

Clinical Study Protocol

Conventional-dose Versus Half-dose Sulfamethoxazole-trimethoprim for the Prophylaxis of Pneumocystis Pneumonia in Patients with Systemic Rheumatic Disease: A Non-blind, Randomized Controlled Trial

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Pneumocystis pneumonia (PCP) due to *Pneumocystis jirovecii* infection is the leading cause of fatal opportunistic infections in immunocompromised patients. We will determine whether a daily sulfamethoxazole-trimethoprim (SMX/TMP) dose of 200/40 mg was non-inferior to 400/80 mg for PCP prevention in patients with systemic rheumatic disease under immunosuppressive therapy. This is a randomized, open-label, multicenter controlled trial. The primary outcome is the rate of PCP prevention at 52 weeks. The secondary outcome is the discontinuation rate of SMX/TMP. The trial will evaluate the optimal dose of SMX/TMP for PCP prevention in patients with systemic rheumatic disease under immunosuppressive therapy.

Key words: pneumocystis pneumonia, prophylaxis, systemic rheumatic disease, sulfamethoxazole-trimethoprim, conventional-dose versus half-dose

Pneumocystis pneumonia (PCP) due to *Pneumocystis jirovecii* (*P. jirovecii*) infection is the leading cause of fatal opportunistic infections in immunocompromised patients [1-5]. PCP in patients with rheumatic disease has a different clinical course from that in patients with acquired immunodeficiency syndrome (AIDS), with a mortality rate as high as 32-50% [6,7]. In patients with systemic rheumatic disease, the overall incidence of PCP is around 2%; however, higher patient age, lower lymphocyte count, coexisting pulmonary disease, the use of moderate to high doses of glucocorticoids, and concomitant immunosuppressive agents increase the risk of PCP [8-11]. The specific underlying rheumatic disease affects the morbidity rate:

8-12% in granulomatosis with polyangiitis, 6.5% in polyarteritis nodosa, 2.7% in polymyositis/dermatomyositis, 2% in systemic lupus erythematosus, and 0.1-0.3% in rheumatoid arthritis [12].

Sulfamethoxazole-trimethoprim (SMX/TMP) has been reported to be effective in preventing PCP in patients with rheumatic disease, resulting in a lower incidence of PCP [13]. The prevention rate has been reported to be 89-100% in HIV-positive patients [14-16] and 91% (95% confidence interval [CI], 68-98%) in HIV-negative patients [17].

However, clinicians often have to discontinue SMX/TMP due to adverse events (AEs), e.g., skin rash, increased serum creatinine, elevation of liver enzymes, hypoglycemia, hyperpotassemia, and hyponatremia

Received July 30, 2018; accepted October 18, 2018.

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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

[18-20]. The frequency of AEs due to SMX/TMP in rheumatic disease patients is higher than in the general population, with a discontinuation rate of 36.4-38.5% [21]. It is important to reduce the discontinuation rate of PCP prophylaxis, because most patients with systemic rheumatic disease require long-term immunosuppressive therapy.

Utsunomiya *et al.* [22] conducted a multicenter, open-label, randomized controlled trial to compare the effectiveness and discontinuation rates among three groups: a single-strength group (SMX/TMP at 400/80 mg daily), a half-strength group (200/40 mg daily), and an escalation group (starting with 40/8 mg daily, increasing incrementally to 200/40 mg daily). They reported that both the half-strength group and the escalation group had an excellent estimated non-incidence rate of PCP, and both groups showed superior safety compared to the single-strength group. However, they also reported that there were no PCP cases in any group at week 24.

Against this background, we designed a trial to demonstrate the non-inferiority of the half-dose prophylaxis group by comparing a conventional therapy group (SMX/TMP at 400/80 mg daily) with a half-dose prevention group (SMX/TMP at 200/40 mg daily). The primary endpoint was the non-incidence rate of PCP, and the major secondary endpoint was the drug continuation rate at week 52.

