Roles of Kampo medicine in treating rheumatic diseases

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An increasing number of reports have recently been published regarding the use of Kampo medicine for treating rheumatic diseases. Corticosteroids are generally prescribed for rheumatic diseases, but in this paper the changes in the disease states after treatment with corticosteroids and Kampo medicines have been examined. As examples of the clinical usefulness of Kampo formulations, Bakumondoto, Jiinkokato, Rokumigan, Hachimijiogan and Unkeito have been reported to increase salivary secretion and improve the immunological disorders of patients with the dry eyes and mouth associated with Sjögren's syndrome. According to several case reports, remission of systemic lupus erythematoses (SLE) and other rheumatic diseases was achieved with Kampo formulations. There are also reports that Saireito shortened the active phase of SLE, reduced the consumption of steroids and lowered the incidence of adverse reactions including increased hepatic transaminases. Research findings suggested that Saireito had an effect on T-lymphocyte subpopulations, directing the clinical course toward a more healthy state, while Hochuekkito was active in producing lowered NK cell activity.

Key words  Kampo medicine, rheumatic diseases, Sjögren's syndrome, SLE, Bakumondoto, Saireito.

Introduction

Rheumatic diseases are systemic autoimmune diseases of unknown cause. In 1947, corticosteroids (hereinafter referred to as "steroids") were introduced as a therapy for rheumatic diseases, producing noticeable improvements in the prognoses. A number of studies have been made on the mechanism of actions of steroids. Steroids are now used in most patients with rheumatic diseases. However, since a rheumatic disease is a generalized disease of unknown origin, mental as well as physical symptoms are frequently involved. Rheumatic diseases are one of the problem disease groups for the structurally divided and specialized Western medicine system.

Kampo medicine treats the mind and the body as a whole, based on an understanding of the complex mental and physical diseases of spatially and temporally complicated human beings. Based on the therapeutic theory of mind-body unity, Kampo medicine identifies treatable pathology and attempts to restore the natural state of the whole body. In treating rheumatic diseases, the advantages of both Kampo and Western medicines should be clearly understood and unified in a complementary way to ensure effective therapy.

I. Clinical efficacy of Kampo formulations against rheumatic diseases

A relatively large number of reports are available concerning the usefulness of Kampo therapy for rheumatoid arthritis (RA). However, no strict randomized controlled trials have been conducted to determine the efficacy of a Kampo therapy for RA, unlike other treatments for rheumatic diseases. Diseases covered by case reports too numerous to mention all individually include systemic lupus erythematosus (SLE), Sjögren’s syndrome (SJs), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), mixed connective tissue disease (MCTD), polyarteritis nodosa (PN) and polymyalgia rheumatica (PMR). In these case reports, remission was clearly attained after suppression of the active phase in some patients, whereas, in many cases, only some of the symptoms were improved or improvement in immunological function was obtained. According to these reports remission in its strictest sense was rarely achieved.

The Kampo treatment of SJs, using Bakumondoto, Kamishoyosan, Saikokeishikanyoto, Ninjin’yoeto, Byakko-kaninjinto, Unkeito, etc. resulted in an improvement in salivary secretion and lacrimation, according to a number of reports. Other reports also cited a relatively large number of patients whose salivary and lacrimal secretion were improved.

SSc is mainly characterized by skin induration. No medicines, Kampo or Western, have proven efficacy in the treatment of skin induration. Even if skin induration is alleviated during treatment, it is hard to distinguish this from natural regression of the disease. Thus, although the effects of Kampo medicine on skin induration in SSc are difficult to examine for these reasons, there are a few reports suggesting that the administration of Ninjin’yoeto, Orengekuto and Tokishakuyakuso had effects on Raynaud’s phenomenon and peripheral circulation deficiency. In basic research, the Kampo drugs Orengekuto, Ninjin’yoeto, Goshajinkigan and Keishibukuryogain were reported to suppress the activation of fibroblasts...
derived from the hardened skin of an SSc patient.\textsuperscript{38)}

Kampo medication given to SLE patients was reported to result in a reduction of the use of steroids and the improvement of certain clinical symptoms,\textsuperscript{13-17} while improvements in immunological abnormalities, including negativization or lowering of antinuclear antibody values, were observed.\textsuperscript{18-20} Although these reports emphasized that the results were not natural regressions of the disease, it would be too hasty to conclude that Kampo drugs alone can improve active SLE. Therapeutic mistakes during the active phase of SLE may lead to a worsening prognosis. Considering the current medical environment, the use of Kampo medicines alone during the active phase of SLE would be very risky.

