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Low-dose Glucocorticoids Plus Rituximab versus High-dose Glucocorticoids Plus Rituximab for Remission Induction in ANCA-associated Vasculitis (LoVAS); a Multicentre, Open Label, Randomised Control Trial

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ABSTRACT

Introduction: Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a form of systemic vasculitides. The current standard induction therapy with the combination of high-dose glucocorticoids and cyclophosphamide or rituximab has high remission rates of 80-90%. However, it is also associated with various side effects including death due to infection or cardiovascular disease. There is an unmet medical need of a new therapy reducing side effects.

Methods and analysis: This is a phase IV multi-centre, open label, randomised controlled trial that aims to evaluate the efficacy and safety of a new remission induction regimen with the combination of low-dose glucocorticoids and rituximab. Newly diagnosed AAV patients are assessed for eligibility at 34 tertiary rheumatology/nephrology centres in Japan. One hundred forty patients are randomized (1:1) to receive low-dose prednisolone (0.5mg/kg daily) plus rituximab (375mg/m^2 weekly) or high-dose prednisolone (1mg/kg daily) plus rituximab. The trial consists of remission induction and maintenance phases. The primary endpoint of the study is the remission rate at 6 months (induction phase). Relapse and long-term safety profile are also assessed until 24 months (maintenance phase).

Ethics and dissemination: The protocol was approved by the Institutional Review Board of each hospital. The trial was registered at the UMIN clinical registry (UMIN000014222) and ClinicalTrials.gov registry (NCT02198248). The LoVAS trial is currently ongoing and is due to finish in September 2019. The findings of this trial will be disseminated through peer-reviewed publications and conference presentations and also be disseminated to participants.

Trial registration number: UMIN000014222 and NCT02198248

Strengths and limitations of this study

- To establish a new remission induction regimen with fewer adverse events is now the biggest remaining issue in the field of AAV. The low-dose glucocorticoid plus rituximab regimen in this trial has potential to resolve it.
- There have been no other trials using the rituximab-based remission induction regimen followed by the rituximab-based maintenance regimen for newly diagnosed AAV patients.
- Electronic data capture system, on-site monitoring and audit in accordance with Good Clinical Practice will increase reliability of the results of this trial.
- This is an open label trial, though the primary endpoint is a relatively hard endpoint.
- The severest forms of AAV, such as severe glomerulonephritis and severe alveolar haemorrhage, were excluded from this trial.

INTRODUCTION

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is characterized by a small to medium-size vasculitis and the presence of ANCA. AAV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss). AAV is a life-threatening disease and the mortality is 80% at 1 year in untreated patients.[1] The randomized controlled trials in the past 20 years have led to the current standard therapy of the combination of high-dose glucocorticoids and cyclophosphamide for remission induction of AAV.[2-4] This combination therapy has high remission rates of 80-90% and has reduced mortality to 25% at 5 years. However, it is also associated with various side effects. Infections and cardiovascular diseases due to the treatment are main causes of death in AAV patients, along with active vasculitis.[5,6] In addition, there are not only fatal side effects but also ones reducing patients' quality of life, such as osteoporosis, peptic ulcer, myopathy, and cataract. Thus, new therapies with lower toxicity are needed.

In the pathogenesis of AAV, importance of B cells has been widely known. The presence of B cells at sites of inflammation,[7,8] correlation of B cell activation with disease activity in GPA,[9] the efficacy of cyclophosphamide which is a relatively B cell-specific immunosuppressant,[10] and the presence of pathogenic autoantibodies, MPO-/PR3-ANCA,[11,12] were previously reported. Those facts led to a rationale for B cell-targeted therapy in AAV. Rituximab is an anti-CD20 monoclonal antibody depleting B cells. The two randomised controlled trials, the RAVE and RITUXVAS trials, evaluated efficacy of rituximab in remission induction of AAV, and the results were published in 2010.[13,14] They demonstrated similar remission rate for newly diagnosed patients between the rituximab and cyclophosphamide groups in combination with high-dose glucocorticoids. As to relapsing patients, the RAVE trial demonstrated higher remission rate in the rituximab group than in the cyclophosphamide group. Contrary to the trial

investigators' expectation, safety profiles in the both trials were also similar between the rituximab and cyclophosphamide groups suggesting that high-dose glucocorticoids are currently the main contributor to adverse events in AAV. Since the results of the RAVE and RITUXVAS trials have been reported, rituximab with high-dose glucocorticoids has been established as another standard therapy for remission induction of AAV. [15,16]

There is an unmet medical need of a new therapy reducing adverse events in AAV. Lowering dose of glucocorticoids is a possibility to resolve the need. