Review Article

Efficacy and Safety of Iguratimod for the Treatment of Rheumatoid Arthritis

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All randomized controlled trials (RCTs) of iguratimod for rheumatoid arthritis (RA) to assess its efficacy and safety are included in this paper. The Review Manager software was used for meta-analysis to assess risk bias of the studies included, and GRADE profiler software was used for the evidence quality of the studies included. Four RCTs involving 1407 patients with RA were included. Meta-analyses showed that, after 24-week therapy, ACR20, tender joint count, swollen joint count, rest pain, physician and patient global assessment of disease activity, HAQ score, ESR, and CRP in iguratimod group were better than those in placebo group and that the difference between those of iguratimod group and those of other DMARDs (MTX and SASP) group was not significant. GRADE evidence classification of the studies included was moderate. Iguratimod for RA had few adverse events, and its efficacy and safety were the same as those of MTX and SASP for RA. The results of this systematic review suggest that more high-quality and large-scaled RCTs were needed to determine the efficacy of iguratimod for RA and whether iguratimod is as effective as other DMARDs besides MTX and SASP.

1. Introduction

Rheumatoid arthritis (RA) is chronic systemic inflammatory and autoimmune disease of unknown etiology that primarily targets synovial tissue and is characterized by an activation of T lymphocyte, an increase in interleukin and tumor necrosis factor, and severe chronic inflammation of the joints, resulting in erosion and destruction of cartilage, bone, and tendon [1, 2]. It is relatively common, with a prevalence of slightly less than 1% in adults all over the world [1]. Prevalence of moderate and severe disability in adults aging over 60 (in millions) due to rheumatoid arthritis by leading health condition associated with disability is 1.7 in high-income countries and 3.7 in low- and middle-income countries in 2012 [3]. Years lost due to disability (YLD) per 100 000 adults aging over 60 due to rheumatoid arthritis is the 11th in the world in 2012 [3]. Current treatments for RA emphasize the early use of traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), salazosulfapyridine (SASP), leflunomide, and cyclophosphamide to minimize or prevent joint damage. In addition, biologic agents such as necrosis factor-α blocker, anti-interleukin antibody, and CD20 monoclonal antibody are also used to treat RA. In the recent ten years, iguratimod (T-614) has been used to treat RA as a novel immunomodulator. It functions by suppressing the production of some inflammatory cytokines, including interleukin-1 (IL-1), IL-4, IL-6, IL-17, tumor necrosis factor, nuclear factor-kappaB, and interferon in vitro (synovial cells and some cell lines) and in vivo (mouse models) [4, 5]. Iguratimod also reduced immunoglobulin production by acting directly on human B lymphocytes without affecting B lymphocyte proliferation [6]. Direct evidence has also showed that iguratimod can dramatically suppress disease progression and markedly protect affected joints.
<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Participants</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcomes</th>
<th>Allocation concealment</th>
</tr>
</thead>
</table>
| Hara et al.   | Double-blind, randomized, placebo-controlled trial | Country: Japan  
Site: multicenter  
Number: 376  
Iguratimod group (n = 147)  
SASP group (n = 156)  
Placebo group (n = 73)  
Sex: female/male = 306:70  