In this paper I report on my experience of the usefulness of Kampo medicines in treating active SLE. Patients requiring high doses of steroids for the treatment of active SLE were first treated with Saireito and then with an appropriate dosage of steroids, resulting in a shortening of the active phase and the alleviation of adverse reactions caused by steroids.

1. Clinical investigation of Kampo medicine in SLE

1) Relationships between corticosteroids and Oketsu/Suidoku

It is unrealistic to discuss treatment of rheumatic diseases without touching on steroids. In order to analyze, in terms of Kampo medicine, what pathological conditions appear after steroidal therapy, I prepared a score chart as shown in Table 1. This chart does not show the diagnostic criteria for Oketsu and Suidoku, but the severity points score for Oketsu and Suidoku.

(1) Steroids and Oketsu

As shown in Fig. 1, there was no correlation between the daily steroid dose in terms of prednisolone (PSL) and the Oketsu scores, however the total steroid dose and the Oketsu scores were correlated (correlation coefficient: r=0.5415). Oketsu scores increased with longer steroid administration periods and with higher total doses (cumulative amount), resulting in a condition indicated for Keishibukuryogan and other Ku-Oketsu-zai drugs.

Nearly all patients with inactive SLE experienced an active phase in the past, and must have received a high accumulated steroid dose. This was the reason Ku-Oketsu-zai was prescribed in many inactive-SLE patients in my study, and to the patients cited in the literature.

2) Steroids and Suidoku

As shown in Fig. 2, Suidoku scores increased with higher daily doses of steroids (correlation coefficient: r=0.6970), though the total steroid doses and the Suidoku scores were unrelated. With regards to Suidoku, a higher daily dose, not the accumulated steroid dose, induced the symptoms that were indicated for body water-regulating agents. Detailed examination showed that steroid doses of \( \geq 30 \) mg/day (on a PSL equivalents basis) intensified this trend.

3) Steroids and Saiko-zai

Compared with non-steroid-treated patients, steroid-treated patients more frequently developed Kyokyo-Kuman, a white furry tongue, a strained pulse and other symptoms.

\begin{table}
\centering
\caption{Score Chart for Oketsu and Suidoku}
\begin{tabular}{|l|c|c|}
\hline
Oketsu item & Intensity of symptom & \multicolumn{1}{c|}{\text{Score}} \\
\hline
1. Purpura, vascular dilation & \( + + + - \) & \( \times 4 \) \\
2. Bleeding (hemorrhoids, etc.) & \( + + + - \) & \( \times 4 \) \\
3. Menstrual disorder & \( + + + - \) & \( \times 5 \) \\
4. Dry mouth, dry skin & \( + + + - \) & \( \times 2 \) \\
5. Poor complexion & \( + + + - \) & \( \times 2 \) \\
6. Purplish red tongue & \( + + + - \) & \( \times 4 \) \\
7. Tenderness to pressure in the lower abdomen & \( + + + - \) & \( \times 5 \) \\
\hline
Suidoku item & & \multicolumn{1}{c|}{\text{Score}} \\
\hline
1. Excessive sweating & \( + + + - \) & \( \times 5 \) \\
2. Edema & \( + + + - \) & \( \times 5 \) \\
3. Polyuria, oliguria & \( + + + - \) & \( \times 5 \) \\
4. Dizziness & \( + + + - \) & \( \times 5 \) \\
5. Thirst & \( + + + - \) & \( \times 5 \) \\
6. Teeth printed tongue & \( + + + - \) & \( \times 5 \) \\
7. Headache & \( + + + - \) & \( \times 5 \) \\
8. Heavy feeling in the stomach & \( + + + - \) & \( \times 5 \) \\
\hline
\end{tabular}
\end{table}

\[ \text{Score} = 2 \times 1 \times 0 \]

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Correlations between the daily and the total dose of corticosteroid and the Oketsu score. The total (cumulative) dose of corticosteroid and the Oketsu score are correlated (\( \gamma = 0.5415 \)).}
\end{figure}
indicated for Saiko-zai, regardless of the daily dose or total steroid doses. The findings suggested that Saireito should be considered for the active phase, while both Saiko-zai and Ku-Oketsu-zai should always be taken into consideration for treatment in the inactive phase.

