Mod Rheumatol (2007) 17:10–16
DOI 10.1007/s10165-006-0543-x

ORIGINAL ARTICLE

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Long-term safety study of iguratimod in patients with rheumatoid arthritis

Received: June 9, 2006 / Accepted: November 28, 2006

Abstract We conducted a 52-week clinical study of iguratimod in 394 Japanese patients with rheumatoid arthritis to evaluate the long-term safety of the drug. Iguratimod was administered orally at a daily dose of 25 mg for the first 4 weeks and 50 mg for the subsequent 48 weeks. Some of the patients continued the treatment for 100 weeks for their benefit. The cumulative incidence of adverse events for 100 weeks was 97.6%. The cumulative incidence of adverse reactions was 65.3%; unfavorable symptoms and signs (excluding abnormal laboratory data changes) accounted for 33.2% of the reactions, and abnormal laboratory data changes accounted for 50.4%. The continued treatment rate was 66.8% at week 28 and 53.6% at week 52. For reference, the American College of Rheumatology (ACR) 20 response rate was calculated for the patients who had assessable disease activity, who did not violate the study protocol, and who continued the study treatment at weeks 28 and 52. The rate was 46.9% at week 28 and 41.0% at week 52. To use iguratimod safely for a long time, patients should be observed closely for adverse reactions such as increased hepatic enzymes.

Key words Disease-modifying antirheumatic drug (DMARD) · Iguratimod · Long-term study · Rheumatoid arthritis

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Introduction

Disease-modifying antirheumatic drugs (DMARDs) have played a central role in the treatment of rheumatoid arthritis to control the disease activity but have several disadvantages (e.g., inter-patient differences in drug response, slow action, the escape phenomenon, and frequent adverse reactions). Thus, antirheumatic drugs with a novel mechanism of action have been awaited.

A novel antirheumatic drug, iguratimod, has been shown to have an anti-inflammatory effect and to improve abnormal immunological findings in animal models of arthritis or autoimmune disease.[1,2] Iguratimod suppresses not only immunoglobulin production through its direct action on B lymphocytes[3] but also inflammatory cytokine production through its inhibitory action on nuclear factor-kappa B activation.[4,5] Iguratimod appears to cause fewer adverse reactions than immunosuppressive agents because it has a milder inhibitory action on lymphocyte proliferation. Because recent reports on the high efficacy of anti-CD20 antibody in rheumatoid arthritis[6,7] suggest the pathogenetic role of B lymphocytes in the disease, iguratimod that acts on B lymphocytes could become a new option for the treatment of rheumatoid arthritis. We conducted a multicenter, open-label, noncontrolled study of iguratimod in patients with rheumatoid arthritis to evaluate the long-term safety of the drug that will be used as a long-term treatment once launched.

Patients and methods

The study was conducted at 90 medical institutions in Japan between September 28, 1998 and July 18, 2002, in compliance with the Declaration of Helsinki (amended by the Word Medical Association General Assembly in the Republic of South Africa in 1996). The study drug was 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 and its amendments were reviewed and approved by the Institutional Review Board of each participating medical institution. Written informed consent was obtained from all the patients before they participated in the study. The planned duration of study treatment was 52 weeks but could be prolonged to 100 weeks at the investigator's discretion for a patient's benefit. For reference, the ACR 20 response rate[8–10] was calculated for the patients with active rheumatoid arthritis (who met the requirements specified in the study protocol, and who had assessable disease activity at the initiation of study treatment). Assessable disease activity was defined as at least six tender joints, at least three swollen joints, and either an erythrocyte sedimentation rate of at least 30 mm/h or a blood C-reactive protein concentration of at least 1.0 mg/dl at baseline.

Patients

The study patients were 394 Japanese patients with rheumatoid arthritis who were 20 years of age or older, who met the American College of Rheumatology (ACR) revised criteria for the classification of rheumatoid arthritis,[11] who suffered from active rheumatoid arthritis for 6 months or longer, and who provided written informed consent. Sex and the inpatient/outpatient status were not specified. Patients on corticosteroid therapy at a prednisolone-equivalent dose of more than 5 mg/day were excluded from the study. The patients enrolled were previous DMARD users or DMARD naïve patients. The concomitant use of other DMARDs or any immunosuppressive drugs was prohibited during the study treatment.

