disease.[5,6] Inflammatory cytokines are known to be involved in synovitis associated with rheumatoid arthritis. Recent studies suggest the efficacy of anti-CD20 antibody in rheumatoid arthritis.[7,8] Because iguratimod acts on both inflammatory cytokines and B lymphocytes, it is a hopeful novel DMARD. We compared the efficacy and safety of iguratimod with those of placebo and salazosulfapyridine, a strong DMARD, in Japanese patients with active rheumatoid arthritis.

Patients and methods

The study was conducted at 81 medical institutions in Japan between October 1999 and April 2002 in compliance with the Declaration of Helsinki (amended by the World Medical Association General Assembly in the Republic of South Africa in 1996). The study drugs were provided by the study sponsors (Toyama Chemical and Eisai, Tokyo, Japan). An independent efficacy and safety evaluation committee was organized to discuss study protocol amendments and premature termination of the study. The study protocol was reviewed and approved by the Institutional Review Board of each participating medical institution. Written informed consent was obtained from all patients before they participated in the study.

Patients

We screened 376 Japanese patients with active rheumatoid arthritis who were 20 years old or older, who met the American College of Rheumatology (ACR) revised criteria for the classification of rheumatoid arthritis,[9] who had suffered from active rheumatoid arthritis for 6 months or longer, and who had never received iguratimod or salazosulfapyridine therapy. Sex and the inpatient/outpatient status were not specified. The patients also fulfilled the following three criteria: (1) six or more tender joints; (2) three or more swollen joints; and (3) either a blood C-reactive protein concentration of at least 1.0 mg/dl, or a Westergren erythrocyte sedimentation rate of at least 30 mm/h. A 4-week washout period was established for DMARDs and immunosuppressive drugs before the initiation of study treatment. The concomitant use of corticosteroids was permitted during the study treatment only when corticosteroids were used at a prednisolone-equivalent dose of 5 mg/day or lower without changes in their dosing regimen at least 4 weeks before the initiation of study treatment.

Study design

The study was conducted in a multicenter, randomized, double-blind, parallel-group manner. The patients were randomly assigned to iguratimod, salazosulfapyridine, or placebo at a ratio of 2:2:1. The study drugs were iguratimod 25-mg tablets, salazosulfapyridine 500-mg tablets, and their placebo tablets. All these drugs were administered orally twice daily (morning and evening) for 28 weeks in a double-dummy manner. The daily dose of iguratimod was 25 mg for the first 4 weeks and 50 mg for the subsequent 24 weeks. The daily dose of salazosulfapyridine was 1000 mg throughout the treatment period.

Efficacy and safety evaluations

After the initiation of study treatment, the improvement in rheumatoid arthritis was evaluated every 4 weeks with the following modified ACR core set measures[10]: tender joint count in 48 joints, swollen joint count in 46 joints, patient's assessment of pain with the visual analogue scale, patient's global assessment of disease activity with the scale, physician's global assessment of disease activity with the scale, the modified Health Assessment Questionnaire score,[11] and either blood C-reactive protein concentration or erythrocyte sedimentation rate. Blood concentrations of rheumatoid factor, IgG, IgM, and IgA were measured at baseline and weeks 16 and 28. Efficacy evaluation used the ACR 20 response rate.[10] The primary variable was the ACR 20 response rate at the completion of study treatment (hereinafter referred to as the ACR 20 response rate unless otherwise specified). Other variables were used to evaluate drug efficacy and safety. For the patients whose plain posteroanterior radiographs of the hands at baseline and at the completion of at least 24-week study treatment were available, three blinded radiographic reviewers (a radiologist, a rheumatologist in orthopedics, and a rheumatologist in internal medicine) scored radiographic changes with the modified Sharp method by Fries and colleagues.[12,13] The mean radiographic scores were used to assess the progression of articular destruction. The safety variable was the incidence of adverse events, particularly adverse events of which relationship with the study drug could not be ruled out (i.e., adverse reactions).

