Effects of combination of Iguratimod and NSAID on clinical indices and inflammatory markers in patients with rheumatoid arthritis

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Abstract: Objectives: We examined the effects of a treatment combining Iguratimod and NSAID on clinical indices and inflammatory markers in patients with rheumatoid arthritis. Patients and Methods: Forty patients with rheumatoid arthritis were randomized to control group (n = 20; treatment with NSAID only, Celebrex 400 mg, b.i.d.) and study group (n = 20; Iguratimod 25 mg b.i.d. and Celebrex 400 mg b.i.d). The treatment went on for 12 weeks. We compared the changes of VAS index and inflammatory markers, including erythrocyte sedimentation rate, levels of C-reactive protein, rheumatoid factor and anti-cyclic citrullinated peptide (CCP antibody). We further analyzed the incidence of adverse effects between patient groups before and during the treatment. Results: Both NSAID alone and the combination of NSAID with Iguratimod were comparable in the effects on patients’ symptoms (VAS index). However, combined treatment was more effective in decreasing inflammatory markers compared with control group (P<0.05 for every marker). Adverse events were mild and rare in both group, indicating good tolerance of both drugs. Conclusion: Iguratimod in a combination with NSAID exerts beneficial effects in RA.

Keywords: Rheumatoid arthritis, Iguratimod, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, ring citrulline peptide, antibody
patients. Lguratimod is purchased form Jiangsu Simcere Pharmaceutical. Twenty patients were randomized to study group and received Iguratimod (25 mg b.i.d.) and Celebrex (400 mg b.i.d.), another 20 patients were randomized to the control group with the treatment of Celebrex 400 mg b.i.d. alone. All patients met the diagnostic criteria for RA and also satisfied the following requirements. First, patients were in an active stage of the disease, which was demonstrated by the presence of four of five symptoms: the presence of above-average pain in the joints at rest, morning stiffness lasting for ≥1 hour, joint swelling of ≥3, joint tenderness of ≥5, and erythrocyte sedimentation rate of ≥28 mm/h. Second, they had to discontinue the use of all types of anti-rheumatic drugs for more than two weeks before the enrollment.

Exclusion criteria were drug allergy, severe diseases of the heart, liver, kidneys or other vital organs, recent severe infections, pregnancy or breast-feeding, mental disorders, alcohol or drug abuse.

Patients information is shown in Table 1. Both groups were comparable for gender distribution and age.

Table 1. Patient gender and age

<table>
<thead>
<tr>
<th></th>
<th>Control group (Celebrex treatment)</th>
<th>Study group (Iguratimod + Celebrex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>3/17</td>
<td>3/17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.90 ± 12.82</td>
<td>41.60 ± 11.35</td>
</tr>
</tbody>
</table>

Upon enrollment, patients were informed their treatment plans. Patients were asked to use drugs according to this plan. To control for proper compliance, we inquired about drug use during clinical outpatient visits. The study went on for 3 months. Clinic visits took place before the treatment, and then on weeks 2, 4, 8, and 12 during the treatment. We recorded patients’ visual analog pain (VAS) index of rest pain and examined erythrocyte sedimentation rate, levels of C-reactive protein, rheumatoid factor and anti-cyclic citrullinated peptide (CCP antibody). We also monitored liver enzymes and kidney metabolism, and recorded adverse events, including their time, severity, duration, administered treatment, outcomes, and whether the use of study medications was terminated.

Results

During the treatment for 12 weeks, there were no patient dropouts. Adverse events occurred in five patients and included two patients in control group (NSAID only) and three patients in study group (Iguratimod combined with NSAID). These adverse events included upper abdominal discomfort, anorexia, diarrhea, and other gastrointestinal symptoms. The adverse effects subsided after administration of oral proton pump inhibitors. Furthermore, one patient in study group exhibited a transient ALT increase. The treatment was stopped and the patient was given reduced glutathione medicine for two weeks. After that, the treatment was resumed. There were no cases of liver or kidney dysfunction, gastrointestinal ulcers, rashes or other adverse events. The overall drug compliance was satisfying.

The results of VAS index changes and laboratory examinations are shown in Tables 2-6. In addition, Figure 1 demonstrates the dynamics of VAS indexes and laboratory examinations.

Both treatments showed comparable effects on clinical indices (VAS). However, combined treatment more profoundly diminished the tested inflammatory markers.

Discussion

In our study, both NSAID and their combination with Iguratimod were comparable in their effects on the improvement of patients’ symptoms. Combining treatment group, however, more effectively decreased inflammatory markers.