Placebo group: placebo tablets | T-614 group: iguratimod 25 mg daily for the first 4 weeks and 50 mg daily for the subsequent 24 weeks  
SASP group: salazosulapyridine (SASP) 1000 mg daily  
Placebo group: placebo tablets | 28 weeks of clinical assessment at 0, 4, 6, 12, 18, 24, and 28 weeks. | ACR20, ACR50, tender joint count, swollen joint count, rest pain, physician's and patient's global assessment of disease activity (VAS, mm), physician's global assessment of disease activity, HAQ score, ESR, CRP, and adverse events. | Described in article but not validated because the author could not be reached via email. |
| Lü et al.     | Double-blind, randomized, placebo-controlled trial | Country: China  
Site: multicenter  
Number: 280  
T-614 group 1 (n = 93)  
T-614 group 2 (n = 92)  
Placebo group (n = 95)  
Sex: female/male = 231:49  
Placebo group: placebo tablets | Group 1: T-614 25 mg daily for the first 4 weeks and 50 mg daily for the subsequent 20 weeks  
Group 2: T-614 50 mg daily  
Placebo group: placebo tablets | 24 weeks of clinical assessment at 0, 2, 4, 6, 12, 18, and 24 weeks. | ACR20, ACR50, ACR70, tender joint count, swollen joint count, tender joint score (TJS), swollen joint score (SJS), rest pain, duration of morning stiffness, grip strength, physician and patient global assessment of disease activity, ESR, CRP, rheumatoid factor, HAQ score, radiological damage, and adverse events. | Detailed in article and validity ascertained through telephone. |
| Lü et al.     | Double-blind, randomized, controlled trial   | Country: China  
Site: multicenter  
Number: 489  
T-614 group 1 (n = 163)  
T-614 group 2 (n = 163)  
MTX group (n = 163)  
Sex: female/male = 418:81  
Placebo group: placebo tablets | T-614 group 1: T-614 25 mg daily for the first 4 weeks and 50 mg daily for the subsequent 20 weeks  
T-614 group 2: T-614 50 mg per day  
MTX group: MTX 10 mg weekly for the first 4 weeks and 15 mg weekly for the subsequent 20 weeks | 24 weeks of clinical assessment at 0, 4, 10, 17, and 24 weeks. | ACR20, ACR50, ACR70, tender joint count, swollen joint count, tender joint score (TJS), swollen joint score (SJS), rest pain, duration of morning stiffness, grip strength, physician and patient global assessment of disease activity, ESR, CRP, and adverse events. | Detailed in article and validity ascertained through telephone. |
| Ishiguro      | Double-blind, randomized, controlled trial  | Country: Japan  
Site: multicenter  
Number: 252  
T-614 + MTX group (n = 164)  
MTX + placebo group (n = 88)  
Sex: female/male = 204:48  
Placebo + MTX group: MTX at low dosages of 6 or 8 mg weekly and folic acid at dosage of 5 mg weekly | T-614 + MTX group: T-614 25 mg daily for the first 4 weeks and 50 mg daily for the subsequent 20 weeks  
MTX + placebo group: MTX at low dosages of 6 or 8 mg weekly and folic acid at dosage of 5 mg weekly | 28 weeks of clinical assessment at 0, 4, 6, 8, 20, 12, 16, 20, and 24 weeks. | ACR20, ACR50, ACR70, tender joint count, swollen joint count, patient's and physician's global assessment of disease activity, HAQ score, DAS28-CRP, ESR, CRP, and adverse events. | Described in article but not validated because the author could not be reached via email. |
against cartilage destruction and bone erosion in collagen-induced arthritis rats [5]. In addition, iguratimod decreased production of matrix metalloproteinases (MMP-1 and MMP-3) and inhibits the migratory expansion of rheumatoid synovial fibroblasts in vitro [7]. Although iguratimod has been used to treat RA for 10 years since 2003, no systematic review has been done on its efficacy and safety. Therefore, we conducted this systematic review to assess the efficacy and safety of iguratimod (T-614) for RA.