2) Effects of combinations of steroids and Saireito on active SLE

(1) Saireito and hypocomplementemia

Hypocomplementemia is one of the most important markers for active SLE, as it indicates an irreversible change in an internal organ such as nephropathy. Highly active SLE requires a steroid dose equivalent to about 60 mg/day of PSL. When hypocomplementemia is improved, the steroid dose is usually reduced. Administration of steroids equivalent to about 60 mg/day of PSL improves most of the clinical symptoms of SLE, and immunoserologic disorders including anti-dsDNA-antibody, decreased white blood cells and immune complex are rapidly improved. Therefore, when administering a relatively high steroid dose combined with a Kampo formulation, evaluation of the efficacy and usefulness of the Kampo medicine is difficult. Further, it is difficult to know whether Kampo findings at that point in time are really the representations of the patient's own Shô or the state modified by the steroid.

Accordingly, taking note of the Suidoku, Kyokyokuman, white furry tongue and the strained pulse induced by a relatively high steroid dose, I concurrently administered Saireito when a relatively high steroid dose was to be started, comparing this group with a group that did not receive Saireito concurrently. As shown in Fig. 3, a group of 37 patients not receiving Saireito treatment needed an average of 58.5 days for an improvement in the total serum complement titer, whereas 18 patients concurrently treated with Saireito required a significantly (p<0.005) shorter average treatment period of 31.8 days. This meant that concurrent administration of Saireito could save an average of 999.5 mg of steroid (based on PSL treatment for 4 months).

(2) Saireito and proteinuria

Saireito is a Kampo medicine which has been shown to be useful for the treatment of proteinuria in a large number of patients.38-42) The proteinuria of many patients is improved with steroids, but hard-to-cure cases are not rare. A comparison was made between patients receiving only steroids and those also receiving Saireito. The patients whose proteinuria was lowered and whose urine tested negative for protein were defined as "improved", those whose proteinuria was unchanged or whose urine did not test negative for protein despite lowered levels were defined as "unchanged" and those with increased proteinuria were defined as "exacerbated". As shown in Table 2, the improvement rate was 56.8% (21/37) in the non-Saireito group and higher

![Fig. 2](Image) Correlations between the daily and the total dose of corticosteroid and Suidoku score: The daily dose of corticosteroid and the Suidoku score are correlated ($r^2 = 0.6970$).

![Fig. 3](Image) Number of days from start of a large dose of corticosteroid to normalization of total serum complement titer: Mean of 31.8 days in Saireito group and 58.5 days in non-Saireito group.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effect of Saireito on proteinuria in SLE</th>
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<tr>
<td></td>
<td>Improved (%)</td>
</tr>
<tr>
<td>with Saireito</td>
<td>n=14</td>
</tr>
<tr>
<td>without Saireito</td>
<td>n=37</td>
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P<0.1
at 78.6% (11/14) in the group co-administered Saireito (p<0.1).

(3) Saireito and other markers for active SLE

No differences were observed between Saireito and non-Saireito groups with respect to the percent improvement or improvement speed of anti-dsDNA antibody titers, WBC counts or other markers for active SLE.

3) Adverse reactions to a large steroid dose at the beginning of administration, and the prophylactic effect of Saireito

It is well known that transaminases (GOT, GPT) increase after a large steroid doses. The results above seem to indicate that Saireito intensifies the effects of steroids, and there is a concern, therefore, that Saireito may also exacerbate the adverse reactions induced by steroids.

As shown in Fig 4, in 48 patients with no concurrent Saireito treatment, the pre-steroid treatment means for GOT and GPT were approximately 50 mU/mL and 35 mU/mL respectively and these values were increased after 4 weeks of steroid treatment. Subsequently, these parameters decreased after liver supporting therapy. In contrast, the GOT and GPT concentrations followed a normalizing trend after the co-administration of steroid and Saireito to 21 patients, and the mean GOT and GPT concentrations were both normalized at 4 weeks. These normal levels were subsequently maintained. A highly significant difference (p<0.05-0.001) was observed between the two groups.

While steroid therapy often induces abnormal glucose tolerance and higher blood glucose levels, none of the 21 patients in the Saireito-treated group experienced high blood glucose levels that required insulin therapy.

4) Kampo therapy for inactive SLE

In general, inactive SLE is treated with maintenance therapy using a low steroid dose. In these inactive SLE, attempts to demonstrate that co-administration of Saireito permits a reduction in the steroid dose have not been successful. As the total serum complement titer, anti-dsDNA antibody titer and other immunoserologic markers for active SLE were already in the normal range, it was difficult to clearly demonstrate the effect of the Kampo medicine itself. Furthermore, a very prolonged observation period would be necessary to determine whether SLE will flare-up in patients whose steroid dose is reduced to the maintenance level and several hundreds of patients and several years observation would be required to demonstrate that intervention with Saireito significantly reduces the recurrence rate.