Statistical analysis

A two-staged closed testing procedure was used to test the superiority of iguratimod to placebo and, after the superiority was shown, to test the noninferiority of iguratimod to salazosulfapyridine within a margin of 10%. The 10% margin was selected as a commonly used margin in noninferiority tests. For the superiority analysis population, the following patients were excluded from patients randomized: patients who stopped visiting the medical institution after the initial visit and had no available efficacy data; patients who received no study drug; patients who violated Good Clinical Practice; patients who did not meet all the inclusion criteria; and patients who met any of the exclusion criteria for efficacy considerations. For the noninferiority analysis population, the following patients were excluded from the superiority analysis population: patients whose duration of study treatment was less than 16 weeks (less than 8 weeks in the case of premature study discontinuation owing to aggravated symptoms/signs or lack of efficacy) and patients whose treatment compliance was less than 70% of the study drug. We used different populations for superiority analysis and noninferiority analysis because intention to treat population type for superiority analysis and per protocol population type for noninferiority analysis were usually employed to lead to more conservative results in the superiority and noninferiority analyses. Nonetheless, we performed the noninferiority analysis in the population which satisfied the eligibility criteria for the superiority analysis to examine the sensitivity and the robustness of the result.

In the superiority and noninferiority evaluations, baseline patient characteristics were compared between the three treatment groups at a significance level of 15% (two-sided) with a parametric or nonparametric method according to data types. When an intergroup difference in the characteristics was detected, the influence of the difference was assessed with statistical adjustment. In the superiority evaluation, Fisher's exact test at a significance level of 2.5% (one-sided) was performed to compare the ACR 20 response rates between the treatment groups; 95% confidence interval (CI) was calculated for differences in the rate. The noninferiority (within a margin of 10%) was evaluated at 95% CI for differences in the ACR 20 response rate at approximate normal distribution. Other variables were compared between the treatment groups at a significance level of 5% (two-sided) with one-sample Wilcoxon test, *U*-test, *t*-test, or Fisher's exact test.

In the safety evaluation, the following patients were excluded from the safety analysis population (patients randomized): patients who stopped visiting the medical institution after the initial visit and had no available safety data; patients who received no study drug; patients who violated Good Clinical Practice; and patients whose duration of study treatment was less than 8 weeks without any adverse reactions or abnormal laboratory data. The incidence of adverse events was calculated by dividing the number of patients with adverse events by the number of patients included in the safety analysis. The incidence of adverse reactions was calculated in the same manner. The incidence of premature study discontinuation was calculated by dividing the number of patients withdrawn from the study by the number of patients randomized. All three incidences were assessed at a significance level of 5% (two-sided) with Fisher's exact test.

Results

Baseline patient characteristics

A total of 376 patients were randomly assigned to the iguratimod group (n = 147), the salazosulfapyridine group (n = 156), or the placebo group (n = 73). The eligibility of all the patients was evaluated with the eligibility criteria (Table 1). The superiority analysis population consisted of 132 patients of the iguratimod group and 64 of the placebo group. The noninferiority analysis population consisted of 103 patients of the iguratimod group and 104 of the salazosulfa-

Table 1. Decision of evaluable/unevaluable patients

Eligibility criteria	Number of patients			Included/Excluded[a]			
	Iguratimod	SASP	Placebo	FAS	Superiority	Noninferiority	Safety
Informed consent							
Failure to obtain re-confirmation of study consent although an occasion was available	1	0	0	×	×	×	×
GCP noncompliance							
Noncompliance with GCP at medical institution	1	2	1	×	×	×	×
Inclusion criteria							
Not satisfied with required level of rheumatic activity	4	7	4	○	×	×	○
Exclusion criteria							
Experienced Iguratimod or SASP therapy	2	1	3	○	×	×	○
Treatment							
Surgical operation during study period	0	1	0	○	×	×	○
Start corticosteroid therapy or change doses	1	4	1	○	×	×	○
Corticosteroid intravenous or intramuscular dosing	1	0	0	○	×	×	○
Arthrocentesis/drainage or corticosteroid intra-articular injection	2	0	0	○	×	×	○
Insufficient drug compliance (less than 70% compliance)	0	5	0	○	○	×	○
No drug compliance (0% compliance)	1	0	0	×	×	×	×
Lack of data							
Lack of efficacy data (data available only before or after study initiation)	4	1	0	×	×	×	○
Lack of efficacy data (data available only before 2 weeks or more from study initiation)	1	0	1	○	×	×	○
Lack of safety data (data available only at study initiation)	4	1	0	○	○	○	×
Early discontinuation							
Discontinued before 8 weeks (occurrence of ADR/abnormal laboratory parameter)	14	27	7	○	○	×	○
Discontinued before 8 weeks (no ADR/abnormal laboratory parameter)	15	9	5	○	○	×	×
Discontinued before 16 weeks (8weeks if "worsened/insufficient effect")	7	9	3	○	○	×	○
Unblinded	1	0	0	×	×	×	○