2. Materials and Methods

2.1. Types of Studies and Inclusion and Exclusion Criteria

2.1.1. Types of Studies. All randomized clinical trials (RCTs) were published in all journals, with a minimum duration of study of at least six months (or 24 weeks).

2.1.2. Types of Participants

(1) Inclusion Criteria. Patients with clinical diagnosis of rheumatoid arthritis (RA) of all eligible RCTs according to the American Rheumatism Association (ARA) criteria are enrolled within the inclusion criteria. Age of patients with only RCTs was at least 18 years old, and sex, race, and region of patients were not limited. These patients must have active rheumatoid arthritis (RA) of all eligible RCTs according to the American Rheumatism Association (ARA) criteria are enrolled within the inclusion criteria. Age of patients with only RCTs was at least 18 years old, and sex, race, and region of patients were not limited. These patients must have active

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(2) Exclusion Criteria. The studies on patients with both RA and cancer, abnormal hepatic dysfunction or renal dysfunction, or pregnant women and patients with diabetes mellitus,
Table 3: Summary of the findings for the main comparison: iguratimod compared to the other DMARDs (MTX and SASP) for rheumatoid arthritis.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
|                                        | Assumed risk Other DMARDs (MTX and SASP) | Corresponding risk Iguratimod | RR 0.87 (0.75 to 1.02)       | 533 (2 studies)                 | ⊕⊕⊕_normalize
d Grade 1 Important |
| ACR20/24 weeks                         | 581 per 1000                            | 505 per 1000 (435 to 592) |                              |                                 |          |
| Tender joint count                     | The mean tender joint count in the intervention groups was −0.01 lower (−0.18 lower to 0.16 higher) | 533 (2 studies) | | ⊕⊕⊕_normalize
d Grade 1 Important |
| Swollen joint count                    | The mean swollen joint count in the intervention groups was −0.15 lower (−0.32 lower to 0.02 higher) | 533 (2 studies) | | ⊕⊕⊕_normalize
d Grade 1 Important |
| Assessment of rest pain                | The mean assessment of rest pain in the intervention groups was −0.10 lower (−0.27 lower to 0.07 higher) | 530 (2 studies) | | ⊕⊕⊕Normalize
d Grade 1 Important |
| Physician global assessment of disease activity | The mean physician global assessment of disease activity in the intervention groups was −0.03 higher (−0.14 lower to 0.20 higher) | 533 (2 studies) | | ⊕⊕⊕Normalize
d Grade 1 Important |
| Patient global assessment of disease activity | The mean patient global assessment of disease activity in the intervention groups was −0.05 lower (−0.22 lower to 0.12 higher) | 531 (2 studies) | | ⊕⊕⊕Normalize
d Grade 1 Important |
| HAQ score                              | The mean HAQ score in the intervention groups was −0.09 higher (−0.08 lower to 0.26 higher) | 533 (2 studies) | | ⊕⊕⊕Normalize
d Grade 1 Important |
| CRP                                    | The mean CRP in the intervention groups was −0.13 lower (−0.3 to 0.04 lower) | 532 (2 studies) | | ⊕⊕⊕Normalize
d Grade 1 Important |
| ESR                                    | The mean ESR in the intervention groups was −0.05 lower (−0.22 lower to 0.12 higher) | 523 (2 studies) | | ⊕⊕⊕Normalize
d Grade 1 Important |

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio; MTX: methotrexate; SASP: salazosulfapyridine.

GRADE working group grades of evidence.

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

1Random sequence of one study cannot mention how to be generated in detail, and no intent-to-treat analysis was included.
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1 of records identified from Chinese databases; 4 from PubMed; 9 from Embase; 2 from Ovid, 5 from ICRTP

15 of records after duplicates removal

15 of records screened

9 of records excluded. 4 among 9 of records excluded with reason of nonclinical trials and 5 of records with reason of ongoing trial without outcomes reported.

6 of full-text articles for eligibility

1 of full-text articles excluded with reason of non-RCT; 1 of full-text articles excluded with reason of the same study.

4 of studies included in qualitative synthesis (meta-analysis)

Figure 1: Search study flow diagram.

(2) Secondary Outcomes. Secondary outcome measures included health-related quality of life (HRQoL) of the patients, reported side effects, total number of patients withdrawn from the studies, and withdrawals due to adverse events.

We defined serious adverse events according to the ICH Guidelines [11] as any event that led to death, that was life-threatening, and required in-patient hospitalization or prolongation of existing hospitalization, and that resulted in persistent or significant disability and as any important medical events, which might have jeopardized the patient or required intervention to prevent them. We did not consider other adverse events to be serious.

2.2. Search Methods for Identification of Studies

2.2.1. Electronic Search. We searched the Cochrane Central Register of Controlled Trials (the Cochrane Library, 11 July 2012), PubMed (1950 to 29 March 2013), Embase (1980 to 29 March 2013), the Chinese Biomedical Database (CBM) (1975 to 18 March 2013), China National Knowledge Infrastructure (CNKI) (1917 to 18 March 2013), VIP Database (1989 to 18 March 2013), and the WHO ICTRP (18 March 2013).

2.2.2. Search Strategy. Search strategy for the Cochrane Library, PubMed, Embase, and so forth, in English is given as follows:

#1 iguratimod
#2 T-614
#3 CAS 123663-49-0

Figure 2: Risk of bias in the 4 studies included.