Several reports are available concerning Kampo therapy in individual patients with inactive SLE.13-20 These reports are a true representation of the characteristics of Kampo medicine. The results given in these reports were natural outcomes from a Kampo viewpoint, but are not reproducible with respect to Western treatment of SLE; therefore, the Kampo drug cannot be immediately incorporated into the SLE treatment guidelines.

2. Effect of Kampo medicine on salivation in Sjögren’s syndrome

SJS is characterized by dry eyes and mouth, as well as by the arthritis typically observed in rheumatic diseases. The clinical research for this disease consists mostly of case reports,26-30 some of which examined a relatively large number of patients.31-34 Some Kampo formulations are classified as moistening agents. I examined the effect of Bakumondoto (a representative Kampo moistening agent) on hyposalivation33 when given alone and also when given in combination with either Rokumigan or Hachimijiogan.34

Effects were evaluated using a 10-minute gum chewing test to measure saliva production. Bakumondoto was administered as a moistening agent, and the patients with evident Jin-inkyo were concurrently treated with Rokumigan, while the patients with Jin-yoko were concurrently treated with Hachimijiogan. The comparator was Hochuekkito, a formulation positioned in between a moistening and a drying agent. Table 3 shows the background factors of the subjects in this study. Hochuekkito administration had no significant effect on salivary secretion in this study with the mean secretion volumes in the test being 8.7 ± 1.3 mL (mean ± S.E.) before Hochuekkito administration and 8.8 ± 1.3 mL (mean ± S.E.) after the administration of Hochuekkito for 1 month. The increase in salivary secretion of 0.1 ± 0.34 mL (mean ± S.E.) was not significant. However, as shown in Fig. 5, the mean salivary secretion of patients treated with Bakumondoto also or Bakumondoto

Fig. 4  Prophylactic effect of Saireito on elevation of GOT/GPT induced by corticosteroid
Table 3 Background factors of patients in the study

<table>
<thead>
<tr>
<th></th>
<th>Bakumonoto</th>
<th>Rokumigan</th>
<th>Hochuekkito</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>30</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Sex Male (M) Female (F)</td>
<td>30</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>54.8±10.3</td>
<td>49.8±13.9</td>
<td></td>
</tr>
<tr>
<td>Disease duration (M)</td>
<td>52.8±34.5</td>
<td>55.7±51.6</td>
<td></td>
</tr>
<tr>
<td>Sialography Grade distribution</td>
<td>Grade I 5</td>
<td>Grade II 12</td>
<td>Grade III 8</td>
</tr>
<tr>
<td></td>
<td>Grade IV 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary secretion (mL) mean ± S.E.</td>
<td>8.2±1.2</td>
<td>8.7±1.3</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 5 Effect of Bakumonoto, Bakumonoto + Rokumigan and Bakumonoto + Hachimijiogan on the salivary secretion of patients with Sjögren's syndrome

plus Rokumigan or Bakumonoto plus Hachimijiogan increased significantly (p<0.005) from 8.2 ± 1.2 mL (mean ± S.E.) before administration to 12.0 ± 1.4 mL (mean ± S.E.) after administration of these formulations for 4 weeks. A comparison of the increases in salivary secretion volumes recorded in the test between the patients treated with Bakumonoto alone or Bakumonoto plus Rokumigan or Bakumonoto plus Hachimijiogan and the Hochuekkito group is shown in Fig. 6. The difference between the mean secretion volumes is significant (p<0.05%)

Enhancement of secretion from mucous membrane by Bakumonoto was also observed with respect to lacrimation, suggesting that Bakumonoto is a Kampo formulation that can moisten the whole body. However, these results did not represent an effect of a Kampo formulation on the underlying pathology of Sjögren's syndrome but are an effect on the symptom of dryness associated with the syndrome. An effect of Bakumonoto on Sjögren's syndrome itself has been reported, though only in a case report, clearly indicating an improvement in immunological function.  

II. Basic research on the effects of Kampo formulations on immune system abnormalities in rheumatic diseases

As mentioned earlier, Saireito is likely to exert favorable effects on the immune function of SLE patients. We examined the incidence of emergence of peripheral blood T-lymphocyte subpopulations in active and inactive SLE, using several different monoclonal antibodies to estimate the size of the subpopulations. The results are given below.