Efficacy and safety evaluations

Iguratimod (25 mg tablet) was administered orally to patients once daily (after breakfast, 25 mg/day) for the first 4 weeks and twice daily (after breakfast and dinner, 50 mg/day) in the subsequent weeks. The efficacy of iguratimod was evaluated with blood concentrations of rheumatoid factor and immunoglobulins G, A, and M as well as the following modified ACR core set measures: [10] tender joint count in 48 joints (excluding DIP joints, all joints of one toe are counted as one), 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, degree of disability with the modified Health Assessment Questionnaire,[12] and either blood C-reactive protein concentration or erythrocyte sedimentation rate. The safety of iguratimod was evaluated with unfavorable symptoms and signs (including laboratory data) during the study treatment.

Statistical analysis

Safety endpoints were the incidence of adverse events (defined as any unfavorable symptoms and signs including abnormal changes in laboratory data) and the incidence of adverse reactions (defined as adverse events of which relationship with the study drug could not be ruled out) during the study treatment. To analyze the time courses of adverse reactions, hazard was calculated with life-table method for adverse reactions with an incidence of at least 3%. Original adverse event terms used in the case report forms by the investigator were coded with the Medical Dictionary for Regulatory Activities, Japanese Version 3.2.[13]

The following patients were excluded from the safety analysis: patients who received no study drug, patients who were not shown to receive the study drug, patients who violated Good Clinical Practice, patients who did not meet all the inclusion criteria stipulated in the study protocol, and patients who were not considered eligible for the study by the medical officer.

Patients who had at least six tender joints, at least three swollen joints, and either an erythrocyte sedimentation rate of at least 30 mm/h or a blood C-reactive protein concentration of at least 1.0 mg/dl at baseline in the safety analysis set were included in the efficacy analysis. However, the following patients were excluded from the analysis: patients who met any of the exclusion criteria; patients who received no study drug for at least 4 weeks or whose dose was not increased after 4-week study treatment at a daily dose of 25 mg; patients whose treatment compliance was less than 70% of the study drugs between any two consecutive hospital visits or throughout the study treatment; and patients who used any prohibited concomitant drugs during the study treatment.

The ACR 20 response rate was calculated by last-observation-carried-forward method. The time courses of ACR core set data and blood concentrations of immunoglobulins and rheumatoid factor were analyzed. The continued treatment rate was determined with the Kaplan–Meier method and was analyzed for two major reasons for premature study discontinuation: lack of efficacy and adverse reactions.

Results

Patient characteristics

A total of 394 patients with rheumatoid arthritis were enrolled in the study. They consisted of 325 women (82.5%) and 69 men (17.5%). The mean age was 56.1 years. The mean duration of the disease was 121.2 months (Table 1).

In the efficacy analysis set, the number of patients was 147 at week 28, and 144 at week 52. In the safety analysis set, it was 380 at week 28, 380 at week 52, 378 at week 76, and 377 at week 100. Of the 394 patients enrolled, 2 patients who received no study drug and 12 patients who violated Good Clinical Practice were excluded from the efficacy and safety analysis sets.

Safety evaluation

The incidence of adverse events was 97.6% (371/380) at week 52 and 97.6% (368/377) at week 100. The incidence of adverse reactions was 61.8% (235/380) at week 52 and 65.3% (246/377) at week 100. For adverse reactions, the incidence of unfavorable symptoms and signs (excluding abnormal changes in laboratory data) was 30.0% (114/380) at week 52 and 33.2% (125/377) at week 100; the incidence of abnormal changes in laboratory data was 48.4% (184/380) at week 52 and 50.4% (190/377) at week 100.

Adverse reactions with an incidence of at least 5% included dermatitis (6.1%, 23/377), upper abdominal pain (5.6%, 21/377), increased alanine aminotransferase (19.4%, 73/377), increased aspartate aminotransferase (18.3%, 69/377), increased γ-glutamyl transpeptidase (17.2%, 65/377), increased blood alkaline phosphatase (13.8%, 52/377), increased β-*N*-acetyl-D-glucosaminidase (9.3%, 35/377), positive fecal occult blood (7.4%, 28/377), increased urine β_2-microglobulin (7.2%, 27/377), and abnormal hepatic function data (5.8%, 22/377), as shown in Table 2. Eleven severe adverse reactions were reported in 11 patients (2.9%, 11/377) between Weeks 0 and 100 (Table 3). All these reactions were resolved after appropriate intervention.

