Conventional and Kampo medicine in the treatment of mild to moderate COVID-19: A multicenter, retrospective observational study protocol by the Integrative Management in Japan for Epidemic Disease (IMJEDI study-Observation)

Shin Takayama,1,2,3* Masayuki Kashima,4 Takao Namiki,5 Takashi Ito,6 Rie Ono,1,2 Ryutaro Arita,1,2 Natsumi Saito,1,2 Hajime Nakae,7 Yasuhiro Irie,7 Seiichi Kobayashi,8 Tetsuhiro Yoshino,9 Tomoaki Ishigami,10 Koichiro Tanaka,11 Tatsuya Nogami,12 Satoko Minakawa,13 Mahiko Nagase,14 Akihiko Kashio,15 Tatsuya Ishige,16 Hiroyasu Maehara,17 Toshiaki Saito,18 Sadahiro Sempuku,19 Mayuko Yamazaki,20 Eiichi Tahara,21 Norio Suda,22,23 Kayo Nakamoto,24 Tadamichi Mitsuma,25 Hiroko Sato,26 Osamu Shimooki,27,28 Yoshinobu Nakada,29 Shuichi Abe,30 Takuya Masuda,31 Hiroki Kai,32 Kenichi Yokota,33 Shigeki Chiba,34 Fumihito Saitoh,35 Yutaka Tanaka,36 Sayaka Koizumi,37 Susumu Fujii,38 Rie Katori,39 Mosaburo Kainuma,40 Kotaro Nochioka,41 Shih-Wei Chiu,42 Akiko Kikuchi,1,2,3 Tomoko Suzuki,43 Masaru Mimura,9,44 Takahiro Yamaguchi45 & Tadashi Ishii1,2,3

1 Department of Kampo Medicine, Tohoku University Hospital, Sendai, Japan
2 Department of Education and Support for Regional Medicine, Tohoku University Hospital, Sendai, Japan
3 Department of Kampo and Integrative Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
4 Department of General Internal Medicine, Japanese Red Cross Kumamoto Hospital, Kumamoto, Japan
5 Department of Japanese-Oriental (Kampo) Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan
6 Akashi Clinic Kanda, Tokyo, Japan
7 Department of Emergency and Critical Care Medicine, Akita University Graduate School of Medicine, Akita, Japan
8 Department of Respiratory Medicine, Japanese Red Cross Ishinomaki Hospital, Ishinomaki, Japan
9 Center for Kampo Medicine, Keio University School of Medicine, Tokyo, Japan
10 Department of Cardiology, Yokohama City University Hospital, Yokohama, Japan
11 Department of Traditional Medicine, Faculty of Medicine, Toho University, Tokyo, Japan
12 Department of Oriental Medicine, Tokai University, School of Medicine, Isehara, Japan
13 Department of Clinical Laboratory, Hirotsu University Hospital, Aomori, Japan
14 Kichijoji Traditional Chinese Medicine Clinic, Department of Medical Education, Juntendo University School of Medicine, Tokyo, Japan
15 Kyuden Family Clinic, Tokyo, Japan
16 Department of Oriental Medicine Research Center, Kitasato University, Tokyo, Japan
17 Department of Otorhinolaryngology, Ekita Maehara Clinic, Tokyo, Japan
18 Kesennuma City Motoyo Hospital, Kesennuma, Japan
19 Sempuku Clinic, Osaka, Japan
20 Department of Kampo and nephrology, Saiseikai Kurihashi Hospital, Saitama, Japan
21 Department of Japanese Oriental (Kampo) Medicine, Oriental Medical Center, Iizuka Hospital, Fukuoka, Japan
22 Department of Internal Medicine and Kampo Medicine, Suda Medical Clinic, Chiba, Japan
23 Department of Psychosomatic Medicine, St. Luke’s International Hospital, Tokyo, Japan
24 Japan Traditional Chinese Medical Foundation of Osaka, Osaka, Japan
25 Department of Kampo Medicine, Aizu Medical Center, Fukushima Medical University, Fukushima, Japan
26 Department of General Medicine, Gunma University Graduate School of Medicine, Maebashi, Japan
27 Iwate Medical University Hospital, Iwate, Japan

*Correspondence. Shin Takayama
Tel: +81227177507
Fax: +81227177508
Email: takayama@med.tohoku.ac.jp
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ABSTRACT

**Aim:** We present the study protocol of a multicenter, retrospective observational study that aims to investigate the efficacy of the actual treatment (the efficacy of conventional and Kampo medicines) of patients with mild to moderate or suspected coronavirus disease (COVID-19).