Figure 3: Summary of risk bias in the 4 studies included.
### 2.2.1 Iguratimod versus placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Iguratimod</th>
<th>Placebo</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Hara (2007)</td>
<td>132</td>
<td>64</td>
<td>22.5%</td>
</tr>
<tr>
<td>Lü (2008)</td>
<td>93</td>
<td>95</td>
<td>24.1%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>225</strong></td>
<td><strong>159</strong></td>
<td><strong>46.6%</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Heterogeneity: χ² = 2.01; df = 1 (P = 0.16); I² = 50% |
| Test for overall effect: Z = 4.47 (P < 0.00001) |

### 2.2.2 Iguratimod + MTX versus placebo + MTX

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Iguratimod + MTX</th>
<th>Other DMARDs</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Ishiguro (2013)</td>
<td>114</td>
<td>88</td>
<td>53.4%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>164</strong></td>
<td><strong>88</strong></td>
<td><strong>53.4%</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Heterogeneity: not applicable |
| Test for overall effect: Z = 4.86 (P < 0.00001) |

### 3.10.1 Iguratimod versus MTX

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Iguratimod</th>
<th>MTX</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Lü (2009)</td>
<td>63</td>
<td>70</td>
<td>57.5%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>163</strong></td>
<td><strong>163</strong></td>
<td><strong>57.5%</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Heterogeneity: not applicable |
| Test for overall effect: Z = 1.94 (P = 0.05) |

### 3.10.2 Iguratimod versus SASP

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Iguratimod</th>
<th>SASP</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Hara (2007)</td>
<td>35</td>
<td>103</td>
<td>42.5%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>104</strong></td>
<td><strong>103</strong></td>
<td><strong>42.5%</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Heterogeneity: not applicable |
| Test for overall effect: Z = 0.10 (P = 0.92) |

| **Total (95% CI)** | **266** | **266** | **100.0%** | **0.78 [0.49, 1.24]** |
| **Total events**  | 104      |        |            |                      |

| Heterogeneity: r² = 0.04; χ² = 1.61; df = 1 (P = 0.20); I² = 38% |
| Test for overall effect: Z = 1.04 (P = 0.30) |
| Test for subgroup differences: χ² = 1.61; df = 1 (P = 0.20); I² = 38.0% |

<table>
<thead>
<tr>
<th>Favors [iguratimod]</th>
<th>Favors [other DMARDs]</th>
</tr>
</thead>
</table>

---

**Figure 4:** (a) Comparison of ACR20 at 24 weeks between iguratimod and placebo groups. (b) Comparison of ACR20 at 24 weeks between iguratimod and other DMARDs (MTX and SASP) groups. (c) Comparison of ACR50 at 24 weeks between iguratimod and other DMARDs (MTX and SASP) groups.
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Study or subgroup                                      | Iguratimod | Placebo | Std. mean difference | Std. mean difference |
------------------------------------------------------|------------|---------|----------------------|----------------------|
|                                                      | Mean       | SD      | Total                | IV, fixed, 95% CI    |
| 2.3.1 Iguratimod versus placebo                      |            |         |                      |                      |
| Hara (2007)                                          | −7.1       | 7.9     | 132                  | −3.6                 |
| Lù (2008)                                            | −6         | 8       | 79                   | −2                   |
| Subtotal (95% CI)                                    | 211        |         |                      |                      |
| Heterogeneity: χ² = 0.02; df = 1 (P = 0.88); I² = 0%|            |         |                      |                      |
| Test for overall effect: Z = 3.95 (P < 0.0001)        |            |         |                      |                      |
| Ishiguro (2013)                                      | −7.4       | 6       | 164                  | −4.6                 |
| Heterogeneity: not applicable                         |            |         |                      |                      |
| Test for overall effect: Z = 3.13 (P = 0.002)         |            |         |                      |                      |
| Total (95% CI)                                       | 375        |         | 218                  | 100.0%               |
| Heterogeneity: χ² = 0.06; df = 2 (P = 0.97); I² = 0% |            |         |                      |                      |
| Test for overall effect: Z = 5.04 (P < 0.00001)       |            |         |                      |                      |
|                                                                                      | −0.5 −0.25 | 0 | 0.25 | 0.5 |

(a)