Based on hazard for adverse reactions with an incidence of at least 3%, the reactions were divided into three groups according to onset patterns: (1) rapid onset (highest incidence during the first 4 weeks; e.g., increased β-*N*-acetyl-D-glucosaminidase); (2) slow onset (highest incidence between weeks 4 and 8; e.g., increased aspartate aminotransferase); and (3) constant onset (constant incidence until week 28; e.g., increased blood urea nitrogen) (Fig. 1). Hazard did not elevate for any of the adverse reactions after week 28. No clinically significant late adverse reactions were reported.

Because an increased hepatic enzyme (increased alanine aminotransferase or aspartate aminotransferase, 24.7%; increased alanine aminotransferase, 19.4%; increased aspartate aminotransferase, 18.3%) seemed to be an adverse reaction characteristic of iguratimod, the time course of the reaction was analyzed (Fig. 2). The most common timing of onset of the reaction was between weeks 4 and 8. The reaction was resolved spontaneously during the continued study treatment or by the discontinuation of study treatment. A

Table 1. Baseline patient characteristics

	No. of patients (%)
Sex	
Male	69 (17.5)
Female	325 (82.5)
Age (years)	
Mean ± SD	56.1 ± 11.4
<65	300 (76.1)
≥65	94 (23.9)
Weight (kg)	
Mean ± SD	52.52 ± 9.31
Stage	
I	21 (5.3)
II	104 (26.4)
III	126 (32.0)
IV	143 (36.3)
Class	
1	41 (10.4)
2	250 (63.5)
3	100 (25.4)
4	3 (0.8)
Duration of disease (years)	
Mean ± SD (months)	121.2 ± 96.6
<2	40 (10.2)
2 to 5	80 (20.3)
5 to 10	107 (27.2)
≥10	167 (42.4)

n = 394

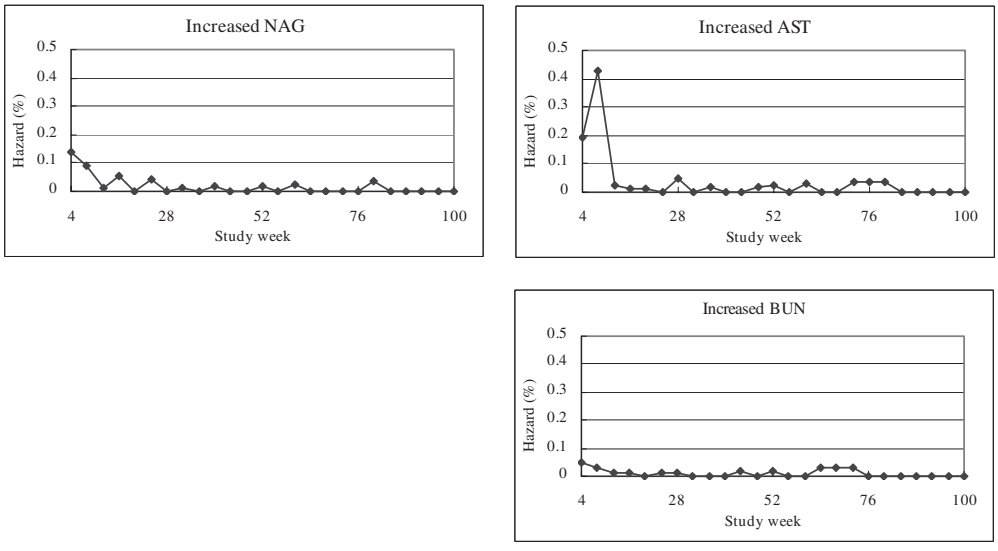

Fig. 1. Representative time courses of adverse reactions of iguratimod with hazard. *NAG*, increased β-*N*-acetyl-D-glucosaminidase; *AST*, increased aspartate aminotransferase; *BUN*, increased blood urea nitrogen

