



Successful Treatment with Traditional Herbal Medicine in the Patient with Rheumatoid Arthritis Even Complicating with Atypical Mycobacterium Infection

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Authors' contributions

This work was carried out in collaboration between all authors. Author TK designed the study, wrote the first draft of the manuscript and managed the analyses of the study. Author NH managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: There are still several problems in rheumatoid arthritis (RA) therapeutic strategies, although its outcome has been changing better than before. We present the RA patient with atypical mycobacterium infection successfully treated with Traditional Herbal Medicine (THM), and discuss the usability of THM for patients with RA under the current European league against rheumatism (EULAR) recommendation for the management of RA.

Study Design: Case Study (Case report).

Case Presentation: The RA patient (72-year-old female) who passed after the onset for 20 years had the moderate RA disease activity, and complicating with atypical mycobacterium infection in her lung during clinical course. THM treatment alone resulted in the good response in disease activity score of RA as well as no aggravation of atypical mycobacterium infection.

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Discussion and Conclusion: We have demonstrated the RA patient with mycobacterium infection successfully treated with THM alone, and discussed in the clinical utility of THM in the trend EULAR recommendation for RA, termed “treat to target”.

Keywords: Rheumatoid arthritis; atypical mycobacterium infection; traditional herbal medicine; EULAR recommendation.

ABBREVIATIONS

THM : Traditional Herbal Medicine,
 KER : Keishinieppiittokaryojutsu buto,
 SSZ : Sarazosulphapyridine,
 MMP-3 : matrix metalloproteinase-3,
 RF : rheumatoid factor,
 EULAR : European league against rheumatis.

1. INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease and gradually progresses being an intractable disease impairing various daily activities due to a chronic inflammation in the synovial joints. In the last 20 years, several superior therapeutic drugs such as methotrexate (MTX) and biologics: tumor necrosis factor (TNF) inhibitors, interleukin-6 (IL-6) antagonist, and a regulator of co-stimulation between antigen presenting-cells (APCs) and CD4-Tcells, have come to be usable and control disease progress from an early stage [1]. However, there are still several problems in RA therapeutic strategies, involving elderly RA patients, RA patients with infection such as tuberculosis (TB) and atypical mycobacterium disease. It is often difficult for these patients to accept a therapeutic strategy that tightly controls RA disease activity [2,3].

The American College of Rheumatology (ACR) and European league against rheumatism (EULAR) announced the ACR/EULAR RA new classification standard and the new remission standard jointly from 2010 through 2011 [1,4]. The target of treatment has become clinical as well as structural remission, but not the relief of arthralgia. To achieve the target, RA has been a disease requiring early detection and early treatment. EULAR Recommendations for the management of RA 2013 update [5] were reported in 2014. The concept is to define a treatment target, and apply tight control and respective therapeutic adaptations to achieve the target. In parallel, it is also documented that treatment of RA patients must be based on a shared decision between patients and rheumatologists, according to aging, complications, and economic reasons [6]. In this regard, the clinical usefulness of Traditional

Herbal Medicine (THM) has been expected in cases involving difficulty in tight control [7].

In Japan, THM plays a role in primary healthcare, as well as therapy for chronic intractable diseases, such as RA. RA is well-known as one of the chronic diseases treated with THM [8]. The clinical efficacy of THM against RA has ever been demonstrated based on case reports and case series studies [9,10], although the evidence is insufficient. Keishinieppiittokaryojutsu buto (KER); a representative kampo formula for RA treatment, is composed of 12 herbs (Table 1). It has been reported that KER has some immunomodulatory effects in RA patients [10,11].

Table 1. The herb composed of Keishinieppiittokaryojutsu (KER)

Component (herb)	Weight (gram)
Atractylodes Lanceae Rhizoma	10.0
Hoelen	5.0
Gypsum Fibrosum	5.0
Zizyphi Fructus	4.0
Cinnamomi Cortex	3.0
Ephedrae Herba	3.0
Paeoniae Radix	3.0
Glycyrrhizae Radix	3.0
Zingiberis Rhizoma	1.0
Aconiti Tuber	1.5
Sinomeni Caulis et Rhizoma	5.0
Astragali Radix	5.0

Twelve herbs were mixed with 600 ml of water and boiled down to 300ml, then the aqueous extract was filtered through a sieve. The extract, called a decoction, was administered twice a day at the morning and evening.