Endpoints

Primary outcome measure. The primary outcome measure will be the number of patients in each treatment arm who are diagnosed with PCP. The diagnosis of PCP will be considered definitive if *P. jirovecii* is identified by a microscopic analysis of respiratory samples from patients who meet each of the following three criteria: clinical manifestations (pyrexia, dry cough, or dyspnea), hypoxemia, and radiologic findings compatible with PCP. The diagnosis of PCP will be considered presumptive if a patient meets all three of the aforementioned criteria and has either a positive polymerase chain reaction for *P. jirovecii* deoxyribonucleic acid or an increased serum level of β -D glucan with an appropriate response to standard treatments for PCP [23].

Secondary outcome measures. The secondary outcome measures are (1) the drug discontinuation rate in each treatment arm for any reason, and (2) the AEs

due to SMX/TMP at week 52.

Eligibility Criteria

The target population will be patients admitted to our 2 hospitals (see below) who fulfill the classification criteria for their respective systemic rheumatic diseases.

Inclusion criteria. (1) Men and women aged over 20 years. (2) Admission to one of our hospitals for the diagnosis and/or treatment of new-onset or relapsed systemic rheumatic disease during the period from April 1, 2018, to March 31, 2021. (3) Current treatment with ≥ 0.6 mg/kg/day of oral prednisolone or an equivalent dose of one or more corticosteroids with or without any immunosuppressant. (4) No prior treatment with SMX/TMP, pentamidine isethionate, dapsone, or atovaquone. (5) Serum creatinine levels within the hospital's normal range. (6) Able and willing to provide written informed consent.

Exclusion criteria. (1) Contraindications to SMX/TMP. (2) Past history of PCP. (3) Prior treatment with a biologic agent. (4) Currently uncontrollable complication(s). (5) Body weight < 40 kg. (6) Currently pregnant or breastfeeding. (7) Unable to begin SMX/TMP within 14 days of starting prednisolone. (8) Unable to provide informed consent.

Methods

Aim and design. This is a 52-week, randomized, open-label, two-arm, parallel-group, multicenter controlled trial. It is a pragmatic clinical trial designed to identify the optimal dose of SMX/TMP for the prophylaxis of PCP in patients with systemic rheumatic disease. Fig. 1 provides the study flow chart.

Our trial hypothesis is that at week 52, SMX/TMP at a daily dose of 200/40 mg will result in a lower drug discontinuation rate and a PCP prevention rate that is similar to that of SMX/TMP at a daily dose of 400/80 mg.

Setting. This trial will be conducted in two hospitals: Juntendo University Hospital and the Juntendo Tokyo Koto Geriatric Medical Center in Tokyo, Japan.

Ethical considerations and registration. This study will be conducted in accordance with the Declaration of Helsinki and the Ethics Guidelines for Clinical Research issued by the Ministry of Health, Labour, and Welfare of Japan. Informed consent will be

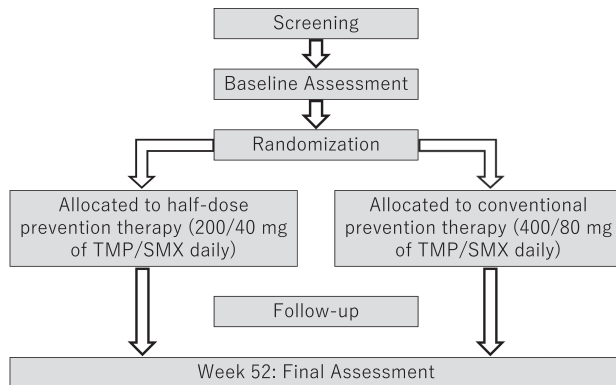


Fig. 1 TMP/SMX: sulfamethoxazole-trimethoprim.

obtained from all patients before registration. The trial has been approved by the Ethics Committees of both institutions involved in the study, and has been reviewed and ethically approved by the Ethics Committee of Juntendo University Hospital (#17-237). The study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry as UMIN000031513.

Withdrawal of participants. Participants will have the right to withdraw from this study at any time for any reason.

Randomization. Three hundred patients will be recruited from the two hospitals, and then randomly allocated in a 1 : 1 ratio (using an online database) to a conventional prevention therapy group or a half-dose prevention therapy group with block randomization. Patients will be randomized automatically on the day of website registration.

