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“The forefront of clinical research on Wakan-yaku (traditional Japanese medicines)”

Therapeutic strategies for rheumatoid arthritis
-Recent topics on Japanese Oriental (Kampo) medicine-

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Introduction

Rheumatoid arthritis (RA) is one of the diseases for which Kampo medicine has been clinically used for a long period.\(^1\) Various Kampo prescriptions such as boiogito, keishikaryojutsubuto, and yokuninto have been administered to patients with RA, playing a certain role in therapeutic strategies for RA in Japan.\(^2\)\(^-\)\(^3\)

Therapeutic strategies for RA have markedly changed. Methotrexate (MTX), which began to be clinically applied for RA in the 1960s, was confirmed to be effective against RA by large-scale controlled trials in the 1980s.\(^4\) Since the end of 1990s, biological agents (infliximab in Japan since 2003) have been clinically used. At present, strict control of biological agents is recommended. To achieve this, the ACR/EULAR classification criteria were established in 2009.\(^5\)\(^-\)\(^6\) The induction rate of clinical remission using biological agents is 40-50%, and the induction of clinical remission still remains a difficult problem. However, compared with results using conventional DMARDs, those using biological agents are excellent.

With this background, we discuss the role and position of Kampo medicine in RA treatment.

Responders to Kampo medicines

Until the 1990s, there have been case reports showing the effects of various Kampo medicines on RA. The major medicines used included keishikaryojutsubuto, boiogito, and epipikajutsuto (or their combinations), and yokuninto, juzentaihoto, and daibofuto. In addition, the effects of makyoyokukanto and hochuekkito have also been reported.\(^7\)\(^-\)\(^8\) However, in many case reports showing the effects of these Kampo medicines on RA, changes in symptoms, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or rheumatoid factor (IgM-RF) were evaluated, and the Lansbury activity index was used for comprehensive evaluation. This was not a problem since these parameters were also used by the Japan College of Rheumatology (JCR) until 1990s. After 2000, with the advent of potent drugs, the diagnosis and evaluation of RA have become more objective. We can only speculate about whether previous reports on Kampo medicines fulfilled such diagnostic and evaluation criteria. However, we consider that there were marked responders to Kampo medicines even employing the present evaluation methods used in 2011.

We administer crude drugs (decoctions) to 80-90% of patients with RA, and these patients often exhibit pathological conditions in Kampo medicine (Syndrome: so-called “SHO” in Japanese Oriental Medicine)\(^9\) indicated for keishinieppiitokaryojutsubu (KER). Since the latter half of the 1980s, we have reported the effectiveness of this prescription, and encountered some patients who showed favorable responses and clinical remission even using a recent evaluation method.\(^10\) (Fig. 1)

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medicines among RA patients showing extremely high activity. Therefore, the clarification of the subtypes of RA that respond to Kampo medicine, i.e., use of the methodology called “objectification of SHO” in RA may be a promising method (Fig.2).

![Kampo Formula](image)

**Fig. 2** Objectification of “SHO: Kampo diagnosis” (Syndrome) in RA
Clarification of the subtypes (closed space) of RA that respond to Kampo medicines using the parameters in the Western medicine, but not traditional methodology.

**Clinical characteristics of responders**

As described in the above section, there are responders to Kampo medicines among RA patients. However, in terms of recent therapeutic strategies for RA, it may be difficult to administer Kampo prescriptions for some months-some years while observing their effects as was performed in the 1990s. In 2008, the American College of Rheumatology (ACR) regarded the “window of opportunity” as 6 months, and recommended the use of a TNF inhibitor in combination with MTX in RA patients within 3 months after onset who show high disease activity and have no problems regarding the payment of medical costs. Based on this recommendation, the JCR also recommended considering biological agents even 3 months after onset in the presence of the progression of bone erosion or disease activity score (DAS) 28-ESR > 3.2. In this trend, to utilize the effects of Kampo medicines in clinical practice, the following method can be considered first; patients with high activity are excluded based on DAS28, and Kampo medicines are clinically administered only to patients with mild-moderate activity, which is similar to the method of using disease-modifying antirheumatic drugs such as Salazosulfapyridine (SASP) and Bucillamine (Buc). However, there are responders to Kampo medicines among RA patients showing extremely high activity. Therefore, the clarification of the subtypes of RA that respond to Kampo medicine, i.e., use of the methodology called “objectification of SHO” in RA may be a promising method (Fig.2).

We previously reported a characteristic of responders to Kampo medicines based on the basal value of anti-CCP antibody (aCCP) titer as a prognostic factor of RA and its changes after treatment. In brief, there were two findings indicating responders to Kampo medicines: i) The aCCP titer is not high even if positive, and ii) even if the aCCP titer is high, it decreases 3 months after treatment. At present, to clarify more detailed patterns, comprehensive analysis of autoantibody expression patterns is in progress.

If we are able to demonstrate the subtype of RA that respond to Kampo, the use of herbal medicine including Kampo by RA patients will be becoming increasingly popular in several developed states such as USA.

**Conclusion**

We discussed the possibility of Kampo treatment in the present RA classification criteria and therapeutic treatment. Kampo medicine is “personalized medicine”. Although there are marked responders, patients to whom Kampo medicines should be administered cannot be clarified until effects are confirmed after administration following diagnosis based on conventional medi-
cine. However, in rheumatology, there are also no useful clinical markers to predict the effects of biological agents and low molecular weight anti-rheumatic drugs before administration. RA is a heterogeneous disease. We consider that Kampo medicines will continue to play an important clinical role in RA treatment from various aspects in the future.

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References


