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Analysis of efficacy and safety of treatment of active rheumatoid arthritis with iguratimod and methotrexate.

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Abstract

Iguratimod (IGU) has been suggested to be a novel and useful DMARD with a unique mechanism of action. It is much less expensive than biologics. We evaluated and compared the efficacy and safety of IGU, methotrexate (MTX), and IGU+MTX for the treatment of rheumatoid arthritis (RA). RA patients were randomly divided into three groups: IGU+MTX, placebo+IGU and placebo+MTX group. Relevant laboratory parameters were periodically reviewed and clinical outcome measures were assessed after 4, 8, 12, 16 and 24 weeks. Symptoms of all patients significantly improved after treatment. After four weeks of treatment, differences in American College of Rheumatology 20% improvement criteria response rate (ACR20) between any of the groups were not significant. However, ACR20 response rate improved more in the MTX+IGU group compared to the monotherapy groups. After 24 weeks of treatment, combined treatment with IGU and MTX was superior to monotherapy with either IGU or MTX. There were no significant differences between the incidences of adverse effects among the three treatment groups. In conclusion: The treatment of RA with IGU is effective, and the effect of IGU treatment becomes apparent earlier than MTX treatment. To some extent, the combination of IGU and MTX results in an additive therapeutic effect. IGU+MTX maybe used as first-line treatment instead of MTX.

Keywords: Iguratimod, IGU, MTX, Rheumatoid arthritis, Therapeutic effect.

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that manifests itself as arthritis, and results in permanent joint damage. It is also associated with high morbidity and mortality. Clinically, RA is characterized by synovial inflammation and hyperplasia, autoantibody production (rheumatoid factor and anti-citrullinated protein antibodies), stiffness of the affected joints, cartilage and bone destruction that can lead to deformities, and systemic features (e.g. cardiovascular, pulmonary, psychological and skeletal disorders) [1].

Current treatments for RA emphasize the early use of disease-modifying antirheumatic drugs (DMARDs) to minimize or prevent joint damage [2]. Methotrexate (MTX) is considered to be the anchor DMARD for initial RA treatment [3,4]. However, no currently available medication has been uniformly effective; and some treatments can be toxic or expensive. Therefore, there is a need for new and reasonably cost-effective agents with high efficacy/toxicity ratios to increase the number of options for the treatment of RA. Iguratimod (IGU), a small-molecule antirheumatic drug, is a member of the family of methanesulfonanilides. Besides acting as a cyclooxygenase 2 (COX-2) inhibitor (similar to most of the members of this family), IGU has been suggested to be a novel and useful DMARD with a unique mechanism of action. And it is much less expensive than biologics.

IGU has been shown to display a steroid-like improvement in several animal models of autoimmunity such as collagen-induced arthritis, MRL-lpr/lpr mice, and experimental autoimmune encephalomyelitis [5,6]. Existing studies have shown that IGU reduced the production of some cytokines including interleukin-1• (IL-1•), IL-6, IL-8, IL-17, tumor necrosis factor-•, and interferon-• *in vitro* (synovial cells and some cell lines) and *in vivo* (mouse models) [5,7-12]. IGU also reduced immunoglobulin (Ig) production by acting directly on human B lymphocytes without affecting B lymphocyte proliferation [13]. In a clinical trial, IGU significantly decreased the rheumatoid factor and production of IgG, IgM and IgA compared with placebo in patients with active RA [14]. In addition, IGU demonstrated anabolic effects on bone metabolism and suppressed bone resorption by elevated expression of the transcription factor osterix [15]. Recently, Du et al. published a study that revealed direct evidence that IGU dramatically suppressed disease progression and markedly protected affected joints against cartilage destruction and bone erosion in rats with collagen-induced arthritis [8].

In several clinical trials, IGU has been reported to be safe and effective for the treatment of active RA in hospitalized patients

[14,16-18]. However, there are few studies on combination therapy that include IGU. Therefore, the current study was carried out to investigate whether combination treatment with IGU and MTX is safe and more effective than treatment with either drug alone.

Materials and Methods

Patients

The study is approved by the appropriate ethics committee of First Hospital, Jilin University, China and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from patients before enrolment into this study.