Table 2. Adverse reactions of iguratimod with an incidence of at least 1%

Symptoms and signs (excluding abnormal laboratory data)	No. of patients	Incidence (%)	Abnormal laboratory data	No. of patients	Incidence (%)
Infections and infestations			Renal and urinary disorders		
Nasopharyngitis	4	1.1	Urinary casts	8	2.1
Metabolism and nutrition disorders			Enzyme investigations		
Anorexia	5	1.3	Beta-*N*-acetyl-D-glucosaminidase increased	35	9.3
Nervous system disorders			Blood alkaline phosphatase increased	52	13.8
Dizziness (excluding vertigo)	4	1.1	Gastrointestinal investigations		
Taste disturbance	4	1.1	Fecal occult blood positive	28	7.4
Gastrointestinal disorders			Hematology investigations including blood groups		
Abdominal distension	5	1.3	Eosinophil count increased	16	4.2
Abdominal pain	8	2.1	Hematocrit decreased	7	1.9
Abdominal pain upper	21	5.6	Hemoglobin decreased	9	2.4
Diarrhea	8	2.1	Lymphocyte count decreased	15	4.0
Gastric ulcer	7	1.9	Red blood cell count decreased	6	1.6
Loose stools	4	1.1	White blood cell increased	4	1.1
Nausea	9	2.4	Hepatobiliary investigations		
Retching	4	1.1	Alanine aminotransferase increased	73	19.4
Stomatitis	18	4.8	Aspartate aminotransferase increased	69	18.3
Vomiting	4	1.1	Blood bilirubin increased	6	1.6
Skin and subcutaneous tissue disorders			Blood cholinesterase decreased	4	1.1
Depilation	4	1.1	Gamma-glutamyl transferase increased	65	17.2
Dermatitis	23	6.1	Liver function tests abnormal	22	5.8
Eczema	5	1.3	Immunology and allergy investigations		
Pruritus	6	1.6	Beta-2 microglobulin increased	10	2.7
			Beta-2 microglobulin urine increased	27	7.2
			Renal and urinary tract investigations and urinalysis		
			Blood urea increased	17	4.5
			Hematuria present	8	2.1
			Proteinuria present	9	2.4
			White blood cells urine positive	6	1.6
			Urinary sediment present	8	2.1
			Water, electrolyte and mineral investigations		
			Blood iron decreased	16	4.2

N = 377

Table 3. Severe adverse reactions of iguratimod

Reason for severity	Suspected relationship with the study drug (11 patients)
Adverse reactions requiring inpatient hospitalization or prolongation of hospitalization	Hepatic dysfunction[a] (with general fatigue and anorexia)
	Anemia
	Interstitial pulmonary disorder*
	Rash
	Nausea, abdominal pain, diarrhea, and fever
	Pyothorax
	Gastric ulcer
	Sepsis
	Hepatic dysfunction,[b] stomach discomfort, stomachache, and nausea
	Hepatic dysfunction,[c] anorexia, and nausea
Adverse reaction considered severe by investigator	Hepatic dysfunction[d]

*Occurred after week 52

The details of hepatic dysfunction (moderate or severe abnormality) are described below.

[a] Increased direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ-glutamyl transpeptidase

[b] Increased aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, and bile acid

[c] Increased total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, and bile acid

[d] Increased total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ-glutamyl transpeptidase

blood alanine aminotransferase concentration was 100 IU or higher in 35 (9.8%) of 377 patients. A blood aspartate aminotransferase concentration was 100 IU or higher in 26 (6.9%) of 377 patients. An increased hepatic enzyme was more common in lighter patients (41.7% [10/24] for patients weighing less than 40 kg versus 23.8% [82/344] for patients weighing 40 kg or more).

The continued treatment rate was determined until week 52 because the planned duration of study treatment was 52 weeks (Fig. 3). The rate was 66.8% at week 28 and 53.6%

