Abstract. – OBJECTIVE: Iguratimod is a new kind of synthetic small molecule disease modified anti-rheumatic drug with good efficacy for rheumatoid arthritis (RA) treatment; meanwhile, it exhibits potency to alleviate alveolar inflammation and pulmonary fibrosis. However, its application in RA interstitial lung disease (ILD) patients is seldomly reported. Thus, the current study aimed to investigate the efficacy and safety of iguratimod plus glucocorticoid/cyclophosphamide vs. glucocorticoid/cyclophosphamide in treating RA-ILD patients.

PATIENTS AND METHODS: Totally 101 RA-ILD patients underwent glucocorticoid/cyclophosphamide (Control group: n=61) or iguratimod plus glucocorticoid/cyclophosphamide (Iguratimod group: n=40) treatment were analyzed. General inflammation, disease activity, serum disease marker levels, high resolution lung computed tomography (HRCT) score, lung function indexes were evaluated within 24-week (W) treatment.

RESULTS: No difference of baseline demographic or disease-related features was observed between Iguratimod group and Control group. Iguratimod group showed lower levels of CRP and ESR at W4, W12 and W24; as well as decreased DAS28 score, rheumatoid factor and anti-cyclic citrullinate peptide antibody levels at W12 and W24 compared to Control group. HRCT score showed no difference between Iguratimod group and Control group at any time points. As to lung function indexes, forced vital capacity percent predicted [FVC (% predicted)], carbon monoxide diffusion capacity percent predicted [DLCO (%predicted)] and 6-minute-walk distance (6MWD) were all higher in iguratimod group compared with Control group at W4, W12 and W24. Besides, no difference in adverse events was discovered between these two groups.

CONCLUSIONS: Iguratimod attenuates general inflammation, disease activity, and improves lung function in RA-ILD patients.

Key Words: Iguratimod, Rheumatoid arthritis, Interstitial lung disease, Efficacy, Safety.

Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases that affects around 0.5-1.0% population worldwide. In recent decades, RA attracts more and more attention, which is not only due to its direct harm to the affected synovium and cartilage, but also result from its indirect extra-articular manifestations such as Sjögren’s syndrome, interstitial lung disease (ILD), vascular damage, etc. Among these RA related extra-articular manifestations, ILD occurs in 7.7-67.0% RA patients; besides, ILD is obligated to the majority of cases of morbidity and/or mortality in RA. In consequence, the effort to explore novel and effective treatment options for RA-ILD patients is never stopped.

Iguratimod, a new kind of synthetic small molecule disease modified anti-rheumatic drug (DMARD) which is recently marketed in China...
and Japan, presents with good treatment potency for RA benefiting from its inhibition of immunoglobulins, inflammatory cytokines, T lymphocytes; and its regulation of bone metabolism/formation via osteoclast differentiation, migration as well as bone resorption\(^5\). In clinical settings, iguratimod attenuates inflammation, disease activity and put off bone erosion to some extent in RA patients, which also shows good tolerance\(^6-8\). Besides, iguratimod exhibits potency to alleviate alveolar inflammation and pulmonary fibrosis via regulating matrix metalloproteinase-9 (MMP9) and fibroblast-to-myofibroblast transition\(^9,10\). Considering the above data, it is hypothesized that iguratimod may be an optional treatment for RA-ILD.

Therefore, the current study aimed to investigate the efficacy and safety of iguratimod plus glucocorticoid/cyclophosphamide versus glucocorticoid/cyclophosphamide in treating RA-ILD patients.

### Grouping and Treatment

Depending on the treatment regimen, patients were categorized as Control group (n=61) or Iguratimod group (n=40). In the Control group, patients received the treatment of glucocorticoid (0.5-1.0 mg/kg/day of prednisone) combined with intravenous drip of cyclophosphamide (20 mg/kg once a month for 6 consecutive months). In the Iguratimod group, patients received the treatment of iguratimod (25 mg each time, twice a day) combined with glucocorticoid and cyclophosphamide (the same usage and dosage as the Control group).