This randomized, double-blind, placebo-controlled phase IV study was conducted at the local Hospital. A total of 105 cases were allocated to this study. Eligible patients were diagnosed with active RA based on the criteria of the American College of Rheumatology (ACR; formerly the American Rheumatism Association) [19]. Active disease was defined by the presence of four of the following five criteria: ≥ 5 tender joints, ≥ 3 swollen joints, morning stiffness lasting for ≥ 60 minutes, Westergren erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour, and blood C-reactive protein (CRP) concentration of at least 1.0 mg/dL. Previous use of DMARDs (including MTX) was only allowed if these had been discontinued for at least four weeks before enrolment in this study. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in 10 mg doses of prednisone (or equivalent) daily was permitted, provided that the dose remained unchanged for at least four weeks before enrolment and during the trial. Intra-articular corticosteroid injections were not allowed within six weeks of the efficacy assessment. Patients aged 20 to 69 years old were eligible for this study. Women of childbearing potential were required to have a urine test to exclude pregnancy before enrolment, and were required to use adequate methods of contraception.

Exclusion criteria were as follows: impaired hepatic function as shown by abnormal results on liver function tests (i.e. elevated aspartate aminotransferase [AST] or alanine aminotransferase [ALT] levels above upper normal limits), known hematopoietic disorders (absolute leukocyte count $<4 \times 10^9$/L, platelet count $<100 \times 10^9$/L, and hemoglobin level <9.0 g/dL), positive for hepatitis B or C by serologic tests, pregnancy or breast feeding, history of drug or alcohol abuse, persistent or severe infection, active digestive diseases, previous treatment with IGU, body weight <40 kg, and RA with Steinbrocker class IV.

Study design

A total of 105 patients were enrolled into the study. Nine patients left the study before completion due to personal reasons or adverse drug reactions. Finally, a total of 96 cases met the inclusion criteria and completed the clinical study. During the 24-week trial, eligible patients were divided into three groups: IGU+MTX group, patients that received the IGU +MTX combination treatment; placebo+MTX group, patients that received placebo+MTX treatment; and placebo+IGU group, patients that received placebo+IGU treatment. Patients were randomly assigned into these three groups at a 1:1:1 ratio. IGU was administered orally at a dose of 50 mg/day (25 mg, twice daily). The daily dose of IGU was decided based on a previous study [13]. The study carried out by LU et al. revealed that IGU therapy at 50 mg/day is effective and well–tolerated by patients, and represents a new option for the treatment of patients with active RA. MTX at doses of 10 mg/week was administered in patients in the IGU+MTX and placebo+MTX groups during the treatment period. The drugs used in this study including placebo were provided by Simcere Ltd.

Measurement of efficacy and safety

Clinical assessments of RA activity were obtained at baseline and at week four and 24. The primary end point for the determination of efficacy was the proportion of patients who achieved a 20% improvement response according to the ACR criteria (ACR20) at week 24 [20]. To be considered an ACR20 responder, a subject had to have 20% improvement in the tender and swollen joint count and in at least three of the following five criteria: patient global assessment, physician global assessment, pain intensity, Health Assessment Questionnaire (HAQ), and CRP level or ESR [20]. Secondary end points included the proportion of patients with 50% improvement (ACR50) or 70% improvement (ACR70) at week 24. Secondary end points included the ACR50, ACR70, ACR components, DAS28-CRP [21,22], and HAQ-DI. A decrease in HAQ-DI scores shows improvement and a decrease greater than 0.22 represents a minimal clinically important difference [23]. The state of disease activity was evaluated based on the DAS28 score as remission (<2.6), low disease activity (<3.2), moderate disease activity (≥ 3.2 and ≤ 5.1), or high disease activity (>5.1) [21,23].

Safety was evaluated by adverse event reports, laboratory assays for changes in hematologic characteristics, as well as blood chemistry, urinalysis, liver function and physical examinations. These evaluations were undertaken during the observation period and at each visit during the treatment period (zero, two, four, six, eight, 10, 12, 16, 20 and 24 weeks after the start of treatment).