AEs and safety. AEs *e.g.*, skin rash, increased serum creatinine, elevation of liver enzymes, hypoglycemia, hyperpotassemia, and hyponatremia, will be recorded as part of the data collection for each session and will be reported to the clinical authorities and to the Ethics Committee. Participants suffering from AEs will be referred for appropriate treatment.

Routine clinical practice. All other clinical procedures (including the use and tapering of glucocorticoids, the use of any immunosuppressant without biological agents, and blood examinations) will be performed according to the routine practice of each institution and independently of trial-arm allocation. In particular, the frequency with which blood examinations and chest X-rays are monitored will be based on existing protocols and clinician preferences.

Statistical Considerations

Sample size. Three hundred patients are to be recruited from the two centers and randomly allocated in a 1 : 1 ratio. As this is a non-inferiority trial, the sample size calculation is based on a baseline PCP incidence of 91% [17], a clinically relevant non-inferiority margin of 10%, a one-sided alpha of 2.5% (equivalent to a two-sided alpha of 5%), and < 10% protocol violations. Due to this anticipated protocol violation rate, a greater number of patients will be recruited to the full study, as not all patients will be included in the final analysis.

Outcome analysis. The outcome measure of this trial will be defined in terms of the numbers of recruited and randomized patients, the protocol fidelity, and the follow-up rates by trial arm. These statistics will inform a Consolidated Standards of Reporting Trials (CONSORT) diagram reporting the patient recruitment, treatment, and retention. All data will be coded for the patients' privacy, locked, and stored in the study office. The trial will be self-monitored at its initiation and at the end of the trial, and at least once a year.

The patients' baseline characteristics, the treatment for underlying diseases and comorbidities, and demographic factors will be summarized for each randomized group. The multiple imputations method will be used to impute missing primary or secondary outcomes. To compare demographic and disease characteristics between groups, the Mann-Whitney *U*-test will be used for non-normally distributed variables. Categorical variables will be compared using Fisher's exact test. The drug discontinuation rates of each group will be compared with Kaplan-Meier curves that are plotted and evaluated using the log-rank test.

Discussion

This trial is intended to determine whether half-dose prevention therapy is non-inferior to conventional prevention therapy with regard to the rate of PCP prevention. In this study, we define the drug discontinuation rate as a secondary endpoint since 200/40 mg of SMX/TMP was reported to result in a lower drug discontinuation rate than 400/80 mg [22]. If the validity of our hypothesis is confirmed by the primary endpoint results, half-dose prevention therapy may be estab-

lished as optimal for the prophylaxis of PCP in patients with systemic rheumatic disease.

Systemic rheumatic diseases include not only those affecting young people, such as systemic lupus erythematosus, but also those affecting the elderly, e.g., microscopic polyangiitis and giant cell arteritis. We reported the continuation rate of SMX/TMP in microscopic polyangiitis patients at the Juntendo Tokyo Koto Geriatric Medical Center, which is one of the facilities involved in the current trial [24]. Low drug tolerability in the elderly is a clinically significant problem, and SMX/TMP is no exception in this regard. We feel that these factors will reflect real-world practices as closely as possible.

This study may have no cases of PCP in either group during the observation period, as in a previous study [22]. If the overall incidence of PCP is 0% in the current trial, the statistical analysis of the primary endpoint is not applicable. In that case, we will report whether 400/80 mg or 200/40 mg of SMX/TMP has a favorable preventive effect against PCP in patients with systemic rheumatic disease, and we will evaluate the drug discontinuation rate as a secondary outcome.

In patients with systemic rheumatic disease, PCP can be a fatal complication. This is a clinically important trial as its ultimate goal is to achieve a decreased discontinuation rate of SMP/TMX without reducing the drug's preventive effect.

Trial status. Issue date: February 28, 2018; Protocol original; Author Y.A. At the time of manuscript submission, the trial was in the recruitment phase.

Recruitment. This trial is currently being established. Recruitment is scheduled to start at the first site by April 1, 2018. The proposed start date is April 1, 2018. The proposed end date is March 31, 2022 (end of follow-up).

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