福岡大医紀（*Med. Bull. Fukuoka Univ.*）：49(1)，19–28，2022

The Efficacy of Add-on Iguratimod for Patients with Rheumatoid Arthritis Who Inadequately Responded to Methotrexate

Yutaro YAMASAKI [1)], Akira MAEYAMA [1)], Koichiro ISHIKAWA [2)], Junichiro ISHIKAWA [2)], Kunihide MURAOKA [1)], Tomonobu HAGIO [1)], Katsuhisa MIYAKE [3)], Naoko HIMURO [3)], Takuaki YAMAMOTO [1)]

1) *Department of Orthopaedic Surgery, Faculty of Medicine, Fukuoka University, Fukuoka, Japan*
2) *Ishikawa Orthopaedic and Rheumatism Clinic, Kumamoto, Japan*
3) *Division of Nephrology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Fukuoka University, Fukuoka, Japan*

Abstract

Objectives: In the current treatment strategy, it is recommended to achieve remission or low disease activity (LDA) as soon as possible from the basic idea of 'Treat to Target.' Iguratimod (IGU) is an anti-rheumatic drug classified as an immunomodulator that suppressed the production of inflammatory cytokines production and inhibited the activity of nuclear factor kappa-light-chain-enhancer. Recent studies suggests that IGU is effective in rheumatoid arthritis (RA) patients with inadequate responses to methotrexate (MTX). Therefore, we analyzed the retention rate and efficacy of add-on IGU in patients with RA and moderate disease activity (MDA) or high disease activity (HDA) after MTX treatment.

Materials and methods: We enrolled patients with RA who received add-on IGU because remission or because LDA was not achieved after MTX administration. We investigated the rate of efficacy of IGU + MTX as determined using Disease Activity Score in 28 joints (DAS28)–C-reactive protein (CRP) ≥ 2.7 at 12, 24, and 52 weeks, and adverse events at 52 weeks were examined via Kaplan–Meier analysis. Predictors of MTX + IGU efficacy at 12 weeks were also assessed.

Results: Overall, 59 patients with RA (7 men, 52 women) were enrolled. At baseline, the mean DAS28-CRP was 4.1 ± 0.9, and 29 and 30 patients had MDA and HDA, respectively. At 12 weeks, the mean DAS28-CRP was 2.9 ± 0.9, and the numbers of patients who achieved remission, LDA, MDA, and HDA were 16, 8, 31, and 4, respectively. At 52 weeks, the mean DAS28-CRP was 2.4 ± 0.8, and the numbers of patients who achieved remission, LDA, MDA, and HDA were 25, 9, 20, and 1, respectively. Multiple logistic regression analysis identified baseline DAS28-CRP as a predictor of MTX + IGU efficacy at 12 weeks.

Conclusions: This study demonstrated that 40.6% of patients with RA who inadequately responded to MTX were able to achieve early remission or LDA at 12 weeks with add-on IGU. Additionally, our study revealed that baseline DAS28-CRP was a predictor of LDA or remission at 12 weeks.

Key words: iguratimod, methotrexate, efficacy, rheumatoid arthritis

Introduction

The 'Treat to Target' concept recommends that the primary target for treatment of rheumatoid arthritis (RA) should be a state of clinical remission, and although remission should be a clear target, low disease activity (LDA) may be an acceptable alternative therapeutic goal, particularly in long-standing disease [1)].

Furthermore, the European League Against

Corresponding to: Akira MAEYAMA, Department of Orthopaedic Surgery, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 810-0180, Japan
TEL: + 81-92-801-1011　FAX: + 81-92-864-9055　E-mail: akira.maeyama0713@joy.ocn.ne.jp

Rheumatology (EULAR) recommends that methotrexate (MTX) should be part of the first-line regimen for the treatment of RA [2]. The mechanism of action of folate antagonist MTX in the treatment of RA is thought that MTX prevents pyrimidine and purine syntheses, required for DNA and RNA syntheses, and consequently inhibits cellular proliferation of lymphocytes involved in the inflammation process [3].

If the treatment target is not achieved with the first conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) strategy, biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) should be added in the presence of prognostic factors; otherwise, if poor prognostic factors are absent, then other csDMARDs should be considered [2].

However, patients with RA who cannot take or tolerate sufficient doses of MTX are often encountered in daily practice and present a treatment challenge. For such patients, a combination of csDMARDs which have a mechanism of action that differs from that of MTX is the therapy of choice [4].

Iguratimod (IGU) is a relatively new csDMARD that has been prescribed in daily medical practice in Japan since 2012. IGU is classified as an immunomodulatar, and previous studies reported that IGU suppressed the production of inflammatory cytokines including tumor necrosis factor-alpha, interleukin (IL)-1β, IL-6, IL-8, and IL-17 [4-8] and inhibited the activity of nuclear factor kappa-light-chain-enhancer of activated B cells [6, 9].

Recent studies suggests that IGU is effective and tolerant as monotherapy or combined therapy especially with methotrexate in patients with active RA [10].

Therefore, we analyzed the retention rate and efficacy of add-on IGU in patients with RA and moderate disease activity (MDA) /high disease activity (HDA) after MTX treatment.

Materials and methods

This study was a multicenter retrospective observational study of patients with RA who received add-on IGU because remission or LDA was not achieved after at least 3 months of MTX administration. Patients were enrolled from September 2012 to July 2020 at five institutions. The observation period was 52 weeks.

