Kampo Medicine - Current Research

Collagen Disease

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Collagen diseases and the relative diseases are immune system disorders and the causes remain to be identified. Because of unexplained causes, the treatment with Western medicine is aimed at control of further progression of the diseases to later stages or relief of worsening conditions and symptoms. Drugs used for the purposes, such as steroids and immunosuppressant drugs, will cause various adverse effects, and medical resources are consumed at the same time. In the situation, the treatment with Kampo medicines, which are relatively cheap with few adverse effects, is meaningful. In effect, there are many reports suggesting Kampo medicines play positive roles in controlling symptoms of collagen diseases as well as a worsening of the diseases, enabling to reduce the volume of immunosuppressant agents and alleviate their side effects.

Many of collagen diseases and the relative disorders often cause pain, swelling, and stiffness of joints and the musculoskeletal system and for the reason, collagen diseases are often generalized as a group of "rheumatic disorders" - a traditional concept of Western medicine after Greek medicine. Kampo medicine has a similar concept called "bi pattern or arthritis." This concept was established and discussed 2,000 years ago in the most old classical book "Yellow Emperor's Canon of Medicine / Plain Conversation". Even in the present days, collagen diseases and the relative diseases of joints and musculoskeletal swelling, pain and stiffness are approached, in principle, with discussions based on the ancient arthritis concept. However, musculoskeletal symptoms cover only part of a wide array of collagen diseases. For other symptoms, Kampo medicine handles individual symptoms as separate clinical conditions and has not regarded them as a single disease concept for long. Therefore, the modern Kampo medicine does not have a unified view of etiology and pathogenic mechanisms that can pinpoint accuracy of the pathological conditions that can explain the natural history including varieties of symptoms, development of diseases, and prognosis. In our time, most individual symptoms of a disease are separately approached. Studies to search for etiology and pathogenic mechanisms of each collagen disease are desired in order to enhance the treatment performance of short-term symptoms and to achieve full-scale improvement of the prognosis.

Introduced hereunder are recent notable clinical trials in Japan on typical collagen diseases and similar diseases such as rheumatoid arthritis, SLE, and Sjogren's syndrome.

Rheumatoid arthritis

Rheumatoid arthritis is known as one of the most common types of collagen diseases. Western medicine of today has made a major breakthrough in the treatment method of rheumatoid arthritis. The main stream treatment is to slow down disease progression with the administration of a group of medications (different types of drugs) known as DMARDs which mainly use immunodepressant agents such as Methotrexate (MTX). Especially in recent years, a new treatment for rheumatoid arthritis has begun to be performed aiming at a complete remission by powerfully controlling disease activities with monoclonal antibody agents, referred to as biologically derived agents, against anti TNF-α antibodies and other immune/inflammation inducing substances. As image inspection technologies advance in recent

years, it has become known that joint destruction starts one to two years after symptoms first appeared, much earlier stages than thought. For this reason, it has begun to be recommended that DMARDs and biological agents be used in as early stages as possible with the objective of preventing joint damage. In compliance with this, the diagnostic criteria have been revised in order to diagnose rheumatoid arthritis in its early stages[1]. Furthermore, efforts are being made to identify, among unclassifiable joint inflammation disorders, a group having the high possibilities of progressing to rheumatoid arthritis[2]. However, given side effects of DMARDs, high costs of biological drugs, and problems of immnosuppression, wariness persists about the thought of lowering the treatment threshold of rheumatoid arthritis in the early stages that has the possibility of spontaneous remission. In view of reductions in the usages of DMARDs and biological drugs, alleviation of their adverse effects, and means of treatment for some refractoy rheumatoid arthritis, relatively low-cost Kampo treatment with less adverse effects may mean a great deal as used to be.

In the Kampo treatment of rheumatoid arthritis in Japan, "*keishikajutsubuto*" and "*eppikajutsuto*" are often used in Japan in light of the historical use of the formulae described in "Shan Han Lun" and "Jin Gui Yao Lue"[3),4),5)]. There are many reports published on the use of "*keishakuchimoto*" for relatively advanced rheumatoid arthritis and "*daibofuto*" for advanced joint deformation. On the other hand, a group of practitioners referred to as Gosei School, who emphasize on the prescriptions of the Ming Era, recently published a report that *jiinkokato* was effective for rheumatoid arthritis in its early stages[6]. There is a notable report on *boiogito*. In this research, relatively a large number of patients with rheumatoid arthritis were tested and an appropriate assessment method was used; Tanaka administered for six weeks *boiogito* to RA32 patients, who met the diagnostic criteria of definite RA under American College of Rheumatoid standard criteria; neither changes to the drugs they had used nor new drug additions were made; and changes in Lansbury indexes of individual patients were monitored. The results revealed effective in 14 patients (44%), slightly effective in 5 (16%), remained unchanged in 5 (16%), and worsened in 4 (13%). The duration of morning stiffness, the number of painful joints, and the number of swollen joints significantly improved. Their grip strength and CRP showed a tendency for improvement. From these results, the group determined *boiogito* was effective for RA[7].