In this table, ○ and × indicate how to handle each patient according to the criteria but do not necessarily reflect the final decision on the eligibility of each patient.
SASP, salazosulfapyridine; FAS, full analysis set; GCP, good clinical practice; ADR, adverse drug reaction
[a] ○: Included; ×: Excluded

Table 2. Demographic and other baseline characteristics of the study population

	Superiority analysis population		Noninferiority analysis population	
	Iguratimod (n = 132)	Placebo (n = 64)	Iguratimod (n = 103)	SASP (n = 104)
Female (%)	81.1	84.4	79.6	84.6
Age (years)[a]	57.5 ± 10.8	57.0 ± 10.8	57.1 ± 10.4	58.2 ± 11.2
<65 (years, %)	74.2	76.6	74.8	70.2
≥65	25.8	23.4	25.2	29.8
Weight (kg)[a]	53.2 ± 9.0	53.0 ± 9.0	53.2 ± 9.1	54.3 ± 10.0
<40 (kg, %)	4.5	4.7	2.9	4.8
≥40	94.7	93.8	96.1	94.2
Unknown	0.8	1.6	1.0	1.0
Stage I (%)	3.8	10.9	2.9	7.7
Stage II (%)	27.3	28.1	26.2	22.1
Stage III (%)	33.3	25.0	33.0	41.3
Stage IV (%)	35.6	35.9	37.9	28.8
Class 1 (%)	9.1	12.5	8.7	14.4
Class 2 (%)	73.5	65.6	73.8	65.4
Class 3 (%)	16.7	18.8	17.5	18.3
Class 4 (%)	0.8	3.1	0.0	1.9
Positive rheumatoid factor (%)	86.4	85.9	86.4	86.5
Duration of disease (months)[b]	110.5	84.5	96.0	84.5
<2 (years, %)	11.4	15.6	11.7	16.3
2–5	16.7	21.9	18.4	22.1
5–10	27.3	23.4	27.2	30.8
≥10	44.7	39.1	42.7	30.8
Previous DMARD therapy (%)	71.2	73.4	66.0	69.2
Concomitant corticosteroid therapy (%)	61.4	54.7	58.3	60.6

SASP, salazosulfapyridine; DMARD, disease-modifying antirheumatic drug
[a]Mean ± standard deviation
[b]Median

pyridine group. In both populations analyzed, no statistically significant difference in eligibility or ineligibility between the groups was noted (Fisher's exact test, $P = 0.650$ for the superiority analysis population and $P = 0.539$ for the noninferiority analysis population). Baseline patient characteristics of the iguratimod group in the superiority analysis population were similar to those in the noninferiority analysis population (Table 2). No statistically significant difference was found between the two populations in the characteristics shown in Table 2 ($P \leq 0.15$). In other characteristics, an unbalanced distribution was detected for body weight at the initiation of study treatment, the inpatient/outpatient status, and complications in the noninferiority analysis population. Each characteristic was analyzed by adjusting the ACR 20 response rate, and the lower limit of 95% CI for the rate difference was found to exceed –10% for all the characteristics. Accordingly, the results of the noninferiority analysis did not change. No unbalanced distribution was noted in the superiority analysis population. The characteristics of the safety analysis population did not differ from those of the efficacy analysis population.

Superiority and noninferiority evaluations

In the superiority analysis population, the ACR 20 response rate was significantly higher for the iguratimod group than for the placebo group (53.8% versus 17.2%; Fisher's exact test, $P < 0.001$; Table 3). This shows the superiority of iguratimod to placebo. In the noninferiority analysis population, the ACR 20 response rate was 63.1% for the iguratimod group and 57.7% for the salazosulfapyridine group; the 95% CI for the rate difference ranged from –7.9% to 18.7%. This indicates that the efficacy of iguratimod is not lower than that of salazosulfapyridine by more than 10%. To examine the sensitivity and the robustness of this result, we performed the noninferiority analysis in the population that satisfied the eligibility criteria for the superiority analysis. The ACR 20 response rate was 53.8% (71/132; 95% CI, 44.9% to 62.5%) for the iguratimod group and 48.2% (68/141; 95% CI, 39.7% to 56.8%) for the salazosulfapyridine group. The 95% CI for the rate difference was –6.3% to 17.4%. With these results, the noninferiority of iguratimod to salazosulfapyridine was considered to be robust. The ACR 50 response rate was 33.0% (34/103) for the iguratimod group (95% CI, 24.1% to 43.0%) and 33.7% (35/104) for the salazosulfapyridine group (95% CI, 24.7% to 43.6%).