Statistical analysis

Demographics and disease history was analyzed using Fisher's exact test for categorical data and F test for age comparisons. Group comparisons were performed by Kruskal-Wallis test. Comparisons of the mean changes of efficacy end points were performed using the Kruskal-Wallis test for group comparisons and Wilcoxon's signed rank test for results within the active treatment groups. The potential correlation between variables was analyzed by Spearman's rank correlation test. All

statistical tests were performed using SPSS 19.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 183 active RA patients were evaluated in this study. Among them, 105 patients were found eligible to participate in this study based on inclusion criteria. Eligible patients were randomly assigned into three groups (at a ratio of 1:1:1): the IGU+MTX group (n=35), placebo+MTX group (n=35), and placebo+IGU group (n=35). The placebo+MTX and placebo +IGU groups are both control groups. A total of nine patients (six patients in the IGU+MTX group, two patients in the placebo+MTX group, and one patient in the placebo+IGU group) were later excluded from the ongoing study due to protocol violations, adverse events, and/or lack of clinical benefit. There were no statistically significant differences in age, sex, baseline disease characteristics, or concomitant use of NSAIDs or corticosteroids among the treatment groups. Demographics and clinical characteristics at baseline of patients with active rheumatoid arthritis are shown in Table 1.

Table 1. *Demographics and clinical characteristics at baseline of patients with active rheumatoid arthritis.*

	Placebo+MTX (n=33)	Placebo+IGU (n=34)	MTX+IGU (n=29)
Men/Female	5/28	7/27	3/26
Age, years	46.31 ± 10.89	46.46 ± 11.01	45.97 ± 10.75
BMI	22.57 ± 2.53	22.01 ± 2.03	22.16 ± 2.46
RF, U/ml	320.92 ± 329.12	410.13 ± 376.72	215.08 ± 223.48
ACPA, U/ml	955.41 ± 985.43	1125.17 ± 920.52	1032.69 ± 1002.28
DAS28	7.07 ± 0.50	7.12 ± 0.63	7.40 ± 0.67
Morning stiff time (minutes)	92.50 ± 38.44	90.00 ± 35.29	87.07 ± 25.79
Previous DMARD treatment No%	8 (24.24%)	9 (26.47)	6 (20.69)
Concomitant NSAIDS No%	19 (57.58%)	20 (58.82%)	19 (65.52%)
Concomitant corticosteroids No%	5 (15.15%)	5 (14.71%)	4 (13.79%)

There were no statistically significant differences between groups at baseline (P<0.05).

The percentages for patients that did not complete the 24-week treatment were 17.14% (6/35) in the IGU+MTX group, 5.71% (2/35)in the placebo+MTX group, and 2.86%(1/35) in the placebo+IGU group.

Clinical efficacy

Efficacy of treatments after four weeks: After four weeks of treatment, the number of painful joints (TEN28), the number of swollen joints (SW28), the visual analogue scale (VAS), Patient Global Assessment of Disease Activity (PaGADA), Physician Global Assessment of Disease Activity (PhGADA), the duration of morning stiffness and HAQ score, ESR and CRP of patients in each group were observed and analyzed. ACR20, ACR50 and ACR70 response rates in the three groups after four weeks of treatment are shown in Table 2. There were no significant differences among any of the groups (Table 2).

Table 2. *Differences of ACR20, ACR50 and ACR70 in each group of patients after 4 and 24 weeks of treatment.*

		Placebo+MTX group	Placebo+IGU group	MTX+IGU group
4 weeks				
ACR20	% (n)	27.27 (9)	29.41 (10)	31.03 (9)
ACR50	% (n)	9.09 (3)	11.76 (4)	10.34 (3)
ACR70	% (n)	3.03 (1)	2.94 (1)	3.45 (1)
24 weeks				
ACR20	% (n)	27.27 (9)	35.29 (12)	37.93 (11)
ACR50	% (n)	12.12 (4)	11.76 (4)	13.79 (4)
ACR70	% (n)	9.09 (3)	5.88 (2)	10.34 (3)[#]