Study or subgroup                                      | Iguratimod 50 mg | Other DMARDs | Std. mean difference | Std. mean difference |
------------------------------------------------------|------------------|--------------|----------------------|----------------------|
|                                                      | Mean             | SD           | Total                | IV, fixed, 95% CI    |
|                                                      | Mean             | SD           | Total                |                      |
| Hara (2007)                                          | −7.8             | 7.5          | 103                  | −7.1                 |
| Lù (2009)                                            | 10.5             | 10.6         | 163                  | 10                   |
| Total (95% CI)                                       | 266              | 267          | 100.0%               | −0.01 [−0.18, 0.16]  |
| Heterogeneity: χ² = 0.71; df = 1 (P = 0.40); I² = 0%|            |         |                      |                      |
| Test for overall effect: Z = 0.06 (P = 0.95)         |            |         |                      |                      |
|                                                                                      | −0.5 −0.25 | 0 | 0.25 | 0.5 |

(b)

Figure 5: (a) Comparison of tender joint count between iguratimod and placebo groups. (b) Comparison of tender joint count between iguratimod and other DMARDs (MTX and SASP) groups.

#4 C17H14N2O6S
#5 Ailamode
#6 N-3-formylamino-4-oxo-6-phenoxy-4H-chrom-en-7-yl-methanesulphonamide
#7 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one
#8 or/#1–7
#9 randomized controlled trials
#10 random
#11 control
#12 trials
#13 or/#9–12
#14 rheumatoid arthritis
#15 (#8, #13, and #14).

We searched the Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), and VIP Database by using the strategy adjusted in Chinese.

2.3. Data Collection and Analysis

2.3.1. Selection of Studies. Three review authors (Jiangtao Li, Hejuan Mao, and Shuo Chen) independently assessed for inclusion all of the potential studies identified as a result of the search strategy. We resolved disagreements through discussion. We included only those studies that used a strict randomization procedure. We telephoned or wrote letter by email to contact the authors of those articles in which “randomly allocated participants” was mentioned to determine whether the randomization procedure was adequate or not.

2.3.2. Data Extraction and Management. We designed a form to extract data for retrieval of records to meet the needs of the project design. For eligible studies, the three review authors extracted the data using the agreed form. We resolved discrepancies through discussion. Where disagreement could not be resolved even through discussion, experts in the area were contacted to make a decision. We input the data into Review Manager software (RevMan Manager version 5.2.4, 2013) and checked them for accuracy.

2.3.3. Assessments Risk of Bias in Included Studies and Quality of Evidence. According to assessing risk of bias in included...
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2.4.1 Iguratimod versus placebo
Hara (2007)

Subtotal (95% CI) 210
Heterogeneity: \( \chi^2 = 1.25; df = 1 (P = 0.26); I^2 = 20\%
Test for overall effect: \( Z = 3.76 (P = 0.0002) \)

Subtotal (95% CI) 210
Heterogeneity: \( \chi^2 = 1.25; df = 1 (P = 0.26); I^2 = 20\%
Test for overall effect: \( Z = 3.76 (P = 0.0002) \)

2.4.2 Iguratimod + MTX versus placebo + MTX
Ishiguro (2013)

Subtotal (95% CI) 164
Heterogeneity: not applicable
Test for overall effect: \( Z = 4.31 (P < 0.0001) \)

Total (95% CI) 374
Heterogeneity: \( \chi^2 = 1.98; df = 2 (P = 0.37); I^2 = 0\%
Test for overall effect: \( Z = 5.65 (P < 0.00001) \)
Test for subgroup differences: \( \chi^2 = 0.73; df = 1 (P = 0.39); I^2 = 0\%

Figure 6: (a) Comparison of swollen joint count between iguratimod and placebo groups. (b) Comparison of swollen joint count between iguratimod and other DMARDs (MTX and SASP) groups.

3. Results and Discussion

3.1 Results

3.1.1 Results of the Search. We identified 21 records by electronic searches and hand searches, including 1 of records indentified from the Chinese database, four from PubMed, nine from Embase, two from Ovid, and five from ICRTP. We excluded 17 records because of duplicate records, non-RCTs, nonclinical trials, the same study, ongoing without outcomes reported, or no full text. At the end, we finalized four studies [2, 14–16] to make quantitative synthesis (meta-analysis) (Figure 1).

3.1.2 Characteristics of Included Studies (Table 1)

1) Types of Studies. All of the four included studies were multicenter, double-blind, randomized controlled trials. Three of them had a placebo control group. The duration of these studies was about six months (from 24 weeks to 28 weeks).
The studies were conducted in China ($n = 2$) and Japan ($n = 2$).