All patients met the 2010 American College of Rheumatology (ACR) /EULAR classification criteria [10].

Disease Activity Score in 28 joints (DAS28) –C-reactive protein (CRP), Simple Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) were used as indicators of disease activity. The DAS28, which is based on 28 joint counts and is calculated using a formula which takes into account the number of tender joints (TJC) and swollen joints (SJC), the patient's global assessment of disease activity on a visual analog scale (Pt VAS), and level of CRP (mg/dL). The joints included in DAS28 are the proximal interphalangeal joints (10 joints), the metacarpophalangeal joints (10), the wrists (2), the elbows (2), the shoulders (2), and the knees (2) [12, 13]. The SDAI is the numerical sum of five outcome parameters: tender and swollen joint count based on a 28-joint assessment, Pt VAS and physician's global assessment of disease activity visual analogue scale (Dr VAS) and level of CRP (mg/dL). An additional index, the CDAI, which is a modification of SDAI through the elimination of the CRP parameter [12, 14]. DAS28-CRP was categorized as follows: remission (DAS28-CRP < 2.3), LDA (2.3 ≤ DAS28-CRP < 2.7), MDA (2.7 ≤ DAS28-CRP ≤ 4.1), and HDA (DAS28-CRP > 4.1). SDAI was categorized as follows: remission (SDAI < 3.3), LDA (3.3 ≤ SDAI < 11), MDA (11 ≤ SDAI ≤ 26), and HDA (SDAI > 26). CDAI was categorized as follows: remission (CDAI < 2.8), LDA (2.8 ≤ CDAI < 10), MDA (10 ≤ CDAI ≤ 22), and HDA (CDAI > 22). Disease activity (DAS28-CRP, SDAI, and CDAI) was evaluated at each visit. An inadequate response to MTX + IGU was defined as DAS28-CRP ≥ 2.7 at 12, 24, and 52 weeks or an inability to continue treatment because of adverse events.

IGU was administered orally at a dose of 25 mg/day for the first 4 weeks and then at 25 or 50 mg/day at the discretion of each attending physician. MTX (≤12 mg/week) and prednisolone (PSL, ≤7.5 mg/day) were administered orally, and the dosages were determined at the physician's discretion. Concomitant use of csDMARDs other than MTX and non-steroidal anti-inflammatory drugs (NSAIDs) was permitted. Patients taking bDMARDs were excluded from the study.

In total, 78 patients at five institutions were treated with MTX + IGU without bDMARDs. Eight patients whose follow-up periods were shorter than 52 weeks because add-on IGU was started after August 2019, nine patients whose disease activity at baseline was remission or LDA, one patient who did not give informed consent, and one patient who was younger than 20 years were excluded;

finally, 59 patients were included.

This retrospective study was approved by the Institutional Review Board of Fukuoka University Hospital (U19-07-017). Informed consent was obtained from all patients.

The collected data included patient demographics (age, sex, RA duration), joint damage (Steinbrocker stage), daily dysfunction (Steinbrocker class), SJC, TJC, Pt VAS, Dr VAS, serum CRP levels (mg/mL), serum rheumatoid factor (RF) levels (IU/mL), the MTX dose (mg/week), the PSL dose (mg/day), concomitant PSL use (%), concomitant use of other csDMARDs (%), and disease activity indices (DAS28-CRP, SDAI, CDAI).

The primary endpoint was the retention rate of MTX + IGU at 52 weeks as evaluated by Kaplan–Meier analysis. The secondary endpoints were the efficacy rate of MTX + IGU at 12, 24, and 52 weeks as evaluated by DAS28-CRP. In addition, the associations of efficacy with age, sex, RA duration, Steinbrocker stage, Steinbrocker class, SJC, TJC, Pt VAS, Dr VAS, CRP, RF, MTX dose, PSL dose, DAS28-CRP, SDAI, and CDAI at baseline, 12, 24, and 52 weeks were assessed via logistic regression analysis.

Statistical analysis

Each patient background variable (age, sex, RA duration, MTX dose, PSL dose, DAS28-CRP, SDAI, CDAI) was expressed as the mean ± standard deviation. The retention rate of IGU + MTX was evaluated by Kaplan–Meier analysis. The dependent variable was MTX + IGU efficacy, and the explanatory variables were age, sex, RA duration, Steinbrocker stage, Steinbrocker class, SJC, TJC, Pt VAS, Dr VAS, CRP, RF, MTX dose, PSL dose, DAS28-CRP, SDAI, and CDAI. These variables were analyzed using logistic regression models. Univariate analysis was performed for each explanatory variable. Based on the results of the univariate analysis, multivariate analysis was performed. The estimated area, sensitivity, and specificity of the receiver operating characteristic (ROC) curve were analyzed to determine the cut-off of each parameter based on the result of multivariate analysis. Statistical analyses were performed using SPSS software (version 23.0, IBM Corp., Armonk, NY, USA). Significance was assumed for $p < 0.05$.

Results

Patients' demographic characteristics are presented in Table 1. The baseline patient age was 61.9 ± 10.5 years, and the study population included 52 women (88.1%). The duration of RA was 10.2 ± 9.4 years. The MTX dose was 8.5 ± 2.1 mg/week, the PSL dose was 2.9 ± 2.1 mg/day, and the concomitant PSL treatment rate was 79.7% (47/59). The mean DAS28-CRP was 4.1 ± 0.9, the mean SDAI was 20.5 ± 9.8, and the mean CDAI was 19.7 ± 9.4. The numbers of patients with MDA and HDA at baseline according to DAS28-CRP were 29 and 30, respectively.

