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Clinical Study Protocol

Conventional versus Rapid Glucocorticoid Tapering in Severe Systemic Lupus Erythematosus Patients: A Non-Blind, Randomized Controlled Trial

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Glucocorticoids (GCs) have long played a central role in the treatment of systemic lupus erythematosus (SLE), but these drugs have many adverse effects. We will determine whether rapid weekly GC tapering is non-inferior to conventional biweekly tapering in patients with severe SLE. This is a randomized, open-label, multicenter controlled trial. The primary outcome is the relapse-free survival rate at 52 weeks. The main secondary outcome is the prevalence of the Lupus Low Disease Activity State at 52 weeks. The trial will determine the optimal method of tapering GCs in patients with severe SLE.

Key words: systemic lupus erythematosus, relapse-free survival rate, glucocorticoid, tapering, Lupus Low Disease Activity State

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown cause in which multiple organs are damaged by various autoantibodies and immune complexes [1]. Although SLE is usually improved by treatment with glucocorticoids (GCs) and/or immunosuppressants (ISs), patients may exhibit a cycle of remission and exacerbation that follows a refractory course.

Hench first reported the effectiveness of GCs for individuals with rheumatoid arthritis in 1948 [2], and Kendall, Hench, and Reichstein were awarded the Nobel prize for this discovery in 1950. Dubois reported the effectiveness of the GCs prednisone and prednisolone in SLE patients in 1956 [3]. Since then, GCs have played a central role in the treatment of SLE. The prognosis of SLE has improved from a 5-year survival rate < 50% in 1955 [4] to a recent 10-year survival rate > 90% [5, 6]. With the advent of antimalarials and various ISs, the treatment of SLE has changed, but the role of GCs has not diminished.

Because GCs also have many detrimental effects, their initial and maintenance doses should be as low as possible while still providing a sufficient therapeutic effect [7]. In 1994, the Textbook of Clinical Rheumatology recommended the following guideline for treating SLE with GCs: "Continue treatment for 4 to 8 weeks until activity is reduced, and then taper. In principle, the taper rate is 10% over 2 weeks, with monitoring of disease activity" [8-10]. In contrast, a consensus report in 2004 by the Ad Hoc Working Group on Steroid-Sparing Criteria in Lupus [11] recommended

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that the administration of a GC to patients with severe SLE should be tapered by 5 mg/week as prednisolone equivalents during the first several weeks. However, no clinical trials have directly compared these 2 tapering methods.

Several clinical guidelines have been published in recent years regarding the definition of severe SLE. Most of these include the following: rash involving >2/9 body surface area, myositis, severe pleurisy and/or pericarditis with effusion, ascites, enteritis, myelopathy, psychosis, acute confusion, optic neuritis, platelets $<25\times10^9$/L, or class III or IV ± V lupus nephritis [7, 12, 13]. The most commonly used SLE classification criteria are those of the 1997 American College of Rheumatology (ACR) and the Systemic Lupus International Collaborating Clinics (SLICC) system [14, 15]. The SLE Disease Activity Index-2K (SLEDAI-2K) and the British Isles Lupus Assessment Group Index (BILAG) are often used for the measurement of SLE disease activity [16, 17]. The Lupus Low Disease Activity State (LLDAS) was defined recently as a possible target when treating SLE [18].

We designed a trial to evaluate the usefulness of rapid GC tapering (5 mg/week) in a comparison with conventional tapering (5 mg/2 weeks). The primary endpoint will be the relapse-free survival rate at week 52, and the major secondary endpoint will be the prevalence of the LLDAS at week 52.

Endpoints

Primary outcome measure. The primary outcome measure will be the number of patients in each treatment arm who die or who are diagnosed with a major SLE flare, based on one or more of the following criteria after the remission or low disease activity state accompanied by an SLEDAI value ≤4: (1) a >12-point change in the SLEDAI value; or (2) a new onset or worsening of central nervous system (CNS)-SLE, vasculitis, nephritis, myositis, thrombocytopenia (platelet count <60,000), or hemolytic anemia (hemoglobin <7 mg/dl) requiring the doubling of the patient's prednisone dose or a dose >0.5 mg/kg/day; or (3) the use of new ISs; or (4) an increase in the patient's Physician Global Assessment score to >2.5 [19].