Changes from baseline in outcomes

ACR core set data at the completion of study treatment were significantly better than those at baseline in both the iguratimod and salazosulfapyridine groups (Table 4).

Table 3. ACR 20 response rate for superiority and noninferiority analysis populations

Analysis population	*n*	Responder	Nonresponder	ACR 20 response rate (%)		*P* value[a]	Difference in the rate (%)	
					95% CI			95% CI
Superiority								
Iguratimod	132	71	61	53.8	44.9–62.5	<0.001	36.6	24.0–49.2
Placebo	64	11	53	17.2	8.9–28.7			
Noninferiority								
Iguratimod	103	65	38	63.1	53.0–72.4	0.257	5.4	–7.9–18.7
SASP	104	60	44	57.7	47.6–67.3			

Superiority, superiority analysis population; Noninferiority, noninferiority analysis population; SASP, salazosulfapyridine; CI, confidence interval
[a] Fisher's exact test (one-sided)

Table 4. Changes from baseline in outcome parameter data at the completion of study treatment (last-observation-carry-forward method)

		Iguratimod		Placebo	
		Baseline	Change	Baseline	Change
a. Superiority analysis population					
Tender joint count	*n*	132	131	64	63
	Mean ± SD	13.4 ± 8.0	–7.1 ± 7.9*	13.6 ± 7.8	–3.6 ± 8.3*
Swollen joint count	*n*	132	131	64	63
	Mean ± SD	10.5 ± 6.9	–5.0 ± 6.2*	10.2 ± 5.5	–3.1 ± 5.7*
Patient's assessment of pain (VAS, mm)	*n*	130	129	64	63
	Mean ± SD	58.5 ± 23.3	–17.9 ± 30.0*	60.7 ± 22.5	–1.7 ± 27.4
Patient's global assessment of disease activity (VAS, mm)	*n*	131	130	64	63
	Mean ± SD	59.6 ± 23.8	–17.1 ± 31.4*	65.5 ± 20.5	–5.7 ± 28.6
Physician's global assessment of disease activity (VAS, mm)	*n*	132	131	64	63
	Mean ± SD	56.6 ± 18.0	–18.9 ± 21.4*	59.1 ± 18.5	–6.9 ± 20.5*
MHAQ score	*n*	131	130	64	63
	Mean ± SD	0.9 ± 0.5	–0.2 ± 0.4*	1.0 ± 0.5	0.1 ± 0.5
ESR (mm/hour)	*n*	128	123	60	59
	Mean ± SD	62.2 ± 25.7	–13.1 ± 23.6*	64.1 ± 28.1	6.2 ± 21.6*
CRP (mg/dl)	*n*	131	127	64	62
	Mean ± SD	3.5 ± 3.1	–0.7 ± 3.8*	3.9 ± 3.0	0.3 ± 2.2
b. Noninferiority analysis population					
Tender joint count	*n*	103	103	104	104
	Mean ± SD	13.0 ± 7.3	–7.8 ± 7.5*	12.7 ± 7.0	–7.1 ± 6.9*
Swollen joint count	*n*	103	103	104	104
	Mean ± SD	10.6 ± 7.0	–5.5 ± 6.0*	9.3 ± 5.1	–4.5 ± 4.6*
Patient's assessment of pain (VAS, mm)	*n*	102	102	104	102
	Mean ± SD	57.0 ± 23.7	–22.0 ± 27.7*	56.0 ± 23.5	–21.0 ± 28.3*
Patient's global assessment of disease activity (VAS, mm)	*n*	103	103	104	102
	Mean ± SD	58.1 ± 24.0	–21.3 ± 30.2*	58.9 ± 22.4	–21.8 ± 26.7*
Physician's global assessment of disease activity (VAS, mm)	*n*	103	103	104	104
	Mean ± SD	55.0 ± 17.8	–23.4 ± 20.9*	58.4 ± 16.3	–29.0 ± 20.8*
MHAQ score	*n*	103	103	104	104
	Mean ± SD	0.8 ± 0.5	–0.3 ± 0.4*	0.9 ± 0.6	–0.3 ± 0.5*
ESR (mm/hour)	*n*	100	97	103	100
	Mean ± SD	64.0 ± 25.8	–16.2 ± 23.4*	61.2 ± 28.4	–17.1 ± 24.4*
CRP (mg/dl)	*n*	103	103	103	103
	Mean ± SD	3.6 ± 3.0	–1.2 ± 3.2*	3.2 ± 2.4	–0.9 ± 2.1*