Table 1. Patient demographics (n = 59)

Patient characteristics	
age (years)	61.9±10.5 (range 28 - 81)
sex (male/female)	7/52
RA duration (years)	10.2±9.4 (range 0.3 - 33)
Steinbrocker stage (Ⅰ/Ⅱ/Ⅲ/Ⅳ)	12/13/12/22
Steinbrocker class (1/2/3/4)	17/39/3/0
MTX dose (mg/week)	8.5±2.1 (range 4 - 12)
PSL dose (mg/day)	2.9±2.1 (range 0 - 7.5)
Concomitant PSL (%)	79.7 (47/59)
DAS28-CRP	4.1±0.9 (range 2.8 – 6.5)
SDAI	20.5±9.8 (range 7.2 – 49.4)
CDAI	19.7±9.4 (range 6 - 48)

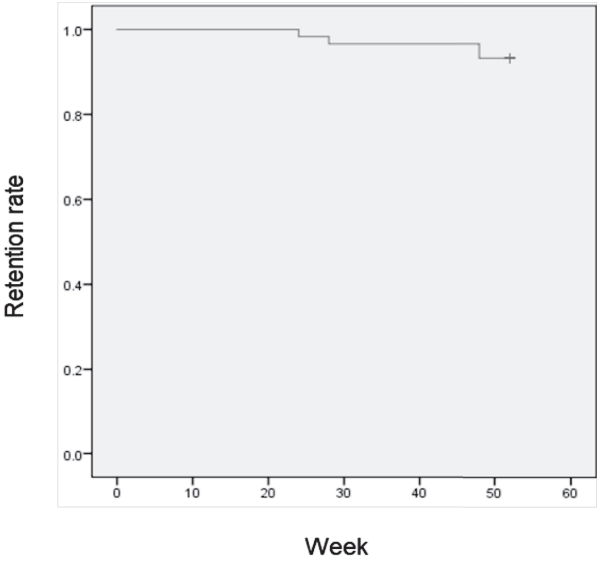
RA: rheumatoid arthritis; MTX: methotrexate; PSL: prednisolone; DAS28: Disease Activity Score in 28 joints; CRP; C-reactive protein; SDAI: Simple Disease Activity Index; CDAI: Clinical Disease Activity Index
Data are presented as the mean ± standard deviation or number of patients unless otherwise indicated.

Twenty-six patients (44.1%) were using other csDMARDs at baseline, with all patients using injectable gold, and the dosage of injectable gold was not changed during the observation period. In total, 29 patients received NSAIDs at baseline, and dose reduction and treatment termination were required for one patient each during the observation period. The NSAID dosage was not increased from baseline in any patient.

The MTX + IGU retention rate at 52 weeks was 93.2% (Figure 1). Retention was not possible in four patients because of adverse events. The patients who did not achieve MTX + IGU retention included a woman in her 60s who discontinued IGU treatment at week 24 because of liver dysfunction and dysgeusia. The second patient was a woman in her 40s who developed liver dysfunction at week 24 and discontinued IGU treatment at week 28. In addition, two women in their 60s discontinued MTX treatment at week 48 because of liver dysfunction.

The distributions of DAS28-CRP at baseline, 12, 24, and 52 weeks are presented in Figure 2. The mean DAS28-

CRP at 12 weeks (n = 59) was 2.9 ± 0.9, and the response was remission in 16 patients, LDA in 8 patients, MDA in 31 patients, and HDA in 4 patients. Thus, 40.7% (24/59) of patients who inadequately responded to MTX achieved remission/LDA at 12 weeks. The mean DAS28-CRP at 24 weeks (n = 59) was 2.6 ± 0.9, and the response was remission in 23 patients, LDA in 10 patients, MDA in 24 patients, and HDA in 2 patients. The mean DAS28-CRP at 52 weeks (n = 55) was 2.4 ± 0.8, and the response was remission in 25 patients, LDA in 9 patients, MDA in 20 patients, and HDA in 1 patient Thus, 57.6% (34/59) of patients with inadequate responses to MTX achieved remission/LDA at 52 weeks.



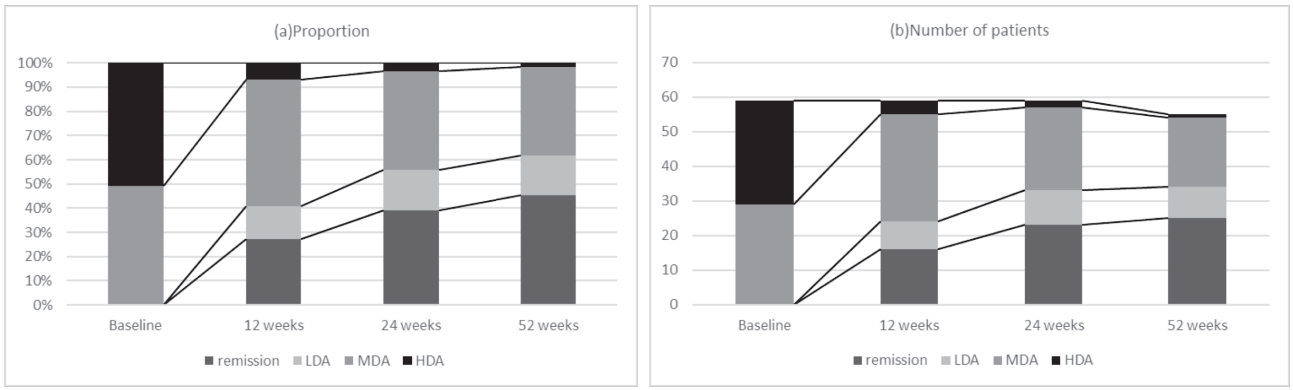
MTX: methotrexate; IGU: iguratimod

Figure 1. MTX + IGU retention rate (Kaplan–Meier analysis). The MTX + IGU retention rate at 52 weeks was 93.2% (55/59).

