Review: Symposium in the 29th Annual Meeting of Medical and Pharmaceutical Society for WAKAN-YAKU

**Immunoregulation by Kampo medicines - Clinical application to RA-**

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**Introduction**

The immunoregulatory effects of Kampo medicines have been reported since the 1970s, and have been analyzed in various diseases since the 1980s to the present. Due to their expected immunoregulatory and biological defense activities, Kampo medicines have been clinically used for chronic hepatitis C, influenza infection, allergic diseases, autoimmune diseases, malignant tumors, and perinatal medicine. Rheumatoid arthritis (RA) is a representative autoimmune disease that has been clinically treated with Kampo medicines. Kampo medicines have played a certain role in the therapeutic strategies for RA. We have clinically used Kampo medicines for RA, and also evaluated their immunoregulatory effects from various aspects. In this study, we discuss part of the clinical effects of Kampo medicines on RA and their immunoregulatory effects while presenting previous results.

**Biological defense**

Immunoregulation by Kampo medicines is discussed separately from two aspects, i.e., effects on susceptibility to infection (host defense) induced by immune abnormalities in RA and anti-rheumatoid drugs including methotrexate (MTX) and biological preparations (Bio.), and effects on immune abnormalities and associated inflammation in RA (anti-rheumatoid effects). Concerning the former effects, the effects on natural killer cell receptor expression were evaluated at the beginning of the 2000s. In addition, in a study on the adjuvant effects of Kampo medicines on influenza vaccination (Scientific Research Group supported by a Grant from the Ministry of Health, Labour and Welfare), the courses of immune responses after influenza vaccination in RA patients were observed (Table 1). As a result, the influenza antibody titer did not differ between healthy subjects and RA patients receiving Kampo medicines. In RA patients receiving Kampo medicines, effects comparable to or more marked than those in previous studies in RA patients were obtained, showing no influences of influenza vaccination on the disease activity of RA.

**Anti-rheumatoid effects**

For the evaluation of the anti-rheumatoid effects of Kampo medicines, randomized controlled trials (RCTs) are the most important. However, for the evaluation of the effects of Kampo medicines, the accumulation of complete responders is considered to be useful, and we previously reported multiple complete responders. Recently, we encountered a patient with RA developing during postoperative chemotherapy for rectal cancer. In this patient, the disease activity of RA could be controlled by Kampo treatment alone. In such patients, since the influences of strong immune suppression on
the underlying disease are unclear, Kampo medicines are extremely useful when they are effective. On the other hand, as we reported in the symposium of this scientific association in 2011, since the appearance of Biologics, the treatment strategies for RA have markedly changed. In this present situation, to clinically make use of the anti-rheumatoid effects of Kampo medicines, the RA patient population who responds to Kampo medicines (responders) should be clarified. In recent years, we have attempted to identify responders to Kampo medicines in terms of both the autoantibody expression pattern in RA patients and the action mechanism (anti-rheumatoid effects) of Kampo medicines. Using these methods, the anti-tumor effects of Kampo medicines can be clinically applied (Figure 1).

### Table 1

GMTs and fold increase in GMT for influenza A/H3N2, A/H1N1, and B strains in RA patients treated with Kampo formulae before and after administration of influenza vaccines.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Without MTX group*</th>
<th>With MTX group**</th>
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</thead>
<tbody>
<tr>
<td><strong>GMT, mean ± SD</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>A/H1N1 strain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.1 ± 14.0</td>
<td>11.0 ± 12.1</td>
<td>14.1 ± 15.0</td>
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<tr>
<td>4 weeks later</td>
<td>78.8 ± 119.7</td>
<td>39.6 ± 39.3</td>
<td>115.9 ± 148.8</td>
</tr>
<tr>
<td><strong>A/H3N2 strain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.5 ± 13.9</td>
<td>16.0 ± 19.7</td>
<td>11.7 ± 10.2</td>
</tr>
<tr>
<td>4 weeks later</td>
<td>35.7 ± 33.6</td>
<td>33.1 ± 21.8</td>
<td>39.1 ± 40.2</td>
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<tr>
<td><strong>B strain</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>12.8 ± 10.3</td>
<td>13.9 ± 9.2</td>
<td>11.4 ± 11.5</td>
</tr>
<tr>
<td>4 weeks later</td>
<td>27.3 ± 27.8</td>
<td>22.8 ± 19.2</td>
<td>31.4 ± 34.0</td>
</tr>
</tbody>
</table>

* without MTX group: patients treated with classical DMARDs alone, patients treated with tacrolimus hydrate.

** with MTX group: patients treated with MTX, but not biologics.

Abbreviation: GMTs: Geometric mean titers, MTX: methotrexate, DMARD: Disease modifying anti-rheumatic drug.

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**Figure 1** Identification of Kampo Responders among the patients with RA. One of several Kampo formulae is usually administered to RA patients. Therefore, we first attempt to demonstrate the status of responder to representative formula: Keishiniepiittokaryoujutubukaboiogi. The studies to assess traditional concept objectively are divided into 3 groups. Subject of the study is as follows: i) diagnostic methods, ii) traditional pathological concept, and iii) target group of a formula (responders to a formula). The methodology of this scheme applies to the method to detect the target group of a formula (iii). Generally, traditional physical examination has been investigated to determine the target group of a Kampo formula. In contrast, we performed the detection of the responders to a Kampo formula within the patients with RA using 2 methodologies as described below. Because, it is considered that it is impossible to detect the clinical features of responders to a Kampo formula among the patients with varied diseases in Western medicine.

Methodology 1: To clarify the immune status of Kampo responders, Methodology 2: To reveal the action of Kampo formulae on RA.
Conclusion

We discussed the immunoregulation by Kampo medicines in clinical observations. A lot of immunomodulatory effects of Kampo formulae have been demonstrated in vivo and in vitro. From now, it is very important to indicate the methodology to clinically make use of the immunomodulatory effects of Kampo medicines.

Acknowledgements

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References