### Data Collection and Assessment

The demographic characteristics including age and gender of patients were recorded, then the assessed data were collected as follows: (1) serum indexes: (a) erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) before treatment (W0), at week 4 after initiation of treatment (W4), at week 12 after initiation of treatment (W12), and at week 24 after initiation of treatment (W24); (b) rheumatoid factor (RF) and anti-cyclic citrullinate peptide antibody (CCP-Ab) at W0, W12 and W24; (2) disease activity: disease activity score using 28 joint counts based on ESR (DAS28 score (ESR)) at W0, W4, W12, and W24; (3) high resolution lung computed tomography (HRCT) assessment\(^13\): HRCT score (the higher score, the more severe disease) at W0, W12, and W24\(^13\); (4) pulmonary function: forced vital capacity percent predicted (FVC (% predicted)), carbon monoxide diffusion capacity percent predicted [DLCO (% predicted)]\(^14,15\), and 6-minute-walk distance (6MWD)\(^16\) at W0, W4, W12, and W24; (5) adverse events occurred during the treatment.

### Statistical Analysis

SPSS 24.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 7.02 (GraphPad Software Inc., San Diego, California, USA) were applied for the data analyses and diagram plotting. The quantitative data were described in the form of median with interquartile range (IQR), or mean with standard deviation (SD). The categorized counting data were described with numbers and proportions. The Chi-square test (or Yates’ corrected Chi-square), the Student’s t-test, or the Mann-Whitney U test were carried out for the difference analyses between two groups. A two-side p-value <0.05 was defined as statistical significance.
Results

Patients’ Characteristics

Patients had a mean age of 59.9±9.4 years with 77.5% females/22.5% males in Iguratimod group; while patients had a mean age of 58.1±9.8 years with 82.0% females/18.0% males in Control group. It was of note that no difference in any characteristics was observed between Iguratimod group and Control group regarding age, gender, CRP, ESR, DAS28 score, RF, CCP-Ab, HRCT score, FVC (%predicted), DLCO (% predicted) and 6MWD (Table I).

Iguratimod Decreased Inflammation and Disease Activity

Iguratimod group showed lower levels of CRP and ESR at W4, W12 and W24 (Figure 1A-B), as well as decreased DAS28 score at W12 and W24 (Figure 1C) compared to Control group. Furthermore, Iguratimod group exhibited lower RF and CCP-Ab levels at W12 and W24 compared to Control group (Figure 1D-E).

Iguratimod Improved Lung Function

HRCT score showed no difference between Iguratimod group and Control group at any time points (Figure 2). Notably, FVC (%predicted), DLCO (% predicted) and 6MWD were all higher in Iguratimod group compared with Control group at W4, W12 and W24 (Figure 3A-C).

Adverse Events

The most common adverse events were WBC decrease (10.0%), followed by ALT increase (5.0%) and upset stomach (2.5%) in Iguratimod group. Further analyses observed no difference of WBC decrease, ALT increase, upset stomach or PLT decrease between Iguratimod group and Control group (Table II).

Discussions

Since introduction to the market, iguratimod has been proposed to treat several autoimmune diseases such as RA, Sjögren’s syndrome and ankylosing spondylitis, etc.6,17,18. In RA patients, a previous randomized controlled trial reveals that iguratimod plus methotrexate attenuate lesioned joints, inflammation, disease activity and quality of life compared to methotrexate alone19; besides, another study20 discloses that for refractory RA patients who respond inadequately to methotrexate, cyclosporin A, hydroxychloroquine and prednisone, the addition of iguratimod would cripple disease inflammation and activity; furthermore, a recent meta-analysis6 reports that addition of iguratimod improves treatment response but does not increase adverse events in RA patients. However, the application of iguratimod in RA-ILD patients is never reported. So, we performed this study and aimed to explore