The results of logistic regression analysis of predictors for MTX + IGU efficacy at 12 weeks are presented in Table 2. Univariate analysis was performed with each explanatory variable at baseline, and seven explanatory variables were significantly associated with MTX + IGU efficacy: Steinbrocker stage (odds ratio [OR] = 1.61, 95% confidence interval [CI] = 1.008–2.581, p = <0.05), SJC (OR = 1.39, 95% CI = 1.159–1.667, $p < 0.01$), TJC (OR = 1.47, 95% CI= 1.176–1.828, $p = 0.01$), CRP (OR = 2.66, 95% CI= 1.018–6.945, p = <0.05), DAS28-CRP (OR = 7.50, 95% CI = 2.723–20.641, $p < 0.01$), SDAI (OR = 1.17, 95% CI= 1.073–1.273, $p < 0.01$), and CDAI (OR = 1.16, 95% CI= 1.068–1.263, $p < 0.01$). Thereafter, multivariate analysis was performed using the aforementioned variables that were significant in univariate analysis. However, DAS28-CRP (OR = 7.50, 95% CI= 2.723–20.641, $p < 0.01$) was the only predictor significantly associated with MTX + IGU efficacy at 12 weeks.

The ROC curve for baseline DAS28-CRP for MTX + IGU efficacy at 12 weeks illustrated that the optimal cut-off for baseline DAS28-CRP was 3.89 (area under the curve = 0.849, sensitivity = 80.0%, specificity = 79.2%, Figure 3).

At 52 weeks, the MTX dose was 8.0 ± 2.1 mg/week, the PSL dose was 2.4 ± 2.2 mg/day, and the concomitant PSL treatment rate was 61.0% (36/55, Table 3). The dosage of MTX was reduced versus baseline in 11 patients, and concomitant MTX use was discontinued in two of these patients. The PSL dosage was reduced versus baseline in 16 patients, and concomitant PSL use was discontinued in seven of these patients. The MTX and PSL dosages were not increased versus baseline in any patient.



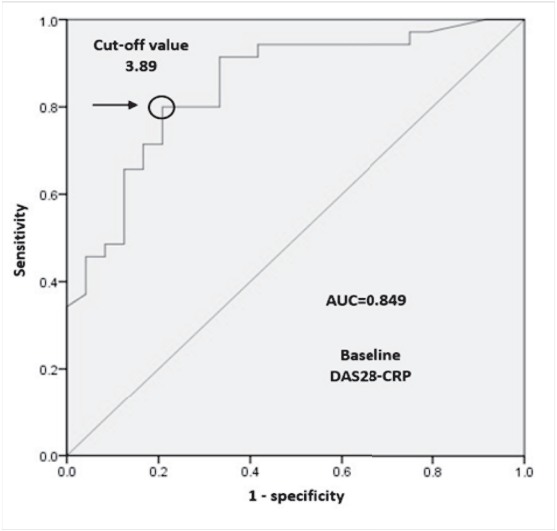
LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity

Figure 2. Distributions of DAS28-CRP at baseline, 12, 24, and 52 weeks. (a) Proportion. (b) Number of patients.

Table 2. Univariate and multivariate analyses of predictors of MTX + IGU efficacy at 12 weeks (logistic regression analysis)

Variables	Univariable analysis		Multivariable analysis	
	p-value	Odd ratio (95%Cl)	*p*-value	Odd ratio (95%Cl)
age (years)	0.77	0.99 (95%Cl：0.944 - 1.044)		
sex (female)	0.35	2.13 (95%Cl: 0.432 – 10.543)		
RA duration (years)	0.21	1.04 (95%Cl: 0.979 – 1.102)		
Steinbrocker stage (Ⅰ / Ⅱ / Ⅲ / Ⅳ)	<0.05	1.61 (95%Cl: 1.008 – 2.581)		
Steinbrocker class (1/2/3/4)	0.11	2.34 (95%Cl: 0.836 – 6.545)		
SJC	<0.01	1.39 (95%Cl: 1.159 – 1.667)		
TJC	0.01	1.47 (95%Cl: 1.176 – 1.828)		
Pt VAS (mm)	0.43	1.01 (95%Cl: 0.980 – 1.049)		
Dr VAS (mm)	0.41	1.02 (95%Cl: 0.978 – 1.057)		
CRP (mg/dL)	<0.05	2.66 (95%Cl: 1.018 – 6.945)		
RF (IU/mL)	0.64	1.00 (95%Cl: 0.998 – 1.004)		
MTX dose (mg/week)	0.67	1.05 (95%Cl: 0.825 – 1.348)		
PSL dose (mg/day)	0.49	0.91 (95%Cl: 0.709 – 1.178)		
DAS28-CRP	<0.01	7.5 (95%Cl: 2.723 – 20.641)	<0.01	7.50 (95%Cl: 2.723 – 20.641)
SDAI	<0.01	1.17 (95%Cl: 1.073 – 1.273)		
CDAI	<0.01	1.16 (95%Cl: 1.068 – 1.263)		