It is well known that suppressor T-lymphocytes are diminished in active SLE. As shown in Fig. 7, there were significantly fewer CD4^+2H4^+ cells (the suppressor inducer that activates suppressor T lymphocytes) in patients with active SLE than in patients with inactive SLE (p<0.01). Saireito administration had no effect on the percentage of CD4^+2H4^+ cells. Although the percentage of CD4^+2H4^+ T lymphocytes in patients with either active or inactive SLE was slightly larger in the Saireito-treated patients than in those not receiving Saireito, the differences were not significant.

In contrast, there was no difference in the percentage of CD4^+4B4^+ cells (the helper inducer T lymphocytes that activate helper T lymphocytes) between patients with active SLE and inactive SLE - see Fig. 8. However, in active SLE, helper inducer T lymphocytes tended to be greater in number in the group of patients concurrently treated with Saireito than in the group not receiving Saireito (p<0.1).

From a clinical point of view, Saireito seems to improve generalized malaise and reduce susceptibility to
infection. The results above may explain such an impression. However, the changes in lymphocyte subpopulations alone cannot be used as evidence of Saireito and other Kampo formulations being effective in treating the immune system abnormalities in rheumatic diseases. A multidirectional approach is required to provide such evidence.

III. Effect of Hochuekkito on the immune system (NK cell activity) of rheumatic disease patients

Hochuekkito is known to have several effects on the immune system as reported in the literature: CD23, a marker for B cell activity, and TNF α were diminished after the administration of Hochuekkito, demonstrating an effect in rheumatoid arthritis.45 Another report cited a patient diagnosed with Ki-deficiency (indication of Hochuekkito) whose NK cells were reduced.46 NK cell activity increased after Hochuekkito administration in rheumatic disease,45 and Hochuekkito was effective in activating NK cells, according to other reports.

NK cells account for 5-15% of lymphocytes, and have a central role in natural immunity. The results of a study of the effects of Hochuekkito on NK cell activity in rheumatoid arthritis and Sjögren's syndrome46 are summarized below.

Hochuekkito, as extract granules distributed by T Company, was administered for 4 weeks to 25 patients with rheumatoid arthritis, 7 patients with Sjögren's syndrome and 3 patients with other diseases, giving a total of 35 subjects. NK cell activity was determined before and after administration of Hochuekkito. As shown in Fig. 9, NK cell activity was 24.6 ± 13.7% (mean ± S.D.) before administration and 30.4 ± 14.4% after administration of Hochuekkito, demonstrating a significant increase (p<0.05).

Conclusion

The usefulness of Kampo formulations in the treatment of rheumatic diseases was examined from clinical and basic research perspectives. The investigation of the efficacy of Kampo medicines in treating rheumatic diseases has only just started. While modern medicine identifies diseases as specific named pathological conditions, Kampo medicine identifies and treats a pathological condition in terms of the "Sho" system. Kampo medicine is said to be incompatible with investigations based of named pathological conditions (diseases). Nevertheless, among 117 patients with rheumatic
diseases currently treated at our hospital (excluding RA), as shown in Fig. 10, 28.2% receive only Western medicine-based conventional therapy including steroids; 30.8% receive both conventional therapy and Kampo medicines; and the highest proportion (41%) receive Kampo formulations alone. Plenty of case reports and the results obtained at our hospital suggest that Kampo medicines can be an effective tool for treating rheumatic diseases. If this paper assists others to provide Kampo medicine in the treatment of rheumatic diseases and facilitates broader acceptance of Kampo medicine in the treatment of other diseases, I will feel more than happy.

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**Japanese abstract**

腎原病に対する漢方薬による治療は近年多くの報告がなされるようになった。腎原病では副腎皮質ステロイド薬による治療が一般的であるが、本剤投与による漢方医学的病態の変化も把握されてきている。臨床的有用性の例として、シューガー陽性症候群の乾燥症状に対して麦冬湯、滋陰降火湯、六味丸、八味地黄丸、温经湯などの漢方薬が唾液分泌を増加させ、免疫学的異常が改善した報告も存在する。SLE その他の腎原病に対して種々の漢方薬の治療により寛解が得られた症例報告や柴苓湯が SLE の活動期を短縮させ、ステロイドの投与量を節約させ、さらに肝機能低下の上昇などの副作用を軽減させる効果が示されている。また基礎医学的な検討では、柴苓湯が T リンパ球分化に影響を与え、より正常な方向への誘導が示唆され、低下した NK 細胞活性を補中益気湯が上昇させたという結果も報告されている。

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