Note: n, represents the number of subjects; %, represents the percentage; P<0.05 was considered statistically significant. [#]compared with Placebo+ IGU group, P<0.05

In addition, all secondary outcome measures (i.e. ESR, CRP level, TEN28, SW28, VAS, PaGADA, PhGADA and HAQ scores) demonstrated a statistically significant improvement after four weeks of treatment in each of the three groups (Table 3). Changes in CRP and ESR levels from baseline at week four in the Placebo+IGU and MTX+IGU groups were significantly greater than in the placebo+MTX group (all values of P<0.05). In addition, the decrease in CRP levels in the MTX+IGU group was significantly greater than in the Placebo+IGU group (all values of P<0.05).

Efficacy of treatment after 24 weeks: After 24 weeks of treatment, CRP, ESR, TEN28, SW28, patient assessment of pain VAS score, PaGADA, PhGADA and HAQ scores significantly improved in each treatment group compared to baseline data (Table 4). Changes in CRP levels from baseline at week 24 in the Placebo+IGU and MTX+IGU groups were significantly greater than in the placebo+MTX group (all values of P<0.05). TEN28 improved significantly more in the IGU+MTX group compared with the monotherapy groups. In addition, SW28 and TEN28 of patients in the placebo+MTX group improved significantly more than in the placebo+IGU group (Table 4).

ACR20ACR50and ACR70 response rates in the three groups after 24 weeks of treatment are shown in Table 2. The

differences between groups were not statistically significant. However, ACR20 and ACR70 of the MTX+IGU group indicated greater improvement than in the monotherapy groups. ACR70 in the MTX+IGU group was significantly greater than in the placebo+IGU group (Table 2).

Table 3. *Changes from baseline of secondary measures of individual efficacy in patients in each group after four weeks of treatment.*

	Placebo+MTX	Placebo+IGU	MTX+IGU
CRP (mg/L)			
Baseline	56.74 ± 23.34	59.10 ± 25.28	54.66 ± 25.38
4 weeks	34.52 ± 16.43[&]	27.65 ± 18.62[&]	18.98 ± 16.90[&]
Changes from baseline	22.22 ± 20.18	31.45 ± 22.20[*]	35.68 ± 21.56[*#]
ESR (mm/h)			
Baseline	81.53 ± 34.33	87.80 ± 38.48	78.24 ± 27.37
4 weeks	53.38 ± 31.77[&]	47.69 ± 28.78[&]	35.66 ± 25.71[&]
Changes from baseline	28.15 ± 33.07	40.11 ± 33.77[*]	42.58 ± 26.55[*]
TEN28 (count)			
Baseline	18.94 ± 6.89	17.31 ± 5.21	21.59 ± 7.39
4 weeks	12.19 ± 4.53[&]	12.31 ± 5.10[&]	14.41 ± 6.41[&]
Changes from baseline	6.75 ± 5.83	5.0 ± 5.16	7.18 ± 6.92
SW28 (count)			
Baseline	16.25 ± 6.57	15.49 ± 5.22	17.76 ± 8.50
4 weeks	10.31 ± 5.23[&]	10.14 ± 5.48[&]	12.24 ± 6.68[&]
Changes from baseline	5.94 ± 5.93	5.35 ± 5.35	5.52± 7.64
VAS			
Baseline	81.72 ± 9.39	83.57 ± 8.10	83.62±7.18
4 weeks	65.91 ± 7.80[&]	68.35 ± 8.26[&]	66.52 ± 8.45[&]
Changes from baseline	15.81 ± 8.63	15.22 ± 1.41	17.1 ± 7.84
PaGADA			
Baseline	81.72 ± 9.39	84.00 ± 8.38	83.62 ± 7.18
4 weeks	67.03 ± 7.92[&]	68.89 ± 8.11[&]	68.31 ± 7.19[&]
Changes from baseline	14.69 ± 1.41	15.11 ± 8.25	15.31 ± 7.19
PhGADA			
Baseline	81.72 ± 9.39	83.71 ± 8.26	83.62 ±7.18
4 weeks	66.28 ± 7.77[&]	67.86 ± 9.50[&]	67.93 ± 8.45[&]
Changes from baseline	15.44 ± 8.62	15.85 ± 8.90	15.33 ± 7.84
HAQ			
Baseline	1.0 ± 0.6	0.9 ± 0.7	1.0 ± 0.8
4 weeks	0.57 ± 0.20	0.53 ± 0.30	0.55 ± 0.27
Changes from baseline	0.43 ± 0.45	0.37 ± 0.54	0.45 ± 0.60