RA: rheumatoid arthritis; SJC: swollen joint count; TJC: tender joint count; Pt VAS: patient's visual analog scale; Dr VAS: doctor's visual analog scale; CRP: C-reactive protein; RF: rheumatoid factor; MTX: methotrexate; PSL: prednisolone; DAS28: Disease Activity Score in 28 joints; SDAI: Simple Disease Activity Index; CDAI: Clinical Disease Activity Index; CI: confidence interval



ROC: receiver operating characteristic; MTX: methotrexate; IGU: iguratimod; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; AUC: area under the curve.

Figure 3. ROC curve for DAS28-CRP at baseline for MTX + IGU efficacy at 12 weeks. The baseline DAS28-CRP cut-off of 3.89 (arrow) discriminated MTX + IGU efficacy.

Table 3. The dosage of MTX and the dosage and ratio of PSL at baseline and 52 weeks

	Baseline (n=59)	52 weeks (n=55)
MTX dose (mg/week)	8.5 ± 2.1 (range 4 – 12)	8.0 ± 2.1 (range 4 – 12)
PSL dose (mg/day)	2.9 ± 2.1 (range 0 – 7.5)	2.4 ± 2.2 (range 0 – 7.5)
PSL concomitant (%)	79.7 (47/59)	61.0 (36/55)

MTX: methotrexate; PSL: prednisolone

Discussion

In this study, we analyzed the retention rate and the efficacy of add-on IGU patients with RA who inadequately responded to MTX, then 93.2% of the patients were able to retain MTX+IGU at 52 weeks, 57.6% of patients were able to achieved remission/LDA at 52 weeks, and 40.7% of the patients were able to achieve remission/LDA at 12 weeks. Additionally, our study revealed that baseline DAS28-CRP was predictive of LDA/remission at 12 weeks.

Several studies reported the efficacy and retention rate of MTX + IGU (Table 4) [15)-24)]. Okamura et al. [18)] reported that the retention rate of IGU was significantly higher with MTX (75%) than without MTX (23.5%) in a 52-week study of the efficacy and safety of daily IGU treatment in patients with RA. Furthermore, their multivariate logistic regression analysis demonstrated that baseline DAS28-CRP was predictive of LDA at week 52. Of note, several patients treated with bDMARDs were included in the MTX + IGU group. Inoue et al. [22)] reported the efficacy of IGU and treatment continuation rate of 35 patients receiving MTX + IGU and 71 patients receiving IGU monotherapy in a single-center retrospective study. They analyzed the retention rate of IGU for 48 months. The retention rates in the MTX + IGU group were 82.9% (29/35) at 24 weeks and 71.4% (25/35) at 54 weeks. Their report excluded patients with RA taking bDMARDs, similarly as our study. However, the of disease activity at baseline in the MTX + IGU group was categorized as LDA or remission, and clinical effectiveness was not evaluated at 12 weeks. The retention rate of MTX + IGU in our study was substantially lower than that reported in previous studies, and this discrepancy might be related to differences in patient background.

Duan et al. [19)] reported a randomized controlled trial in which the MTX + IGU group had a significantly different ACR50 score at 24 weeks than the MTX + placebo group. These results differed from our study in that the observation period was short (24 weeks) and the endpoints were the ACR20, ACR50, and ACR70 scores. Xia et al. [30)] reported a prospective study of the therapeutic effect of MTX + IGU, MTX alone, and IGU alone in patients with active RA. They reported that the

Table 4. Clinical trials of MTX + IGU for rheumatoid arthritis patients.

Authors [Reference]	Design		Number of patients	Endpoint
Yamasaki et al.	Retrospective	DAS28-CRP ≥ 2.7	n = 59	52 weeks
Ishiguro et al. 2013 [15)]	RCT	TJC ≥ 6, SJC ≥ 4 ESR ≥ 28mm/h or CRP ≥ 1.0㎎ /dL	n = 165	24 weeks
Hara et al. 2014 [16)]	RCT	TJC ≥ 6, SJC ≥ 4 ESR ≥ 28mm/h or CRP ≥ 1.0㎎ /dL	n = 165	52 weeks
Okamura et al. 2015 [18)]	Retrospective	Patients who were treated with IGU for 52 weeks	n = 24	52 weeks
Yoshioka et al. 2016 [20)]	Retrospective	Patients who were treated with IGU for 24 weeks	n = 65	24 weeks
Duan et al. 2016 [19)]	RCT	Patients who were not treated with any rheumatism medicine	n = 30	24 weeks
Suto et al. 2019 [21)]	Retrospective	Patients who were treated with IGU for 36 months	n = 28	36 months
Inoue et al. 2020 [22)]	Retrospective	Patients who were not treated with bDMARDs	n = 35	54 weeks

MTX: methotrexate; IGU: iguratimod; PSL: prednisolone; RCT: randomized controlled trial; DAS28: Disease Activity Score in 28 joints; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; SJC: swollen joint counts; TJC: tender joint counts; IGU: iguratimod; bDMARDs: biological disease-modifying antirheumatic drugs

ACR20 and ACR50 scores were significantly higher in the MTX + IGU group than in the IGU and MTX groups. Their study also set the observation period to 24 weeks, and the inclusion criteria were as follows: more than six tender joints, more than four swollen joints, erythrocyte sedimentation rate (ESR) ≥ 28 mm/h, and CRP > 8.0 mg/L. Ishikawa et al. [29] reported that patients with good or moderate responses according to DAS exhibited a progressive reduction of DAS28-ESR up to week 104. Conversely, patients with non-responses according to DAS exhibited no significant reduction of DAS28-ESR at weeks 4 and 8. Their observation period was 2 years, which exceeded that our study, and their study included a larger number of patients. However, the efficacy of MTX + IGU without bDMARDs in patients with RA was not evaluated.