VAS, visual analogue scale; MHAQ, modified Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SASP, salazosulfapyridine
*$P \leq 0.05$ (intra-group paired *t* test or one-sample Wilcoxon test)

Immunological tests

Figure 1a illustrates the time courses of mean blood concentrations of rheumatoid factor, IgG, IgM, and IgA in the superiority analysis population. All these concentrations were increased in the placebo group but were reduced in the iguratimod group with a statistically significant difference between the groups (repeated measures analysis of variance, $P \leq 0.001$). In the noninferiority analysis population, changes from baseline in these concentrations in the iguratimod group were compared with those in the salazosulfapyridine group. The mean change from baseline in

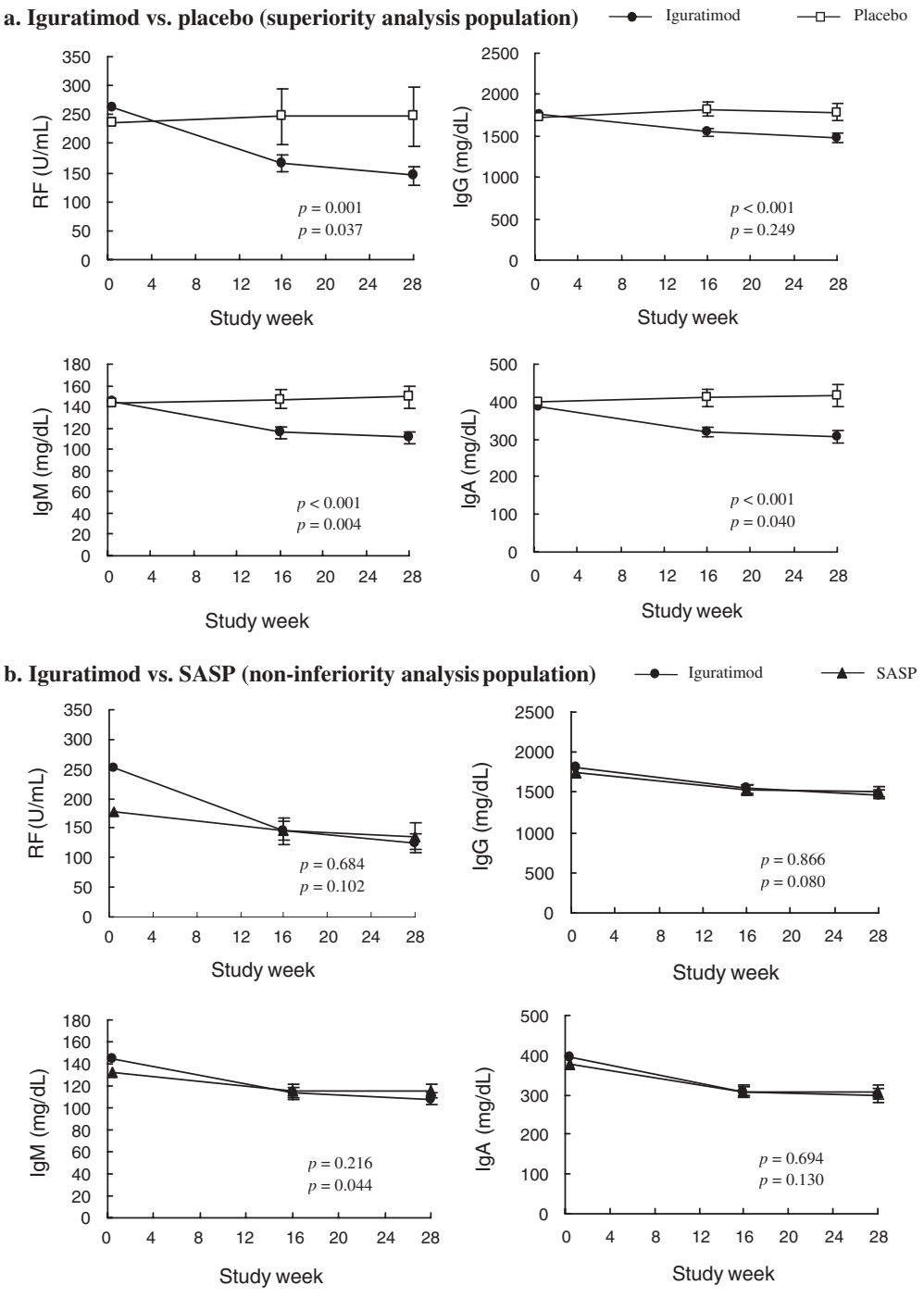

Fig. 1a,b. Time courses of immunological test values in superiority and noninferiority analysis populations. **a** Iguratimod vs. placebo (superiority analysis population). **b** Iguratimod vs. SASP (noninferiority analysis population). Adjusted means ±95% confidence intervals of immunological test data are shown. In all the panels, upper *P* values are for the main effect of individual drugs in a repeated-measures analysis of variance, and lower *P* values are for the interaction between the treatment groups and measurement points in the analysis. SASP, salazosulfapyridine; RF, rheumatoid factor; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A

blood IgM concentrations in the iguratimod group was significantly greater than that in the salazosulfapyridine group (*U*-test, $P = 0.020$). No statistically significant difference was noted in three other concentrations between the groups (*U*-test, $P = 0.206$ to 0.438). These results agree with the time courses of these concentrations (Fig. 1b).

Onset of therapeutic effects

The ACR 20 response rate was 41.7% for the iguratimod group at week 8 and 68.6% for the iguratimod group at week 28 (Table 5).

Subgroup analysis

For patients who received at least one DMARD within 6 months before the initiation of study treatment but had a poor response to the drug(s), the ACR 20 response rate was 61.3% (38/62) for the iguratimod group (95% CI, 48.1% to 73.4%) and 53.1% (34/64) for the salazosulfapyridine group (95% CI, 40.2% to 65.7%). No statistically significant difference was noted in the rate between the groups (Fisher's exact test, $P = 0.228$). For patients who received methotrexate within 6 months before the initiation of study treatment but had a poor response to the drug, the ACR 20 response rate was 56.3% (9/16) for the iguratimod group (95% CI,

Table 5. Time course of ACR 20 response rate in noninferiority analysis population

	Study week						
	4	8	12	16	20	24	28
Iguratimod							
Responder/*n*	14/103	43/103	52/98	56/98	59/97	52/89	59/86
Response rate (%)	13.6	41.7	53.1	57.1	60.8	58.4	68.6
SASP							
Responder/*n*	17/104	31/104	48/98	52/98	56/93	54/87	57/87
Response rate (%)	16.3	29.8	49.0	53.1	60.2	62.1	65.5

SASP, salazosulfapyridine

29.9% to 80.2%) and 42.1% (8/19) for the salazosulfapyridine group (95% CI, 20.3% to 66.5%). No statistically significant difference was noted between the groups (Fisher's exact test, $P = 0.311$).

Premature study discontinuation

The incidence of premature study discontinuation was 37.4% (55/147) for the iguratimod group, 41.0% (64/156) for the salazosulfapyridine group, and 45.2% (33/73) for the placebo group. No statistically significant difference was noted in the incidence between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.557$) as well as between the iguratimod group and the placebo group (Fisher's exact test, $P = 0.307$).

Among the patients who were withdrawn from the study, the incidence of premature study discontinuation owing to adverse reactions was 32.7% (18/55) for the iguratimod group, 42.2% (27/64) for the salazosulfapyridine group, and 9.1% (3/33) for the placebo. No statistically significant difference was found in the incidence between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.345$). The incidence was significantly higher for the iguratimod group than for the placebo group (Fisher's exact test, $P = 0.019$). The incidence of premature study discontinuation owing to lack of efficacy was 27.3% (15/55) for the iguratimod group, 23.4% (15/64) for the salazosulfapyridine group, and 57.6% (19/33) for the placebo group. No statistically significant difference was found in the incidence between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.676$). The incidence was significantly lower for the iguratimod group than that for the placebo group (Fisher's exact test, $P = 0.007$).