We focused on anti-inflammatory effects and suppression of immunoglobulins by Iguratimod.
Iguratimod cooperate with NSAID in RA

Table 2. Changes of VAS

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (Celebrex treatment)</td>
<td>5.87 ± 1.02</td>
<td>3.74 ± 0.91</td>
<td>2.84 ± 0.69</td>
<td>2.02 ± 0.66</td>
<td>1.74 ± 0.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Study group (Iguratimod + Celebrex)</td>
<td>6.02 ± 1.11</td>
<td>3.39 ± 0.85</td>
<td>2.55 ± 0.71</td>
<td>1.83 ± 0.45</td>
<td>1.51 ± 0.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P</td>
<td>0.649</td>
<td>0.209</td>
<td>0.198</td>
<td>0.295</td>
<td>0.115</td>
<td></td>
</tr>
</tbody>
</table>

Footnote: data are shown as mean ± SD.

Table 3. Changes of erythrocyte sedimentation rates

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (Celebrex treatment)</td>
<td>47.95 ± 6.62</td>
<td>38.30 ± 7.73</td>
<td>35.35 ± 7.29</td>
<td>29.95 ± 6.81</td>
<td>23.35 ± 5.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Study group (Iguratimod + Celebrex)</td>
<td>49.80 ± 7.10</td>
<td>27.55 ± 4.26</td>
<td>21.35 ± 4.40</td>
<td>16.80 ± 3.02</td>
<td>14.95 ± 3.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P</td>
<td>0.399</td>
<td>&lt;0.001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Footnote: data are shown as mean ± SD.

Table 4. Changes of C-reactive protein

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (Celebrex treatment)</td>
<td>32.95 ± 7.44</td>
<td>27.30 ± 5.89</td>
<td>24.00 ± 5.04</td>
<td>18.85 ± 4.36</td>
<td>11.65 ± 2.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Study group (Iguratimod + Celebrex)</td>
<td>31.70 ± 8.02</td>
<td>18.40 ± 4.20</td>
<td>13.95 ± 3.44</td>
<td>10.95 ± 2.70</td>
<td>7.55 ± 2.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P</td>
<td>0.61</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Footnote: data are shown as mean ± SD.

Table 5. Changes in rheumatoid factor

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (Celebrex treatment)</td>
<td>492.9 ± 121</td>
<td>393.4 ± 95.78</td>
<td>395.5 ± 108</td>
<td>308.8 ± 94.32</td>
<td>238.1 ± 80.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Study group (Iguratimod + Celebrex)</td>
<td>465.2 ± 130.4</td>
<td>307.5 ± 114.4</td>
<td>248.8 ± 101.4</td>
<td>179.8 ± 78.37</td>
<td>115.2 ± 51.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P</td>
<td>0.49</td>
<td>0.014</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Changes of antibody-cyclic citrullinated peptide

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (Celebrex treatment)</td>
<td>36.50 ± 7.66</td>
<td>29.75 ± 7.95</td>
<td>27.75 ± 8.51</td>
<td>24.10 ± 7.64</td>
<td>22.10 ± 6.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Study group (Iguratimod + Celebrex)</td>
<td>36.60 ± 6.58</td>
<td>25.95 ± 6.36</td>
<td>22.55 ± 5.42</td>
<td>17.70 ± 6.02</td>
<td>13.85 ± 6.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P</td>
<td>0.965</td>
<td>0.103</td>
<td>0.027</td>
<td>0.006</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

In previous studies, Iguratimod significantly reduced IgM levels, inhibited generation of IgG antibodies without affecting cell proliferation, and modulated immunoglobulin subsets levels [17-20]. Also, Iguratimod down-regulated expression of TNF-α, INF-γ, IL-1β, IL-4, IL-6, and IL-17 in experimental studies, and production of MMP-1 and MMP-3 both in clinical and experimental studies [21-23]. In addition, this drug was shown to modulate fibroblast production of collagen which addresses ossification in RA. Furthermore, by activating osteoclasts and fibroblasts, the drug exerted bone-protecting effects [24-28], promoted osteoblast differentiation, increased expression of osteoblast-specific transcription factor Osx, and facilitated the bone morphogenetic protein-2 mediated bone formation. Thus, due to beneficial changes in bone cell metabolism, bone or joint damage in RA is reduced or reversed.

Importantly, adverse events were rare and were mild, indicating good tolerance of this drug.

In conclusion, we demonstrate that Iguratimod in combination with NSAID exerts beneficial effects in RA.

Disclosure of conflict of interest

None.
Lguratimod cooperate with NSAID in RA

![Graphs showing treatment effects](image)

**Figure 1.** Treatment effects.

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References


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