(2) **Participants of Included Studies.** In the four RCT studies included [2, 14–16], in total, 1407 patients with RA were enrolled (1159 females and 248 males; mean age was from 45.9 to 58.2 years old). Diagnosis of RA was based on the American Rheumatism Association (ARA) criteria in 1987 [17] in the two Japanese studies [15, 16] and on the American Rheumatism Association (ARA) criteria in 1991 [18] in the two Chinese studies [2, 15].

(3) **Interventions of Studies Included.** Among the four studies included [2, 14–16], four different types of intervention were used: (a) iguratimod versus placebo and iguratimod versus SASP [14], (b) iguratimod versus placebo [2], (c) iguratimod versus MTX, and (d) iguratimod + MTX versus placebo + MTX [16]. The low dose of MTX (6–8 mg per week) was in the study of iguratimod + MTX versus placebo + MTX, and the low dose of MTX (15 mg per week) was in the study of iguratimod versus MTX. Duration of treatment was 24 weeks [2, 15, 16] and 28 weeks in one study [14].

(4) **Measures of Outcomes.** Primary outcomes (ACR20) and secondary outcomes (tender joint count; swollen joint count; assessment of rest pain; physician global assessment of disease activity; patient global assessment of disease activity; HAQ score; ESR; CRP; adverse events, etc.) were all reported in the four studies included.

### 3.1.3. Assessment of Methodological Quality of Studies Included [13] (Figures 2 and 3)

(1) **Randomized Method and Allocation Concealment.** In all of the four studies included [2, 14–16], randomization was described. In two studies [2, 15], random sequence generation and allocation concealment were detailed, and the validity of method was ascertained by telephone. In the other two studies [14, 16], random sequence generation and allocation concealment were described but not ascertained because the author could not be reached via email. For this reason, some degree risk of selection bias of two studies included [15, 16] existed.

(2) **Blinding of Participants and Personnel.** In all of the four studies [2, 14–16] blinding of participants and personnel was described. Double blinding was detailed in three studies [2, 14, 15] and not mentioned in one study [16]. The author could not be reached via email. For this reason, some degree risk of selection bias of two studies included [15, 16] existed.

### Table 1: Subgroup Analysis (Continued)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Iguratimod 50 mg vs Other DMARDs Study or subgroup Mean</th>
<th>Placebo Mean</th>
<th>Placebo SD</th>
<th>Placebo Total</th>
<th>Weight</th>
<th>Std. mean difference IV, fixed, 95% CI</th>
<th>Std. mean difference IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hara (2007)</td>
<td>$-22.7$</td>
<td>27.7</td>
<td>102</td>
<td>$-21$</td>
<td>28.3</td>
<td>102</td>
<td>$38.5$</td>
</tr>
<tr>
<td>Lü (2009)</td>
<td>$24.9$</td>
<td>28.4</td>
<td>163</td>
<td>$28.7$</td>
<td>26.1</td>
<td>163</td>
<td>$61.5$</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>$265$</td>
<td>$100.0$</td>
<td>$-0.10$</td>
<td>$[-0.27, 0.07]$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Figure 7: (a) Comparison of assessment of rest pain between iguratimod and placebo groups. (b) Comparison of assessment of rest pain between iguratimod and other DMARDs (MTX and SASP) groups.
not be reached via email. Thus, low risk of performance bias and detection bias of outcome assessment existed.

(3) Incomplete Outcome Data. Withdrawals, dropouts, loss of followup, and intent-to-treat analysis were reported in detail in two studies included [2, 15] and were not described in the other two studies included [14, 16]. Therefore, high risk of attrition bias in general existed.

(4) Selective Reporting Bias. The four studies [2, 14–16] included reported all outcomes, including adverse events. There was no selective reporting bias.

(5) Other Biases. Baseline information including sex, age and secondary outcomes of the four studies [2, 14–16] was described in detail, and outcomes of different groups had robust comparability. Sample sizes of three studies [2, 15, 16] were estimated. All of the studies included were conducted in general hospitals or good clinical practice bases of medical universities, with all of which having high scientific research level and thus reducing other risk biases of these studies to a large extent.