Progression of articular destruction

The mean total Sharp score, which is the sum of erosion score and joint space narrowing score, at baseline was 31.9 for the iguratimod group ($n = 79$), 29.0 for the salazosulfapyridine group ($n = 76$), and 33.5 for the placebo group ($n = 33$). The mean increase from baseline in the total Sharp score at the completion of study treatment was 1.2 for the iguratimod group, 0.5 for the salazosulfapyridine group, and 2.7 for the placebo group. No statistically significant difference was noted in the increase between the iguratimod group and the salazosulfapyridine group (U-test, $P = 0.122$) as well as between the iguratimod group and the placebo group (U-test, $P = 0.584$).

Safety evaluation

None of the patients died during the study. In the iguratimod group, serious adverse events occurred in nine patients. In seven of the nine patients, the events were regarded as adverse reactions: abnormal changes in laboratory data, such as increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), in three patients (one with abnormal hematological data and one with jaundice); gastric ulcer in one; melena in one; interstitial pneumonia in one; and fever in one. In the salazosulfapyridine group, serious adverse events occurred in nine patients. In three of the nine patients, the events were regarded as adverse reactions: fever, vomiting, rash, leucopenia, and increased AST and ALT in one patient; fever and rash in one; and leucopenia and neutropenia in one. No unknown serious adverse events that could not be anticipated during the study and of which a relationship with the study drug could not be ruled out were reported from any treatment group.

The incidence of adverse events was 94.6% (123/130) for the iguratimod group, 91.0% (132/145) for the salazosulfapyridine group, and 85.1% (57/67) for the placebo group. A statistically significant difference was noted between the iguratimod group and the placebo group (Fisher's exact test, $P = 0.032$), but not between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.353$). The incidence of adverse reactions was 50.0% (65/130) for the iguratimod group, 48.3% (70/145) for the salazosulfapyridine group, and 31.3% (21/67) for the placebo group. A statistically significant difference was noted between the iguratimod group and the placebo group (Fisher's exact test, $P = 0.015$), but not between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.810$).

The incidence of increased AST or ALT was 21.5% (28/130) for the iguratimod group, 12.4% (18/145) for the salazosulfapyridine group, and 3.0% (2/67) for the placebo group. The incidence of increased AST or ALT regarded as an adverse reaction was 17.7% (23/130) for the iguratimod group, 9.7% (14/145) for the salazosulfapyridine group, and 3.0% (2/67) for the placebo group. The incidence of blood AST or ALT concentration of 100 IU or higher was

10.0% (13/130) for the iguratimod group, 2.8% (4/145) for the salazosulfapyridine group, and 0.0% (0/67) for the placebo group. The incidence of the elevated concentration regarded as an adverse reaction was 7.7% (10/130) for the iguratimod group and 2.1% (3/145) for the salazosulfapyridine group. The increased AST or ALT was resolved in all of the patients except one who could not be followed up because of no visit to the medical institution. In the iguratimod group, 14 patients who continued the study treatment regardless of increased AST or ALT recovered with no remedy. In 21 of 25 patients who continued the study treatment regardless of increased AST or ALT, the subsequent laboratory test revealed that a blood AST or ALT concentration returned to the reference range.

The incidence of gastrointestinal disorder was 37.7% (49/130) for the iguratimod group, 25.5% (37/145) for the salazosulfapyridine group, and 17.9% (12/67) for the placebo group. The incidence of the disorder regarded as an adverse reaction was 19.2% (25/130) for the iguratimod group, 9.0% (13/145) for the salazosulfapyridine group, and 9.0% (6/67) for the placebo group. In the iguratimod group, the most common gastrointestinal adverse reaction was upper abdominal pain (6.9%, 9/130), followed by stomatitis (4.6%, 6/130). As a serious adverse reaction, peptic ulcer was reported in two patients. The incidence of abnormal changes in hematological data was 33.8% (44/130) for the iguratimod group, 35.2% (51/145) for the salazosulfapyridine group, and 26.9% (18/67) for the placebo group. The incidence of the changes regarded as an adverse reaction was 12.3% (16/130) for the iguratimod group, 11.0% (16/145) for the salazosulfapyridine group, and 1.5% (1/67) for the placebo group. In the iguratimod group, all the abnormal changes in laboratory data were resolved, except the changes that began before the initiation of study treatment or were associated with rheumatoid arthritis. The incidence of dermatological disorder was 13.8% (18/130) for the iguratimod group, 30.3% (44/145) for the salazosulfapyridine group, and 9.0% (6/67) for the placebo group. The incidence of the disorder regarded as an adverse reaction was 3.8% (5/130) for the iguratimod group, 17.2% (25/145) for the salazosulfapyridine group, and 4.5% (3/67) for the placebo group.