[&]Significant difference compared to baseline values; [*]significant difference compared to the Placebo+MTX group, P<0.05; [#]significant difference compared to the Placebo+IGU group, P<0.05

Evaluation of disease activity: DAS28 score is a measure of disease activity, which ranges from 0-10. A DAS28 score greater than 5.1 indicates a high degree of disease activity, while a DAS28 score less than 3.2 indicates low disease activity. The DAS28 score is suited to reflect both the early effect of treatment and sustained treatment capability of a drug or a drug combination.

The effects of different treatment regimens on the DAS28 score are shown in Table 5. The DAS28 scores of patients in all three groups before treatment were higher than 5.1 (Table 1), indicating highly active disease. All DAS28 scores demonstrated statistically significant improvement after both four and 24 weeks of treatment, compared to baseline data in all three treatment groups (data not shown, all values of P<0.05). After four weeks of treatment, changes in DAS28 scores were significantly greater in the placebo+IGU group than in the placebo+MTX group; suggesting that the effect of IGU treatment manifested earlier than the effect of MTX treatment. After four and 24 weeks of treatment, changes in DAS28 scores were significantly greater in the IGU+MTX group than in the other groups; suggesting that IGU and MTX treatment had an additive effect (Table 5).

Table 4. *Changes from baseline of secondary measures of individual efficacy in patients of each group after 24 weeks of treatment.*

	Placebo+MTX	Placebo+IGU	MTX+IGU
CRP (mg/L)			
Baseline	56.74 ± 23.34	59.10 ± 25.28	54.66 ± 25.38
24 weeks	19.90 ± 7.39[&]	6.92 ± 1.62[&]	5.69 ± 0.80[&]
Changes from baseline	36.84 ± 17.31	52.18 ± 17.91[*]	48.97 ± 17.96[*#]
ESR (mm/h)			
Baseline	81.53 ± 34.33	87.80 ± 38.48	78.24 ± 27.37
24 weeks	21.28 ± 19.46[&]	21.97 ± 13.50[&]	16.69 ± 13.45[&]
Changes from baseline	60.25 ± 27.90	65.83 ± 28.84	61.55 ± 21.56
TEN28 (count)			
Baseline	18.94 ± 6.89	17.31 ± 5.21	21.59 ± 7.39
24 weeks	4.06 ± 1.21[&]	5.34 ± 2.85[&]	3.41 ± 2.29[&]
Changes from baseline	14.88 ± 1.41[#]	11.97±5.77	18.18 ± 5.47[*#]
SW28 (count)			
Baseline	16.25 ± 6.57	15.49 ± 5.22	17.76 ± 8.50
24 weeks	3.22 ± 2.61[&]	4.83 ± 2.80[&]	3.24 ± 3.12[&]
Changes from baseline	13.03 ± 5.0[#]	10.66 ± 4.19	14.52 ± 6.40[#]
VAS			
Baseline	81.72 ± 9.39	83.57 ± 8.10	83.62 ± 7.18

24 weeks	38.43 ± 15.22[&]	35.00 ± 13.28[&]	39.48 ± 15.02[&]
Changes from baseline	43.29 ± 12.65	48.57 ± 11.0	44.14 ± 11.77
PaGADA			
Baseline	81.72 ± 9.39	84.00 ± 8.38	83.62 ± 7.18
24 weeks	38.41 ± 15.22[&]	35.54 ± 13.27[&]	39.76 ± 14.81[&]
Changes from baseline	43.31 ± 12.65	48.46 ± 11.10	43.86 ± 11.64
PhGADA			
Baseline	81.72 ± 9.39	83.71 ± 8.26	83.62 ± 7.18
24 weeks	39.06 ± 16.48[&]	34.71 ± 12.77[&]	39.14 ± 14.70[&]
Changes from baseline	42.66 ± 13.41	49.0 ± 10.75	44.48 ± 11.57
HAQ			
Baseline	1.0 ± 0.6	0.9 ± 0.7	1.0 ± 0.8
24 weeks	0.21 ± 0.16[&]	0.21 ± 0.23[&]	0.24 ± 0.21[&]
Changes from baseline	0.79 ± 0.44	0.69 ± 0.52	0.76 ± 0.58