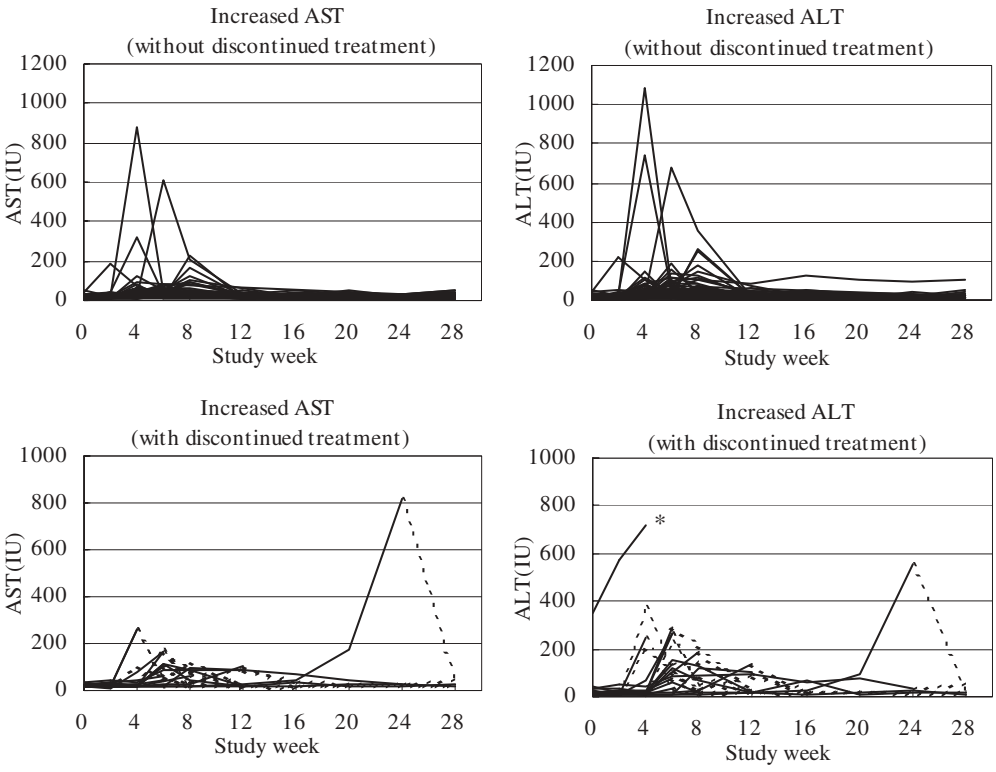

Fig. 2. Time courses of increased hepatic enzymes after the initiation of iguratimod therapy. *Upper panels* illustrate the time courses of data for patients who continued iguratimod therapy after aspartate aminostransferase (*AST*) or alanine aminotransferase (*ALT*) increased. *Lower panels* illustrate the time courses of data for patients who discontinued iguratimod therapy after AST or ALT increased. A *broken line* indicates the time courses of data after the discontinuation of the therapy. *Asterisk* indicates that the normalizing of increased ALT level was confirmed at a local hospital. The abnormality resulted from concomitant primary biliary cirrhosis

at week 52. The incidence of premature study discontinuation due to adverse reactions was 15.5% at week 28 and 16.3% at week 52. The incidence of the discontinuation due to lack of efficacy was 9.3% at week 28 and 16.1% at week 52.

Efficacy evaluation

The ACR 20 response rate was 46.9% (95% confidence interval, 38.7% to 55.3%) at week 28, 41.0% (95% confidence interval, 32.9% to 49.5%) at week 52 (Table 4). ACR core set data improved rapidly during the first 16 weeks of the study treatment and slowly throughout the subsequent weeks. Blood concentrations of immunoglobulins and rheumatoid factor were reduced during the first 16 weeks and then remained unchanged (Table 4).

In 120 patients who had a poor response to other DMARDs used within 6 months before the initiation of study treatment, the ACR 20 response rate was 48.3% (58/120) at week 28. The rate was 50% or higher for patients who had a poor response to previous methotrexate or salazosulfapyridine therapy, which has been used widely in the treatment of rheumatoid arthritis (57.6% [19/33] for methotrexate and 50.0% [13/26] for salazosulfapyridine).

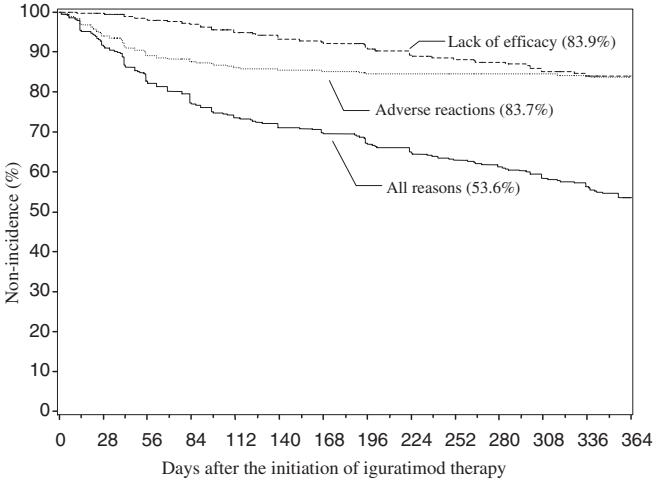

Fig. 3. Kaplan-Meier plots of the continued treatment rate for iguratimod according to reasons for premature study discontinuation

Discussion

The objective of the study was to evaluate the long-term safety of iguratimod in patients with rheumatoid arthritis. In the long-term study of iguratimod, hepatic dysfunction occurred as a severe adverse reaction in four patients. Although the dysfunction included transiently increased hepatic enzymes, attention should be paid to abnormal hepatic function data during iguratimod therapy, especially in patients weighing less than 40kg. Attention should also be paid to other potential severe adverse reactions of iguratimod, including gastrointestinal disorder (e.g., gastric ulcer) and hematological disorder.