Discussion

Our clinical study of iguratimod used salazosulfapyridine, which is a widely used DMARD with well-established effectiveness, as an active control because methotrexate was not approved for the treatment of rheumatoid arthritis in Japan at the planning of the study. In baseline patient characteristics, the percentages of patients for each stage, class, and duration category of rheumatoid arthritis in our study were similar to those in two previous Japanese clinical studies of salazosulfapyridine.[14,15] This suggests no major differences in study populations between our study of iguratimod and the studies of salazosulfapyridine. We used placebo as an index of internal validity. Because some researchers reported that the ACR 20 response rate for the placebo group was 11.3% (9/80) and 28.6% (26/91),[16,17] our placebo group (ACR 20 response rate, 17.2%) seems to have served as an appropriate index of internal validity.

The superiority of iguratimod to placebo in efficacy was demonstrated in not only the superiority analysis population but also the full analysis set (139 patients of the iguratimod group and 72 patients of the placebo group) that included patients who were excluded from the superiority analysis population because of either violation of inclusion criteria or fulfillment of any exclusion criteria for efficacy considerations.

Our study demonstrated that the efficacy of iguratimod was not lower than salazosulfapyridine by more than 10%. ACR 20 core set data improved in both the iguratimod group and the salazosulfapyridine group, and the mean change from baseline in modified Health Assessment Questionnaire scores for the iguratimod group was similar to that for the salazosulfapyridine group. These results suggest that iguratimod is expected to improve the quality of life in patients with rheumatoid arthritis. For immunological tests (measurement of blood concentrations of rheumatoid factor, IgG, IgM, and IgA), the improvement in immunological data in the iguratimod group was significantly greater than that in the placebo group. Our study definitely demonstrated that iguratimod improved immunological data including blood IgM concentrations. This improvement seems to result from the immunomodulating effect of iguratimod on B lymphocytes.

Changes from baseline in the ACR 20 response rate determined every 4 weeks and the rate of 17.2% for the placebo group suggest that iguratimod began exhibiting its therapeutic effect within 8 weeks after the initiation of treatment. Because the rate was 61.3% for patients who had a poor response to previous DMARD therapy in the iguratimod group, iguratimod could be effective in such patients.

The assessment of progression of articular destruction revealed no statistically significant difference in efficacy between the iguratimod group and the salazosulfapyridine group or between the iguratimod group and the placebo group. This result can be explained by three characteristics of the study. First, the number of evaluable patients was insufficient for the assessment because the primary objective of the study was not to assess the progression of articular destruction. Second, the study period (6 months) was short for the assessment. Finally, most of the patients in the study had advanced rheumatoid arthritis with articular destruction. Some researchers have reported that the progression of articular destruction is best assessed in patients with early rheumatoid arthritis in which bone erosion is not involved.[18,19] In future studies, patients with early rheumatoid arthritis should be selected as the patient population to assess inhibitory effects of iguratimod on articular destruction.

No statistically significant difference was noted in the incidence of adverse events or reactions between the iguratimod group and the salazosulfapyridine group. Adverse event profiles, however, differed between the two groups.

A characteristic adverse event in the iguratimod group was increased hepatic enzyme. Although this event included transient increase, attention should be paid to hepatic function data during iguratimod therapy based on the frequency of increased hepatic enzymes in our study. Another characteristic adverse event in iguratimod group was dermatological disorder, of which frequency was relatively low. Attention should also be paid to abdominal pain, anemia, and other symptoms and signs related to gastrointestinal disorder during iguratimod therapy because peptic ulcer was reported in the iguratimod group. Hematological disorder does not seem to be an iguratimod-specific adverse event because the disorder reported in the iguratimod group did not differ from that in the salazosulfapyridine group.

In conclusion, the efficacy of iguratimod is not inferior to that of salazosulfapyridine. Iguratimod could be effective even in patients who have a poor response to currently available DMARDs. Adverse reaction profiles of iguratimod are different from those of salazosulfapyridine. If used carefully, iguratimod could become a novel DMARD that is useful to improve physical condition and the quality of life in patients with rheumatoid arthritis.

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