Yoshioka et al. [20] used data from a Japanese multicenter registry to assess the efficacy of IGU and determined the optimal period and disease activity for deciding whether to continue IGU therapy. They revealed that DAS28-ESR at baseline and at 4, 8, and 12 weeks after initiating IGU therapy were independent significant predictors of achieving LDA at 24 weeks. Furthermore, DAS28-ESR at 12 weeks was most significantly associated with LDA at 24 weeks in patients with concomitant MTX use. This report assessed endpoints as 24 weeks. In addition, patients whose DAS28-ESR at baseline indicated remission were included. However, Ishiguro et al. [23] reported a post-marketing surveillance study in which DAS28-CRP < 2.6 was achieved at 52 weeks in patients with RA and good or moderate EULAR responses at 24 weeks after the start of IGU. They suggested that 24 weeks was the optimal timepoint for predicting the effects of IGU therapy. Although this was a post-marketing surveillance study with large-scale data, no criteria were set for cases in which IGU was administered.

To our knowledge, this is the first study to evaluate the efficacy of add-on IGU in patients with RA who inadequately responded to MTX using DAS28-CRP ≥ 2.7 at baseline as the criterion. In this study, we analyzed the efficacy of add-on IGU at 12 weeks, and 40.7% (24/59) of patients achieved remission/LDA. We also found that a baseline DAS28-CRP cut-off of 3.89 was associated with the achievement of remission/LDA at 12 weeks. This suggested that add-on IGU may not lead to early remission/LDA in patients with RA with baseline DAS28-CRP ≥ 3.89.

There are few reports on the long-term efficacy of MTX+IGU in patients with RA. Suto et al. have examined the three-year efficacy of IGU in patients with RA. They reported that the mean DAS28-CRP at 3 years was significantly decreased in the MTX+IGU group compared with baseline [21]. From this report, MTX+IGU is considered to be relatively effective even in the long term. In our study, the observation period was short. Therefore, further studies to evaluate the long-term efficacy of add-on IGU for Patients with RA who inadequately responded to MTX are needed.

We also evaluated add-on IGU therapy in terms of safety. Many studies reported the safety of IGU therapy [15)-32)]. In our study, 6.8% (4/59) of patients discontinued MTX + IGU therapy because of adverse events. Ishiguro et al. [15] reported a discontinuation rate attributable to adverse events of 4.2% in MTX + IGU-treated Japanese patients with RA in a placebo-controlled comparative study. This result was similar to our findings, and it suggests that add-on IGU in clinical practice is relatively safe for patients with inadequate responses to MTX. By contrast, Yoshioka et al. [20] reported a treatment discontinuation rate attributable to adverse events of 9% (6/65) of MTX + IGU. In contrast to the report by Ishiguro et al.[15], 41.5% (27/65) of patients in this report had a baseline MTX dose exceeding 8 mg/week. Therefore, differences in the baseline MTX dose might have influenced the results.

In our study, all cases of discontinuation of IGU were due to liver dysfunction. Okamura et al. reported that the reasons for IGU discontinuation were interstitional pneumonia, *Pneumocystis jiroveci* pneumonia, and disorder of liver dysfunction [18]. However, there were no patients whose IGU was discontinued due to pneumonia in our study.

Additionally, Inoue et al. have reported the safety of IGU. They reported that 1.7 % (6/35) in the MTX+IGU group discontinued due to adverse events at 48 months. The reasons for IGU discontinuation were eruption (2 cases), nausea (1 case), paresthesia (1 case), hypoglobulinemia (1 case), and lymphadenopathy (1 case) [22]. From this result, MTX + IGU was considered to be relatively safe.

Our study had several limitations. First, this was a retrospective study, and the administration of MTX, PSL, other csDMARD, and NSAIDs was decided by individual physicians with no unified protocol. Therefore, there was bias regarding medication selection. However, although some patients required dose reduction for concomitant

drugs such as MTX, PSL, and NSAIDs versus baseline, no patient required dose escalation. Second, this was a single-arm study without a control group. Third, the sample size was limited, which might have affected the power and accuracy of the analysis. Fourth, some parameters related to disease activity were not evaluated, such as anti-cyclic citrullinated protein antibody, matrix metalloproteinase, and Health Assessment Questionnaire scores. Consequently, there was parameter selection bias. Further research is needed to identify other predictors of efficacy other than baseline disease activity.

In conclusion, this study demonstrated that 40.7% of patients with RA who received add-on IGU following inadequate responses to MTX were able to achieve early remission/LDA at 12 weeks. Baseline DAS28-CRP was significantly associated with MTX + IGU efficacy at 12 weeks.