Here, we present the RA patient with atypical mycobacterium infection successfully treated with THM, and discuss the usability of THM for patients with RA under the current European league against rheumatism (EULAR) recommendation for the management of RA [5].

2. CASE PRESENTATION

A 71-year-old Japanese female (a housewife) visited our department (Gunma Central &

General hospital, Gunma, Japan) due to polyarthralgia, requesting treatment with THM.

[10,11]; a representative kampo formula for RA treatment.

About 20 years ago, she had the pain of bilateral wrist, knee, right elbow and right toe. She visited a nearby hospital and received some medicines. However, she discontinued going to hospital due to the improvement of her joint symptoms. Four years ago, polyarthralgia appeared again, and visited our department. She complained of pain of the bilateral wrist, knee, and right elbow joints, but not morning stiffness. The blood analyses were follows: C-reactive protein (CRP) 2.62 mg/dL; erythrocyte sedimentation rate (ESR) 46 mm/hour; class-IgM rheumatoid factor (RF) 172 IU/mL; matrix metalloproteinase-3 (MMP-3) 349.0 ng/mL; and disease activity score28 ESR (DAS28(ESR)) 4.87. Anti-nuclear antibody (ANA) was 80X (Speckled) and anti-SS-A antibody was negative. Bilateral wrist joints X-ray revealed the destructive change of bilateral carpal bones (Fig. 1). On examination with a stethoscope, an abnormal breathing sound was not heard on both sides of the lung field, and an infiltrative or reticular shadow was not observed by chest X-ray. Thus, we diagnosed her with RA moderate disease activity. We treated her with Kampo medicine alone, because she refused the application of the standard anti-rheumatic drugs, such as methotrexate or tacrolimus, and biologics. She was treated with KER



Fig. 1. Radiography of the bilateral hands
There is a joint space narrowing between the distal end of the radius and the proximal row of carpal bones, the proximal ends of the metacarpals and the distal row carpal bones, and among each carpal bone. The left hand is more remarkable than the right hand in these findings

KER treatment resulted in the decrease in the joint symptoms as well as the serum levels of CRP and MMP-3. Additionally, good response in DAS28-ESR was determined by the EULAR responsive criteria (Fig. 2), and radiographic damage did not progress.

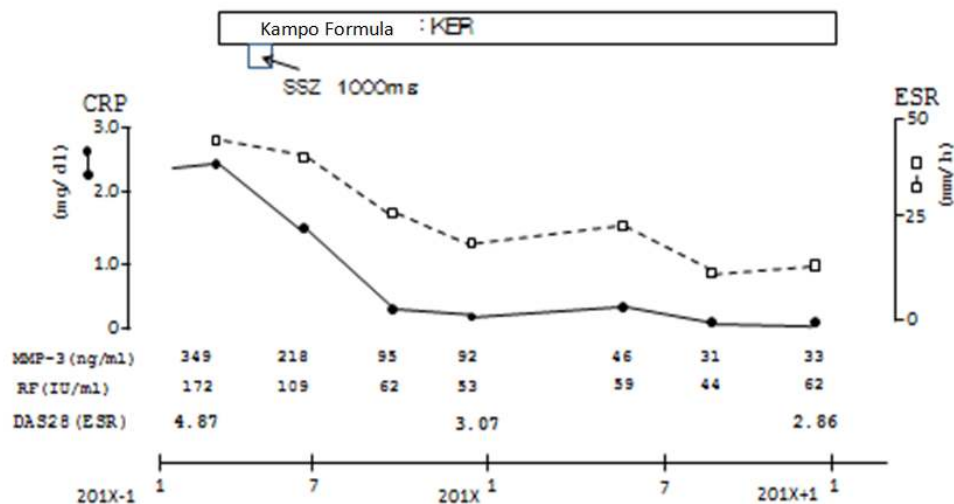


Fig. 2. Clinical course

Six-month treatment with KER resulted in a decrease in serum levels of serological markers as well as DAS28-ESR.