[&]Significant difference compared to baseline values; [*]significant difference compared to the Placebo+MTX group, P<0.05; [#]significant difference compared to the Placebo+IGU group, P<0.05.

Safety

After 24 weeks of treatment, patients in each group reported adverse events. Major adverse events included hepatic dysfunction, leucopenia and upper digestive tract disorder. The incidences of all adverse events are shown Table 6. There were no significant differences between groups. The most common adverse event among the groups was the increase in liver transaminases (ALT and AST). Most adverse events were mild or moderate. No fatal adverse events were reported. Nine of 105 patients did not complete the 24-week treatment. Seven of the nine patients withdrew from the study due to adverse events, while the other two patients discontinued the study for unrelated reasons. The percentage of adverse events in the IGU +MTX, placebo+MTX and placebo+IGU groups were 11.42%, 5.88% and 2%, respectively. Two patients in the IGU+MTX group discontinued their treatment due to unrelated reasons (Table 6).

Table 5. *Changes in DAS28 in each patient group after four and 24 weeks of treatment.*

DAS28	Placebo+MTX group	Placebo+IGU group	MTX+IGU group
4 weeks	1.29 ± 0.61	1.78 ± 0.66[*]	2.52 ± 1.41[*#]
24 weeks	3.76 ± 0.60	3.43 ± 0.73	4.63± 0.89[*#]

[*]Compared with the Placebo+MTX group, P<0.05; [#]Compared with Placebo +IGU group, P<0.05.

Patients with abnormal liver function in each group are listed in Table 6. Two patients (5.7%) in the IGU+MTX group had ALT and AST concentrations above 100 U/L, resulting in the suspension of treatment. In contrast, no patient in the placebo +MTX and placebo+IGU groups discontinued treatment due to elevated ALT or AST. One patient in the placebo+MTX group experienced a significant drop in the number of white blood cells ($<2.0 \times 10^9$/L) and red blood cells ($<2.5 \times 10^{12}$/L). These abnormalities reversed to normal values after suspension of treatment. There was no increase in blood pressure in any patient in any of the treatment groups.

Table 6. *Adverse reactions with an incidence ≥ 5% in at least one of the three treatment groups.*

	Placebo+MTX group (n=34)	Placebo+IGU group (n=36)	IGU+MTX group (n=35)
Upper respiratory tract infection	2 (5.9%)	1 (2.8%)	3 (8.6%)
Stomatitis	1 (2.9%)	0 (0%)	1 (2.9%)
Leukopenia	3 (8.8%)	1 (2.8%)	2 (5.7%)
Thrombocytopena	2 (5.9%)	2 (5.6%)	3 (8.6%)
Hemoglobin decrease	1 (2.9%)	1 (2.8%)	1 (2.9%)
Increase of AST	5 (11.7%)	3 (8.3%)	6 (17.1%)
Increase of ALT	4 (20.6%)	5 (13.9%)	6 (17.1%)
Gastrointestinal reactions	3 (8.8%)	3 (8.3%)	2 (5.7%)

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase.

Discussion

In this study, we found that the treatment of RA with IGU is effective and safe, and that its effect on RA symptoms becomes apparent earlier than that of MTX treatment. To some extent, the combination of IGU with MTX exhibited an additive effect. After treatment for four or 24 weeks, CRP, ESR, TEN28, SW28, VAS, PaGADA, PhGADA and HAQ score of patients significantly improved over baseline levels. In comparing the compliance rate improvement of ACR20, ACR50, ACR70 and DAS28, we found that changes in DAS28 were significantly greater in the IGU+MTX group than in the other groups.