3.1.4. Meta-Analysis

(1) Primary Outcomes

(a) ACR20, ACR50, and ACR70 at 24 Weeks. Superiority pooled analysis of three studies [2, 14, 16] included shows that ACR20 at 24 weeks among patients with RA in the iguratimod group was significantly superior to that of the placebo group (RR = 2.35, 95% CI: 1.82, 3.02 in Figure 4(a)). Noninferiority pooled analysis of two studies [14, 15] included showed that ACR20 at 24 weeks among patients with RA in iguratimod group did not differ significantly from that of other DMARDs (MTX and SASP) group (RR = 0.87, 95% CI: 0.75, 1.02 in Figure 4(b)). Only in one study [2], ACR50 at 24 weeks did not differ significantly between the iguratimod group and the placebo group (RR = 0.62, 95% CI: 0.21, 1.82), and ACR70 at 24 weeks differed significantly (RR = 0.06, 95% CI: 0.01, 0.51). ACR50 at 24 weeks did not differ significantly between the iguratimod group and the other DMARDs (MTX and SASP) group [14, 15] (RR = 0.78, 95% CI: 0.49, 1.24 in Figure 4(c)). Only in one study [15], ACR70 at 24 weeks did not differ
significantly between the iguratimod group and the other DMARDs (MTX) group (RR = 0.75, 95% CI: 0.43, 1.32).

(b) Tender Joint Count. Superiority analysis of three studies [14] included showed that tender joint count among patients with RA in the iguratimod group reduced more than that of the placebo group with a significant difference (MD = −0.44, 95% CI: −0.61, −0.27 in Figure 5(a)). Noninferiority analysis of two studies [14, 15] included showed that tender joint count among patients with RA in the iguratimod group and in the other DMARDs (MTX and SASP) group did not differ significantly (MD = −0.01, 95% CI: −0.18, 0.16 in Figure 5(b)).

c) Swollen Joint Count. Superiority analysis of three studies [2, 15, 16] included showed that swollen joint count among patients with RA in the iguratimod group reduced more than that of the placebo group with a significant difference (MD = −0.49, 95% CI: −0.66, −0.32 in Figure 6(a)). Noninferiority analysis of two studies [14, 15] included showed that swollen joint count among patients with RA in the iguratimod group and in the other DMARDs (MTX and SASP) group did not differ significantly (MD = −0.15, 95% CI: −0.32, 0.02 in Figure 6(b)).

d) Assessment of Rest Pain. Superiority analysis of three studies included [2, 14, 16] showed that assessment of rest pain among patients with RA in the iguratimod group was worse than that of the placebo group with a significant difference (MD = −0.71, 95% CI: −0.89, −0.54 in Figure 7(a)). Noninferiority analysis of two studies included [14, 15] shows that assessment of rest pain among patients with RA in the iguratimod group and in the other DMARDs (MTX and SASP) group did not differ significantly (MD = −0.10, 95% CI: −0.27, 0.07 in Figure 7(b)).

e) Physician Global Assessment of Disease Activity. Superiority analysis of three studies included [2, 15, 16] showed that physician global assessment of disease activity among patients with RA in the iguratimod group reduced more than that of the placebo group with a significant difference (MD = −0.74, 95% CI: −0.93, −0.57 in Figure 8(a)). Noninferiority analysis of two studies included [14, 15] showed that physician global assessment of disease activity among patients with RA in the iguratimod group and in the other DMARDs (MTX and SASP) did not differ significantly (MD = 0.06, 95% CI: −0.32, 0.44 in Figure 8(b)).

(f) Patient Global Assessment of Disease Activity. Superiority analysis of three studies included [14–16] showed that patient
global assessment of disease activity among patients with RA in the iguratimod group reduced more than that of placebo group with a significant difference (MD = −0.58, 95% CI: −0.80, −0.36 in Figure 9(a)). Non-inferiority analysis of two studies included [14, 15] showed that ESR among patients with RA in the iguratimod group and in the other DMARDs (MTX and SASP) group did not differ significantly (MD = −0.13, 95% CI: −0.30, 0.04 in Figure 11(b)).

\( (i) \) Erythrocyte Sedimentation Rate (ESR). Superiority analysis of three studies included [14–16] showed that ESR among patients with RA in the iguratimod group decreased more than that of the placebo group with a significant difference (MD = −0.64, 95% CI: −0.81, −0.46 in Figure 12(a)). Non-inferiority analysis of two studies included [14, 15] showed that ESR among patients with RA in the iguratimod group and in the other DMARDs (MTX and SASP) group did not differ significantly (MD = −0.05, 95% CI: −0.22, 0.12 in Figure 12(b)).