KER: Keishinieppiittokaryojutsubuto, SSZ: Sarazosulphapyridine, MMP-3: matrix metalloproteinase-3, RF: rheumatoid factor, DAS28: disease activity score 28



Fig. 3A. Radiography of the chest
The cystic lesion like a cavity was observed in right upper lobe of lung



Fig. 3B. Computed tomography of the chest
The bronchodilatation and pneumatocele was observed at posterior segment (S2) in the right lung

However, under follow-up, her chest radiological appearance demonstrated a wedge-shaped consolidation and cystoid shadow in right upper lung field (Fig. 3A) and chest CT revealed the pneumatocele in right 2nd pulmonary segment (S2) (Fig. 3B). We consulted her respiratory medicines and she was diagnosed as RA with atypical mycobacteriosis (AM) due to mycobacterium avium complex (MAC), because mycobacterium avium was detected in sputum culture twice. She was treated with the oral administration of erythromycin 400 mg/day from Jan. 201X+2. The dosage of erythromycin has been increased to 600 mg/day, and oral administration of ethambutol hydrochloride (500 mg/day: 15 mg/kg) has been added on at Aug 201X+2. The aggravation of pathological change of lung has not been observed, and she maintained low disease activity in DAS28-ESR. Additionally, both erythromycin and ethambutol did not influence on the disease activity in RA.

3. DISCUSSION AND CONCLUSION

The therapeutic strategy for RA has changed over the last ten years, and 2014 update of the recommendations in treating RA to target aims at clinical remission using MTX and biologics (anti-TNF drugs, anti-IL-6 drug, and suppressor of T-cell activation) from an early stage [5]. Regarding this trend, we have reported case reports and case series studies demonstrating the efficacy of THM [9,10]. In this paper, we present the RA patient with mycobacterium

infection successfully treated with THM alone, and consider that THM may be a useful agent for the treatment of RA patients involving difficulty in tight control. Namely, there may be the clinical utility of THM among the alternative target strategy in treating RA to target: 2014 update of the recommendations. However, the evidence for THM remains weak [8].

Recently, “ACR recommendations 2015” was demonstrated in Jan.2016 [12]. This guideline has been established using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, and showed the recommendation for RA patients with high-risk condition such as hepatitis, congestive heart failure, malignancy, and serious infections. For the patients with previous serious infections, combination DMARDs (disease modified anti-rheumatic-drugs) or abatacept over TNF inhibitor were recommended, while level of evidence concerning these recommendations is very low. It is considered that there may be a clinical utility of THM for these populations, because there is still no standard treatment that has high evidences for the RA patients in the alternative target in 2014 update of recommendation.

Besides, it is difficult for not only general rheumatologists but also experts of THM to apply THM for RA when using the treating RA to target: 2014 update of the recommendations. There are mainly 2 reasons for that. Firstly, THM is administered according to the traditional

diagnostic system [8], but not therapeutic guidelines in Western medicine. Secondly, the period to evaluate the efficacy of THM is shorter than before. In this regard, we have been prompt to search for biomarkers that distinguish THM responders from non-responders. We have reported that pretreatment serum levels of anti-citrullinated peptide antibody (ACPA) are a useful predictor of a good response to treatment with KER [10,11]. The procedure of proteomics has been used to determine biomarkers for THM responders. Recently, we demonstrated candidate biomarkers to predict a good or no response to THM among RA patients [13]. Furthermore, we attempt to develop the methodology to give each RA patient the THM based on its mechanism in treating RA [14]. These attempts may open the way to include THM treatment in the recommendations in treating RA to target.

Finally, we have demonstrated the RA patient with mycobacterium infection successfully treated with THM, and discussed in the clinical utility of THM in the trend therapeutic strategy for RA, termed "treat to target".

CONSENT AND ETHICAL APPROVAL

The patient was approved under the comprehensive agreement of Gunma Central and General Hospital. Informed consent was obtained from the patient before the treatment with THM was initiated. Furthermore, the authors received training in performing clinical trials at Gunma University and Gunma Central and General Hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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