Acknowledgements

We would like to thank Drs. Masafumi Hara, Michiya Hara, and Akiyoshi Kage for providing the data. We thank Joe Barber Jr., PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

References

1) Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, Kvien TK, Navarro-Compán MV, Oliver S, Schoels M, Scholte-Voshaar M, Stamm T, Stoffer M, Takeuchi T, Aletaha D, Andreu JL, Aringer M, Bergman M, Betteridge N, Bijlsma H, Burkhardt H, Cardiel M, Combe B, Durez P, Fonseca JE, Gibofsky A, Gomez-Reino JJ, Graninger W, Hannonen P, Haraoui B, Kouloumas M, Landewe R, Martin-Mola E, Nash P, Ostergaard M, Östör A, Richards P, Sokka-Isler T, Thorne C, Tzioufas AG, van Vollenhoven R, de Wit M, van der Heijde D. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an internal task force. Ann Rheum Dis 2016, 75: 3-15.

2) Smolen JS, Landewè RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, McInnes IB, Sepriano A, van Vollenhoven RF, de Wit M, Aletaha D, Aringer M, Askling J, Balsa A, Boers M, den Broeder AA, Buch MH, Buttgereit F, Caporali R, Cardiel MH, De Cock D, Codreanu C, Cutolo M, Edwards CJ, van Eijk-Hustings Y, Emery P, Finckh A, Gossec L, Gottenberg JE, Hetland ML, Huizinga TWJ, Koloumas M, Li Z, Mariette X, Müller-Ladner U, Mysler EF, da Silva JAP, Poór G, Pope JE, Rubbert-Roth A, Ruyssen-Witrand A, Saag KG, Strangfeld A, Takeuchi T, Voshaar M, Westhovens R, van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020, 79: 685-99.

3) Wessels JA, Huizinga TW, Guchelaar HJ. Recent insights in the pharmacological actions of methotrexate in the treatment of rheumatoid arthritis. Rheumatology (Oxford) 2008, 47: 249-55.

4) Nozaki Y. Iguratimod: novel molecular insights and a new csDMARD for rheumatoid arthritis, from Japan to the world. Life (Basel) 2021, 11: 457.

5) Du F, Lü LJ, Fu Q, Dai M, Teng JL, Fan W, Chen SL, Ye P, Shen N, Huang XF, Qian J, Bao CD. T-614, a novel immunomodulator, attenuates joint inflammation and articular damage in collagen-induced arthritis. Arthritis Res Ther 2008, 10: R136.

6) Kohno M, Aikawa Y, Tsubouchi Y, Hashiramoto A, Yamada R, Kawahito Y, Inoue K, Kusaka Y, Kondo M, Sano H. Inhibitory effect of T-614 on tumor necrosis factor-alpha induced cytokine production and nuclear factor-kappaB activation in cultured human synovial cells. J Rheumatol 2001, 28: 2591-6.

7) Luo Q, Sun Y, Liu W, Qian C, Jin B, Tao F, Gu Y, Wu X, Shen Y, Xu Q. A novel disease-modifying antirheumatic drug, iguratimod, ameliorates murine arthritis by blocking IL-17 signaling, distinct from methotrexate and leflunomide. J Immunol 2013, 191: 4969-78.

8) Kawakami A, Tsuboi M, Urayama S, Matsuoka N, Yamasaki S, Hida A, Aoyagi T, Furuichi I, Nakashima T, Migita K, Kawabe Y, Nakashima M, Origuchi T, Eguchi K. Inhibitory effect of a new anti-rheumatic drug T-614 on costimulatory molecule expression, cytokine production, and antigen presentation by synovial cells. J Lab Clin Med 1999, 133: 566-74.

9) Aikawa Y, Yamamoto M, Yamamoto T, Morimoto K, Tanaka K. An anti-rheumatic agent T-614 inhibits NF-kappaB activation in LPS- and TNF-alpha-stimulated THP-1 cells without interfering with IkappaBalpha degradation. Inflamm Res 2002, 51: 188-94.

10) Hu CJ, Zhang L, Zhou S, Jiang N, Zhao JL, Wang Q, Tian XP, Zeng XF. Effectiveness of iguratimod as monotherapy or combined therapy in patients with