Nagasaka, et al administered Kampo treatment to RA54 patients and assessed its effectiveness. Their average disease duration was 13 years and mean values of Steinbrocker's functional/stage classification were class2.3 and stage2.5. The 35 patients had been using Western-style medicines since before the initial visit. The overall effect was "markedly effective" in 41% of the patients, "effective" 10%, "slightly effective" 18%, and "ineffective or exacerbated" 31%. Twenty-six patients were able to discontinue the Western medicines/reduce the body weight. Among the prescriptions that yielded the result of "slightly effective" or more assessed by the modified Lansbury Index, *boiogito* had the highest respose rate. Next followed by modified *keishikaryojutsubuto bushito*, then modified *keishinieppiichito*. *Boiogito* increased the response rate with more-than-usual amounts of *Astragali* Radix and *Sinomeni* Caulis et Rhizoma. And, Nagasaka, et al. further claimed that if no effect was obtained from the single use of *keishikaryojutsubuto*, the administration combined with *boiogito* increased the response rate[8]. As just described, *boiogito* is often applied

to rheumatoid arthritis in Japan - a characteristic methodology of Japanese Kampo medicine. However, this is not the case in other countries. It should be noted that unlike in other countries, that *Sinomenim acutum* Rehder et Wilson instead of *Stephania tetrandra* S.Moore (Fen fang ji) is the main ingredient of boiogito in Japan.

SLE

SLE in many collagen diseases shows the richest varieties of symptoms and prognoses. It is also known as a disease that can cause dramatic symptoms and outcomes both in short and long terms. It is difficult to say that similarly to Western medicine, Kampo medicine has acquired complete comprehension of the real clinical conditions. Therefore, in most cases, SLE treatment is given only to respond to individual patients and symptoms from beginning to end, so trial reports in a comprehensive way are scarce. Even the same types of SLEs have different patterns of symptom developments in individual patients and the disease conditions ranges from extreme severity to the severity for which only follow-up is necessary but treatment is not required and the severity to the extent that transient worsening is repeated but the condition spontaneously becomes stable. Here lies the problem of difficulty to judge the effective degrees of treatment interventions. In such situation, multiple cases were reported in which clinical conditions improved by the use of Extract of *ninjinto*[9]. The report on the use of *ninjinto*, having the efficacy of dissipating cold and warming yang, for SLEs with fever symptoms is out of common and noteworthy.

Sjogren's syndrome

In recent years, notable reports on randomized clinical trials of Sjogren's syndrome have been published.

Nishizawa, et al. tested *bakumondoto* in a clinical trial of 229 patients suffering from primary Sjogren's syndrome with six-month administration. They were divided into two groups. A group of 115 patients were given *bakumondoto*. B group of 114 patients were given a placebo. The results revealed that the amounts of both saliva and tears significantly increased more in A group than baseline values. This increase was negatively correlated with the increasing rate of the saliva secretion group and the progression degree of salivary gland destruction on Lubins & Holt sialographic intensity classification. Saliva secretion amounts continuously increased in A group after the administration and became stable after six weeks and onward. The amounts of salivary gland secretion decreased in B group. Subjective symptoms improved in A group, whereas those became worse in B group. Inflammatory reactions such as CRP and ESR findings significantly improved in A group with a fewer adverse effects in terms of the number of episodes and patients. In A group, pain improved and keeping the health and QOL significantly improved compared to pre-administration. The overall rates significantly differed in all items between the two groups with 80.9% of "improvement" or above in A group and 0.9% in B group and those who desired re-administration were 92.0% in A group and 6.1% in B group[10].

Ohno administered 64 patients with a definite diagnosis of Sjogren's syndrome *bakumondoto* as a medicine with the action of water retention and additionally given drugs to tonify the kidney ("*rokumigan" and "hachimijiogan*") to the patients who were diagnosed by Kampo medicine as having kidney-deficiency. The results were compared with the control group of Kampo treatment (*hochuekkito*). In the group that received the Kampo medicine having the action of

water retention, 2 of 32 patients dropped out. In the control group, 4 of 32 dropped out. Monitoring was made with 30 vs. 28. The results showed that "*bakumondoto*," "*bakumondoto* + *rokumigan*," and "*bakumondoto* + *hachimijiogan*" showed significant differences after four weeks of administration in the amounts of saliva secretion compared to "*hochuekkito*". Moreover, the groups of additional administration of "*rokumigan*" and "*hochuekkito*" had a significant increase in the amounts of saliva secretion compared to the group of *bakumondoto* only[11].

The above results are noteworthy in the sense that Kampo medicines having the action of water retention were used for the main symptom of dryness of Sjogren's syndrome and effectiveness of the Kampo medicines was verified.

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