**Methods:** This study is designed as a multicenter, retrospective observational study. Outpatients and inpatients will be recruited from Japanese hospitals. The inclusion criteria are as follows: having or suspected to have COVID-19, mild to moderate COVID-19, symptomatic, ≥20 years of age, male or female, able to communicate in Japanese, and treated with conventional and Kampo medicine. The exclusion criteria are: unable to provide informed consent due to dementia, psychosis, or psychiatric symptoms, severe COVID-19, or determined unsuitable for this study. The sample size is set at 1000, as this number of people can be treated at the collaborating medical institutions during the study period.

**Results:** The main outcome is the number of days without fever, with a body temperature of less than 37°C. The secondary outcome is set at common cold-like symptoms other than fever (fatigue, cough, shortness of breath, sputum, diarrhea) and severity of illness and hospitalization up to 14 days after the visit.

**Trial registration:** The trial was registered in the University Hospital Medical Information Network (Reservation No. UMIN000041301) on August 4, 2020.

**Conclusion:** Our study will explore the contribution of conventional and Kampo medicine in the treatment of patients with mild and moderate COVID-19.

**KEY WORDS:** Conventional treatment, COVID-19, Kampo medicine, prevention for severe stage, protocol, retrospective observational study, symptom relief

INTRODUCTION

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was discovered in Wuhan, Hubei, China, in November 2019. The World Health Organization declared the coronavirus disease (COVID-19) outbreak a public health emergency of international concern on 30 January 2020, and a pandemic on March 11, 2020. More than 30 million cases of COVID-19 have been identified worldwide, along with more than 960,000 deaths. In Japan, there have been over 78,000 cases of COVID-19 and over 1,500 deaths (as of 21 September 2020). The symptoms of COVID-19 include fever, cough, and shortness of breath. The rapid development of pneumonia and respiratory failure can also occur. About 81%, 14%, and 5% of cases are classified as mild, severe, and critical, respectively, and the overall case fatality rate has been reported as 2.3% [1]. Although coronaviruses were originally discovered as pathogenic viruses of the common cold, other highly pathogenic viruses such as severe acute respiratory syndrome and the Middle East respiratory syndrome have previously been reported. SARS-CoV-2 is characterized by the presence of an asymptomatic period of 1–14 days (median 5 days). COVID-19 can lead to severe disease and death, particularly in the elderly and patients with comorbidities, and no efficacious treatments are available to prevent worsening to severe stage.

Kampo medicine can be used to treat viral infections. During the Spanish influenza pandemic in 1918, many
patients were treated with Kampo, such as kakkonto, shosaikoto, daiseiryuto, shoseiryuto, kososan, shomakakkonto, and saikatsugekito [2,3]. Recent randomized controlled trials (RCTs) and systematic reviews have shown the effectiveness of the Kampo medicine, maoto, for influenza symptoms [4]. Kampo medicine can have antiviral, immune-modulating, and anti-inflammatory effects [5–7], and many clinical practice guidelines recommend its use according to the results of randomized controlled trials (RCTs) [8–10]. Recently, various medicines, including antiviral drugs, antiparasitic drugs, cytokine modulators, and steroids, have been investigated for their efficacy in COVID-19. Some Kampo medicines may be efficacious in the treatment of COVID-19. However, their efficacy in mild and moderate-stage COVID-19 patients remains contentious. Therefore, it is important to investigate the efficacy of the actual treatment (the efficacy of conventional and Kampo medicines) of COVID-19.

Here, we present the study protocol of our multicenter, retrospective observational study that aims to investigate the contribution of conventional and Kampo medicine in the treatment of patients with mild to moderate or suspected COVID-19, the Integrative Management in Japan for Epidemiologic Disease (IMJEDI study-Observation).

METHODS

Trial design
The study was designed as a multicenter, retrospective observational study.

Participants
Outpatients and inpatients will be recruited from Japanese academic and non-academic hospitals. The inclusion criteria are: having or suspected to have mild to moderate COVID-19, symptomatic, ≥20 years of age, male or female, able to communicate in Japanese, and treated with conventional and Kampo medicine. The exclusion criteria are: unable to provide informed consent due to dementia, psychosis, or psychiatric symptoms, severe COVID-19, or determined unsuitable for this study by a physician.