Secondary outcome measures. The secondary outcome measures are the following parameters at 52, 104, and 156 weeks, respectively: (1) the relapse-free survival rate, (2) the prevalence of LLDAS, (3) the cumulative dose of GCs, (4) the maintenance dose of GCs, and (5) the rate of comorbid infection requiring hospitalization. The definition of the LLDAS was as follows: (1) SLEDAI ≤4, with no activity in major organ systems (*i.e.*, renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity; (2) no new lupus disease activity compared with the previous assessment; (3) a Physician Global Assessment ≤1 (scale 0-3); (4) a current prednisolone (or equivalent) dose ≤7.5 mg/day; and (5) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents. The maintenance dose of GCs was defined as the dose of GCs at the last observation in patients with remission or a low disease activity state.

Eligibility Criteria

The target population will be patients who fulfill the classification criteria described below for SLE and who are admitted to our 2 hospitals (see below).

Inclusion criteria. The inclusion criteria are as follows: (1) men and women aged >20 years, (2) with the ability and willingness to provide written informed consent, (3) fulfilling the 1997 ACR SLE classification criteria or the SLICC SLE classification criteria and a prior diagnosis of SLE [14, 15], (4) current treatment with ≥0.5 mg/kg/day and >40 mg/day of oral prednisolone or an equivalent doses of a GC with or without any IS, and not yet tapered in this term.

Exclusion criteria. The exclusion criteria are as follows: (1) unable to provide informed consent, (2) experiencing currently uncontrollable complications, (3) currently pregnant or nursing, and (4) men or women who have a pregnancy planned within 52 weeks, (5) patients who have never achieved remission or a low disease activity state within the observation period. The remission or low disease activity state was defined as an SLEDAI value ≤4.

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 method of GC tapering in patients with severe SLE. Figure 1 is the study flow chart.

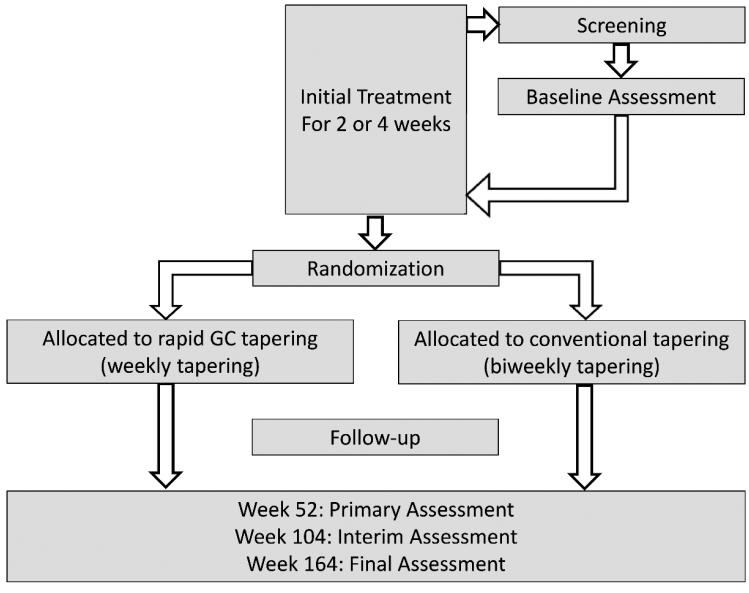

Fig. 1 General schema of allocation.

The conventional GC tapering group will receive initial GC treatment for 2 or 4 weeks, and then the GC will be tapered by 10 mg once every 2 weeks to 50 mg/day, then tapered by 5 mg every 2 weeks to 40 mg/day, and finally tapered by 2.5 mg every 2 weeks to 30 mg/day.

The rapid GC tapering group will receive initial GC treatment for 2 or 4 weeks and then the GC dose will be tapered by 10 mg/week to 50 mg/day and then tapered by 5 mg/week to 30 mg/day. The taper rate for doses < 30 mg/day will be left to each physician's discretion.