<table>
<thead>
<tr>
<th>Table I. Characteristics of RA-ILD patients.</th>
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<tbody>
<tr>
<td><strong>Items</strong></td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Gender, No. (%)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>CRP (mg/L), median (IQR)</td>
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<tr>
<td>ESR (mm/h), median (IQR)</td>
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<tr>
<td>DAS28 score (ESR), mean ± SD</td>
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<td>RF (IU/mL), median (IQR)</td>
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<tr>
<td>CCP-Ab (U/mL), median (IQR)</td>
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<tr>
<td>HRCT score, mean ± SD</td>
</tr>
<tr>
<td>FVC (% predicted), mean ± SD</td>
</tr>
<tr>
<td>DLCO (% predicted), mean ± SD</td>
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<tr>
<td>6MWD (m), mean ± SD</td>
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RA-ILD, rheumatoid arthritis (RA) associated interstitial lung disease (ILD); SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS28, disease activity score using 28 joint counts; RF, rheumatoid factor; CCP-Ab, cyclic citrullinated peptide antibody; HRCT, high-resolution computed tomography; FVC, forced vital capacity; DLCO, carbon monoxide diffusion capacity; 6MWD, 6-minute-walk distance.
this issue, which found that iguratimod plus glucocorticoid/cyclophosphamide significantly decreased inflammation, disease activity and serum markers compared to glucocorticoid/cyclophosphamide in RA-ILD patients. The possible explanations were as follows: (1) iguratimod attenuated systemic inflammatory cytokines and regulated T cell subsets to decrease inflammation and serum marker levels; (2) iguratimod relieved synovium hyperplasia and inflammation, as well as cartilage damages/absorption to decrease overall disease activity.

Apart from the effect of iguratimod on general disease activity of RA-ILD patients, its effect on HRCT score and lung function indexes were also evaluated in our study. We observed that iguratimod plus glucocorticoid/cyclophosphamide did not decrease HRCT score, but markedly increased lung function indexes such as FVC (% predicted), DLCO (% predicted) and 6MWD compared to glucocorticoid/cyclophosphamide in RA-ILD patients. The possible explanations were as follows: (1) iguratimod alleviated alveolar inflammation and pulmonary fibrosis via regulating MMP9 and fibroblast-to-myofibroblast transition, therefore increased the lung function of patients; (2) iguratimod showed better efficacy regarding overall inflammation and disease activity of RA, then indirectly increased the lung function.

Figure 1. Comparison of inflammation and disease activity. Comparison of CRP (A), ESR (B), DAS28 (C), RF (D) and CCP-Ab (E) at each time point between Iguratimod group and Control group.

Figure 2. Comparison of HRCT score at each time point between Iguratimod group and Control group.
Iguratimod for RA-ILD patients

Function of patients. Besides, iguratimod plus glucocorticoid/cyclophosphamide showed similar adverse events compared to glucocorticoid/cyclophosphamide, indicating the iguratimod was well tolerated in RA-ILD patients.

There were some limitations in this study: (1) The study was a cohort-study design instead of randomized, controlled study, so some potential compounding factors might exist to affect the results; (2) the follow-up duration was a little short with 24 weeks, thus, long-term efficacy and safety profile of iguratimod in treating RA-ILD patients needed further exploration; (3) this was a single-center study, evaluation and patient chosen bias existed, therefore, subsequent multiple-center study was needed.

Conclusions

In summary, iguratimod attenuates general inflammation, disease activity, and improves lung function in RA-ILD patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Table II. Adverse events.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group (n = 61)</th>
<th>Iguratimod group (n = 40)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>WBC decrease, No. (%)</td>
<td>0 (0.0)</td>
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<td>ALT increase, No. (%)</td>
<td>5 (8.2)</td>
<td>2 (5.0)</td>
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<td>Upset stomach, No. (%)</td>
<td>3 (4.9)</td>
<td>1 (2.5)</td>
<td>0.930</td>
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<tr>
<td>PLT decrease, No. (%)</td>
<td>2 (3.3)</td>
<td>0 (0.0)</td>
<td>0.670</td>
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</tbody>
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WBC, white blood cell; PLT, platelet; ALT, alanine transaminase.
References