Hazard analysis revealed that the incidence of adverse reactions was highest during the first 8 weeks and that no adverse reactions increased between Weeks 16 and 100

Table 4. ACR 20 response rate and outcome parameter data for iguratimod

	Study week			
	0	16	28	52
ACR 20 response rate (%) (95% confidence interval)	–	–	46.9 (38.7–55.3)	41.0 (32.9–49.5)
Responder/*n*	–	–	69/147	59/144
Tender joint count	12.2 ± 6.6	6.7 ± 6.6	5.9 ± 6.7	5.6 ± 6.5
Swollen joint count	10.9 ± 6.7	6.5 ± 6.2	6.0 ± 6.5	5.6 ± 6.0
Patient's assessment of pain (mm)	59.4 ± 22.3	41.2 ± 24.3	36.7 ± 24.0	39.9 ± 26.3
Physician's global assessment (mm)	63.0 ± 16.1	41.2 ± 20.3	33.8 ± 21.1	33.5 ± 20.5
Patient's global assessment (mm)	62.8 ± 21.8	41.1 ± 23.9	37.7 ± 23.1	40.6 ± 25.1
MHAQ score	1.0 ± 0.6	0.7 ± 0.5	0.7 ± 0.6	0.7 ± 0.6
Erythrocyte sedimentation rate (mm/h)	68.2 ± 27.1	53.4 ± 31.1	50.0 ± 29.0	55.3 ± 28.8
C-reactive protein (mg/dl)	4.62 ± 3.17	3.26 ± 3.19	3.08 ± 3.04	3.37 ± 2.74
Immunoglobulin G (mg/dl)	1796.1 ± 483.5	1590.9 ± 461.1	1491.9 ± 438.0	1524.4 ± 420.1
Immunoglobulin M (mg/dl)	144.1 ± 98.3	119.2 ± 74.1	115.8 ± 73.3	124.7 ± 74.1
Immunoglobulin A (mg/dl)	367.7 ± 169.3	318.0 ± 186.9	293.7 ± 159.1	314.1 ± 174.1
Rheumatoid factor (U/ml)	246.5 ± 345.7	179.8 ± 278.9	186.3 ± 291.0	213.7 ± 365.0

Outcome parameter data are expressed as means ± standard deviation
ACR, American College of Rheumatology; MHAQ, modified Health Assessment Questionnaire

when iguratimod was administered for 100 weeks. The continued treatment rate at week 52 for iguratimod was as high as that for 20 mg/day of leflunomide (53.6% versus 51.8%).[15] Fifty-seven patients continued iguratimod therapy for more than 100 weeks, and some of them have continued it for more than 7 years. This suggests that iguratimod has a sustained therapeutic effect.

In conclusion, the safety evaluation of iguratimod used for up to 100 weeks in patients with rheumatoid arthritis suggests that the drug could be used for a long time with close observation of the patients for adverse reactions such as increased hepatic enzymes.

More than a half of the patients enrolled were excluded from the efficacy analysis because the inclusion criteria did not include any criteria regarding disease activity markers. The ACR 20 response rate at week 52 was as high as that at week 28 (41.0% versus 46.9%). This indicates that the therapeutic effect of iguratimod continued for 52 weeks.

The study demonstrated that iguratimod was effective in patients who had a poor response to currently available DMARDs. The ACR 20 response rate at week 28 was 57.6% for patients who had a poor response to previous methotrexate therapy and 50.0% for patients who had a poor response to previous salazosulfapyridine therapy.

A simultaneous, controlled, double-blind, parallel-group study of iguratimod in Japanese patients with rheumatoid arthritis demonstrated that the efficacy of iguratimod was not inferior to that of salazosulfapyridine.[14] The ACR 20 response rate was 63.1% (65/103) for iguratimod and 57.7% (60/104) for salazosulfapyridine. The onset of therapeutic effect of iguratimod was more rapid than that of salazosulfapyridine. The ACR 20 response rate at week 8 was 41.7% (43/103) for iguratimod and 29.8% (31/104) for salazosulfapyridine. The rate at week 12 was 53.1% (52/98) for iguratimod and 49.0% (48/98) for salazosulfapyridine. Iguratimod could thus become a new option for the treatment of rheumatoid arthritis.

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