MTX is one of the most common and oldest drugs used in the treatment of RA. When MTX accumulates in the body to a certain level, it triggers significant and serious adverse events including liver toxicity, pulmonary toxicity and bone marrow suppression [24]. According to the 2012 ACR guidelines, it was recommend that clinicians should use MTX in combination with other DMARDs or biologics based on disease duration, disease activity, prognosis of patients with RA and experience before taking DMARDs when MTX treatment alone is not sufficient to alleviate the condition of the patient. MTX combination therapy is the cornerstone of RA treatment. IGU is a small molecule anti-rheumatic drug with a unique mechanism of action. Li et al. [25] reviewed randomized controlled trials (RCTs) of iguratimod for RA to assess its efficacy and safety. This meta-analysis showed that, after 24 weeks of therapy, ACR20, tender joint count, swollen joint count, pain at rest, physician and patient global assessment of disease activity, HAQ score, ESR, and CRP in

the iguratimod-treated group were better than in the placebo group [25]. The combination therapy of IGU with MTX in patients with RA has received much attention. It has been confirmed that the combination of IGU with MTX for long-term treatment (52 weeks) is effective for patients with active RA and with an inadequate response to MTX [16].

Based on mechanistic considerations, the combination of IGU and MTX may have an additive therapeutic effect. In fibroblast-like synoviocytes, IGU mainly inhibited the expression of IL-17, while MTX mainly inhibited the expression of IFN-γ; IGU mainly reduced immunoglobulin (Ig) production by acting directly on human B lymphocytes without affecting B lymphocyte proliferation, while MTX mainly inhibited cytokine production by T lymphocytes. In bone tissue, both IGU and MTX can inhibit the production of osteoclasts to some extent. IGU also promotes osteoblast differentiation [3,14,26]. The results of this study reveal that after four weeks of treatment, DAS28 improvement in the placebo+IGU group was slightly better compared to the placebo+MTX group. However, after 24 weeks of treatment, the efficacy of MTX treatment was significantly better than IGU treatment. IGU+MTX combination therapy resulted in significantly greater improvement after either four or 24 weeks of treatment compared to monotherapy treatment. These results suggest that IGU and MTX have an additive effect in the treatment of RA. So our data suggested the use of IGU+MTX as first-line treatment instead of MTX.

Reported adverse effects suggest that the most significant safety issue of IGU+MTX combination therapy is potential liver toxicity [8,14]. In our study, there was no significant difference in the incidence of elevated AST and/or ALT among groups. In the current clinical study, major adverse events after 24 weeks of treatment included upper respiratory tract infection, stomatitis, leukopenia, thrombocytopenia, decrease of hemoglobin, elevated liver transaminases and gastrointestinal reactions (anorexia, bloating, etc.). There were no significant differences in the overall incidence of adverse reactions among the different treatments. Liver transaminases markedly increased during the first six weeks of treatment. Patients recovered when given glycyrrhizin tablets (a treatment for liver injury) or when treatment with DMARDs was temporarily suspended. These results indicate that IGU and MTX combination therapy did not increase the risk of liver toxicity.

In 2012, Japan became the first country to approve combination therapy with IGU and MTX when MTX treatment alone did not achieve complete remission in patients with active RA. At present, the treatment of RA often relies on biologic DMARDs. Biologics are expensive, and most patients cannot afford them. Treatment is determined mainly by the preference of the patient and physician, side effects of treatment, and costs. The combination of IGU and MTX provides additional treatment options in addition to biologics; in particular, to reduce adverse reactions and decrease costs (compared to biological agents).

It should be mentioned that the concomitant use of both NSAIDs and corticosteroids was allowed in our study. However, the dose of NSAIDs and corticosteroids remained unchanged during the trial and for at least four weeks before enrolment. We reasoned that these drugs would not have a significant effect on the results of our study, since the doses of these drugs were very low and all patients had active disease at the time of enrolment.

In summary, our study was able to prove that IGU can improve the symptoms of RA patients, reduce disease activity and laboratory parameters of inflammation, improve the joint function status, and improve the quality of life of patients. Combination therapy with IGU and MTX is clearly superior to monotherapy with either drug.

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