\( (j) \) Radiographic Change of Bone and Joint Damage. Radiographic change of bone and joint damage was not analyzed for trials of under one year of duration.
Study or subgroup | Iguratimod 50 mg | Placebo | Std. mean difference IV, fixed, 95% CI | Std. mean difference IV, fixed, 95% CI
---|---|---|---|---
2.9.1 Iguratimod versus placebo | Hara (2007) | 0.7 | 3.8 | 127 | 0.3 | 2.2 | 62 | 31.0% | −0.30 | [−0.60, 0.01] |
| Lü (2008) | −1.81 | 19.55 | 79 | 0 | 15.26 | 67 | 27.2% | −0.10 | [−0.43, 0.22] |
| Subtotal (95% CI) | 206 | 129 | 58.1% | −0.21 | [−0.43, 0.02] |

Test for overall effect: $Z = 1.81 (P = 0.07)$

Adverse events of the four studies included reported. No fatal adverse events were reported. No adverse events were reported.

(3) Quality of GRADE Evidence. Assessment for quality of evidence was made using GRADE profiler software recommended by the Cochrane Collaboration. The result of assessment for the four studies included was moderate quality (Tables 2 and 3).

3.2. Discussion. This systematic review included four eligible studies [2, 14–16]. In three studies, superiority pooled analysis of outcomes showed a significant difference between the iguratimod group and the placebo group with RA. Results showed that iguratimod obviously improved ACR20 and ACR70 at 24 weeks, and patients’ health assessment questionnaire (HAQ) score showed reduced rest pain, tender joint count, and swollen joint count; lowered CRP level and ESR; and lowered physician and patient global assessment level of disease activity, but ACR50 at 24 weeks has no significant difference. In two studies [14, 15], noninferiority pooled analysis showed no significant difference between the iguratimod group and the other DMARDs (MTX and SASP) group. Iguratimod was not superior to the other DMARDs (MTX and SASP) in treating RA. All of the four studies [2, 14–16] reported adverse events of iguratimod in treating RA. No significant difference was found in adverse events between the iguratimod group and the placebo group (RR = 1.17, 95% CI: 0.41, 3.31 in Figure 13(b)) or between the iguratimod group and the other DMARDs group (MTX and SASP) (RR = 1.14, 95% CI: 0.80, 1.62 in Figure 13(b)). Adverse events mainly included leucopenia, abnormal level function, upper digestive tract disorder, skin rash, or pruritus. No fatal adverse events were reported.
The units carrying out studies included are all general hospitals or good clinical practice bases of medical universities that have high scientific research diathesis and abilities. Duration and dosage of iguratimod had homogeneity. The evidence of the studies included is moderate quality by carrying out GRADE profiler 3.6 software in spite of some degree-selective biases and no intent-to-treat analyses.

This systematic review has two limitations. First, both the number and the sample size of the studies included are too small. Second, these studies were conducted either in China or in Japan. Similar trials in other countries and regions were not indentified in this review, thus making our review results not representative enough.

In the four studies included [2, 14–16], two described in detail the randomization procedure, allocation concealment, and blinding. We ascertained the validity of the two studies [14, 15] by telephone. For the other two studies [14, 16], we could not reach the authors by email to validate the randomization procedure, allocation concealment, and blinding. Two studies [14, 16] did not have intent-to-treat analysis, and we speculated that participants enrolled were included because of incomplete data. This shortage of two studies [15, 16] made it difficult for us to assess the rationality of study design, and reliability and validity of study results, to some degree, have affected the application of evidence. We hope that future researchers can try to avoid such weaknesses.

4. Conclusions

In summary, this systemic review shows that iguratimod is relatively safe and effective in treating RA and its efficacy is the same as that of MTX and SASP. Nevertheless, due to methodological defects, small number, and small sample size of the studies included, we still do not know whether iguratimod is as effective as other DMARDs besides MTX and SASP. We suggest that more high-quality and large-scaled RCTs should be done to determine the efficacy and safety of iguratimod for RA and whether iguratimod is as effective as other DMARDs besides MTX and SASP.

Conflict of Interests

The authors of the paper have no conflict of interests with the manufacturers of iguratimod, RevMan, and GRADE profiler.
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### References