The trial hypothesis is that at week 52, the rapid-tapering group will have a lower cumulative GC dose than the conventional-therapy group but a similar relapse-free survival rate.

Setting. This trial will be conducted at two hospitals: the Juntendo University Hospital and the Juntendo University Nerima Hospital, both in Tokyo, Japan.

Ethical considerations and registration. This study will be conducted in accord with the Declaration of Helsinki and the Ethics Guidelines for Clinical Research issued by Japan's Ministry of Health, Labour, and Welfare. Informed consent will be obtained from all patients before the registration. The trial has been approved by the Ethics Committees of both hospitals involved in the study and has been reviewed and approved by the Ethics Committee of Juntendo University Hospital (J18-004). The study was registered at the Japan Registry of Clinical Trials as no. jRCT1031180196.

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

Randomization. One hundred patients will be recruited from the 2 hospitals and then randomly allocated in a 1 : 1 ratio using an online database to either the conventional GC tapering group or the rapid GC tapering group, with block randomization. The patients will be randomized automatically on the day of website registration. Blocked randomization will be performed in the following 2 blocks: (A) lupus nephritis, neuropsychiatric SLE, other; and (B) with or without steroid pulse.

Adverse effects and safety. Adverse effects will be recorded as part of the data collection at each time point and will be reported to clinical authorities and the Ethics Committee. Participants experiencing adverse effects will be referred for appropriate treatment.

Routine clinical practice. All other clinical procedures (including any IS administration and blood examinations) will be performed according to the routine practice of each hospital, and independently of the trial allocation. In particular, the frequency with which blood and urine examinations are performed will be

based on existing protocols and clinician preferences.

Statistical Considerations

Sample size. One hundred patients are to be recruited from the 2 hospitals and randomly allocated in a 1 : 1 ratio. As this is a non-inferiority trial, the sample size calculation is based on the baseline relapse-free survival rate of 96.2% identified in our previous study [20], as well as 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 larger number of patients than statistically necessary will be recruited to the full study, as not all patients will be included in the final analysis.

Outcome analysis. The outcome measures 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, 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 1 ×/year.

The patients' baseline characteristics, the treatment(s) of their underlying diseases or comorbidities, and their demographic factors will be summarized for each randomized group. The multiple imputation method will be used to impute missing primary or secondary outcomes. For the comparison of the outcomes 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 relapse-free survival rate of each group will be compared with Kaplan-Meier curves that are plotted and evaluated using the log-rank test.

Discussion

This study is intended to investigate whether rapid GC tapering is non-inferior to conventional GC tapering with regard to the relapse-free survival rate. We will determine the prevalence of LLDAS, the cumulative doses of GCs, and comorbidities. If our hypothesis (*i.e.*, that rapid GC tapering is non-inferior to conventional GC tapering with regard to the relapse-free survival rate) is supported by the results of the primary endpoint, then rapid GC tapering may be established as the optimal tapering approach in patients with severe SLE.

Since high-dose GC therapy has many adverse effects, the European League Against Rheumatism (EULAR) has already published recommendations on the management of medium- to high-dose GC therapy in rheumatic diseases [21]. The present study is expected to reduce the problems caused by these adverse effects in patients with severe SLE by reducing the cumulative GC dose.

It is possible that no patients in either study group will experience an SLE flare during the observation period. If the overall SLE flare incidence is 0%, the statistical analysis of the primary endpoint will not be applicable. In that case, we will report comparisons between the 2 groups in terms of the prevalence of LLDAS and any differences in therapeutic effects.

The primary outcome and the relapse-free survival rate as secondary outcomes are similar but not the same. We consider that the primary outcome is analyzed cross-sectionally with Mann-Whitney's *U*-test, and the relapse-free survival rate is analyzed over time with Kaplan-Meier curves and log-rank tests.

In patients with SLE, the cumulative dose and the taper rate of GCs are of major concern. This study is a clinically important trial that will directly compare conventional and rapid GC tapering and will investigate the safety of the latter.

Recruitment. This trial is currently being established. Recruitment began at the first site on April 1, 2019. The study's start date was also April 1, 2019. The proposed end date is March 31, 2022 (the end of the follow-up).

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