Outcomes
The main outcome is the number of days without fever, with a body temperature of less than 37°C. The secondary outcome is set at common cold-like symptoms other than fever (fatigue, cough, shortness of breath, sputum, diarrhea) and severity of illness (oxygen administration) and hospitalization up to 14 days after the visit.

Sample size
A target sample size of 1000 patients is planned in light of the feasibility of the study. Since there are currently no drugs that have shown efficacy in mild or moderate COVID-19, and the efficacy of the symptomatic drugs used in this study is unknown, the sample size was set to a number that could be treated in the outpatient clinic of the collaborating medical institutions during the study period.

Statistical analysis
For patient background factors, descriptive statistics are calculated for continuous variables and comparisons between groups are made using t-tests. For categorical variables, the number of cases and proportions will be calculated, and between-group comparisons will be made using the \( \chi^2 \) test.

For each group, we will estimate the Kaplan–Meier survival curves of days to symptom relief of the primary endpoint (fever), calculate point estimates of median survival and 95% confidence intervals, and compare the results between groups by the Log-rank test. In addition, point estimates of the restricted mean survival time (RMST) for days to relief of primary endpoint will be calculated in an exploratory manner, and a comparison of RMST between groups will be made.

The secondary endpoints, common cold-like symptoms other than fever (fatigue, cough, shortness of breath, sputum, diarrhea), will be analyzed in the same way as the primary endpoint. As a complementary analysis, combinations of symptoms as a single composite endpoint will also be analyzed.

Point estimates of the proportion of severe disease (oxygen administration) and the proportion of hospitalizations up to day 14 from the date of consultation and the difference between groups will be estimated for the secondary endpoints. The \( \chi^2 \) test will be performed for group comparison.

As the severity of the disease has been reported to vary with age and comorbidities, a complementary analysis will also be considered which adjusts age and type of comorbidity or clinically important factors for group comparisons of primary and secondary endpoints. Statistical analyses will be performed using SAS software (ver.9.4; SAS Institute Inc., Cary, NC, USA).

Trial status
Protocol version 1.0 as of 20 July 2020.
Recruitment start (expected): 1 January 2020.
Recruitment finish (expected): 31 August 2021.

Trial registration
The trial was registered in the University Hospital Medical Information Network (UMIN) (Reservation No. UMIN000041301) on August 4, 2020 (see https://upload.umin.ac.jp/cgi-open-bin/ctr ctr_view.cgi? recptno=R000047163).

Declarations
Ethics approval and consent to participate.
This protocol was approved by the Certified Clinical Research Review Board, Tohoku University, Sendai, Miyagi, Japan, on 20 July 2020 (Certification No. 19728). The authors certify that this study has received ethical approval from the appropriate ethical committee.

This research will not use samples or other materials obtained from human subjects and is purely academic research. Informed consent will not be obtained from the research subjects. However, information about the research, including its purpose, will be made available to the public, and subjects will be allowed to refuse participation. Disclosure of research-related matters will be made by posting disclosure materials on the website or hospital bulletin board of each institution. The principal investigator or researcher will respond to any inquiries.

**DISCUSSION**

The possible application of Kampo medicine for COVID-19, according to the stage of disease, was reported by the COVID-19 Special Research Working Group in the Japan Society for Oriental Medicine [5,6]. Sixty-four clinical trials on COVID-19 are registered in the University Hospital Medical Information Network [11], of which three trials include Kampo or traditional medicine. As of 21 September 2020, 20 RCTs on COVID-19 are registered in the Japan Registry of Clinical Trials [12], among which one trial includes Kampo medicine [13]. These trials include some medicines that have already been approved for other conditions. If an existing medicine is found to be effective for COVID-19, then the approval period and discovery cost will be reduced. The results of the current study will be awaited.

This study is introduced on the home page of several societies, including the Japan Society for Oriental Medicine, the Japanese Association for Infectious Diseases, the Japanese Respiratory Society, Japan Primary Care Association, and the Japanese Society of Hospital General Medicine. Some case reports suggested the possible treatment of COVID-19 in mild to moderate stage by Kampo medicines [14–16]. Especially, Irie et al. reported three cases successfully treated with saikatsugetsukito, which is the combination of kakkonto and shosaikotokakikyosekko [17].

We hope that many medical institutions will register for this study early on. Our study will investigate the possibility of using conventional and Kampo medicine to treat patients with mild and moderate COVID-19.

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**CONFLICTS OF INTEREST**

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