rheumatoid arthritis: a systematic review and meta-analysis of RCTs. J Orthop Surg Res 2021, 16: 457.
11) Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham 3rd CO, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010, 62: 2569-81.
12) Matsui T, Kuga Y, Nishino J, Kaneko A, Eto Y, Tohma S. Comparison of composite disease activity indices for rheumatoid arthritis. Mod Rheumatol 2011, 21: 134-43.
13) Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995, 38: 44-8.
14) Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, van Riel PL, Tugwell P. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003, 42: 244-57.
15) Ishiguro N, Yamamoto K, Katayama K, Kondo M, Sumida T, Mimori T, Soen S, Nagai K, Yamaguchi T, Hara M; Iguratimod-Clinical Study Group. Concomitant iguratimod therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: a randomized, double-blind, placebo-controlled trial. Mod Rheumatol 2013, 23: 430-9.
16) Hara M, Ishiguro N, Katayama K, Kondo M, Sumida T, Mimori T, Soen S, Nagai K, Yamaguchi T, Yamamoto K; Iguratimod-Clinical Study Group. Safety and efficacy of combination therapy of iguratimod with methotrexate for patients with active rheumatoid arthritis with an inadequate response to methotrexate: an open-label extension of a randomized, double-blind, placebo-controlled trial. Mod Rheumatol 2014, 24: 410-8.
17) Okamura K, Yonemoto Y, Okura C, Kobayashi T, Takagishi K. Efficacy of the clinical use of iguratimod therapy in patients with rheumatoid arthritis. Mod Rheumatol 2015, 25: 235-40.
18) Okamura K, Yonemoto Y, Suto T, Okura C, Takagishi K. Efficacy at 52 weeks of daily clinical use of iguratimod in patients with rheumatoid arthritis. Mod Rheumatol 2015, 25: 534-9.
19) Duan XW, Zhang XL, Mao SY, Shang JJ, Shi XD. Efficacy and safety evaluation of a combination of iguratimod and methotrexate therapy for active rheumatoid arthritis patients: a randomized controlled trial. Clin Rheumatol 2015, 34: 1513-9.
20) Yoshioka Y, Takahashi N, Kaneko A, Hirano Y, Kanayama Y, Kanda H, Takagi H, Ito T, Kato T, Saito K, Funahashi K, Asai S, Takemoto T, Terabe K, Asai N, Ishiguro N, Kojima T. Disease activity early in treatment as a predictor of future low disease activity in RA patients treated with iguratimod. Mod Rheumatol 2016, 26: 169-74.
21) Suto T, Yonemoto Y, Okamura K, Sakane H, Takeuchi K, Tamura Y, Kaneko T, Ayabe K, Chikuda H. The three-year efficacy of iguratimod in clinical daily practice in patients with rheumatoid arthritis. Mod Rheumatol 2019, 29: 775-81.
22) Inoue A, Nozaki Y, Hirooka Y, Kinoshita K, Chiba Y, Funauchi M, Matsumura I. The effectiveness and retention rate of iguratimod in Japanese rheumatoid arthritis patients with/without methotrexate in daily medical care. Life (Basel) 2020, 10: 261.
23) Ishiguro N, Shibata K, Yoshimura A, Ikeuchi S, Ishii M. Investigation of the predictors of the response to Iguratimod therapy: a post-hoc analysis of post-marketing surveillance. Mod Rheumatol 2020, 30: 626-32.
24) Lu LJ, Bao CD, Dai M, Teng JL, Fan W, Du F, Yang NP, Zhao YH, Chen ZW, Xu JH, He PG, Wu HX, Tao Y, Zhang MJ, Han XH, Li XF, Gu JR, Li JH, Yu H. Multicenter, randomized, double-blind, controlled trial of treatment of active rheumatoid arthritis with T-614 compared with methotrexate. Arthritis Rheum 2009, 61: 979-87.
25) Yoshikawa A, Kotani T, Matsuda S, Hata K, Matsumura Y, Takeuchi T. The addition of iguratimod can reduce methotrexate dose in rheumatoid arthritis with clinical remission. Mod Rheumatol 2021. doi: 10.1080/14397595.2021.1892945.
26) Nozaki Y, Inoue A, Kinoshita K, Funauchi M, Matsumura I. Efficacy of iguratimod vs. salazosulfapyridine as the first-line csDMARD for rheumatoid arthritis. Mod Rheumatol 2020, 30: 249-58.
27) Hara M, Abe T, Sugawara S, Mizushima Y, Hoshi

K, Irimajiri S, Hashimoto H, Yoshino S, Matsui N, Nobunaga M. Long-term safety study of iguratimod in patients with rheumatoid arthritis. Mod Rheumatol 2007, 17: 10-16.

28) Mimori T, Harigai M, Atsumi T, Fujii T, Kuwana M, Matsuno H, Momohara S, Takei S, Tamura N, Takasaki Y, Ikeuchi S, Kushimoto S, Koike T. Safety and effectiveness of 24-week treatment with iguratimod, a new oral disease-modifying antirheumatic drug, for patients with rheumatoid arthritis: interim analysis of a postmarketing surveillance study of 2679 patients in Japan. Mod Rheumatol 2017, 27: 755-65.

29) Ishikawa K, Ishikawa J. Iguratimod, a synthetic disease modifying anti-rheumatic drug inhibiting the activation of NF-κB and production of RANKL: its efficacy, radiographic changes, safety and predictors over two years' treatment for Japanese rheumatoid arthritis patients. Mod Rheumatol 2019, 29: 418-29.

30) Xia Z, Lyu J, Hou N, Song L, Li X, Liu H. Iguratimod in combination with methotrexate in active rheumatoid arthritis: Therapeutic effects. Z Rheumatol 2016, 75: 828-33.

31) Mimori T, Harigai M, Atsumi T, Fujii T, Kuwana M, Matsuno H, Momohara S, Takei S, Tamura N, Takasaki Y, Yamamoto K, Ikeuchi S, Kushimoto S, Koike T. Safety and effectiveness of iguratimod in patients with rheumatoid arthritis: final report of a 52-week, multicenter postmarketing surveillance study. Mod Rheumatol 2019, 29: 314-23.

32) Ishigro N, Shibata K, Yoshimura A, Ikeuchi S, Ishii M. Factors influencing physician decisions to discontinue treatment after onset of liver dysfunction: post-hoc analysis of an all-case post-marketing surveillance study of iguratimod. Mod Rheumatol 2020, 30: 633-9.

(Received on October 4th, 2021; Accepted on November 30th, 2021)

「The authors declere no conflict of interest.」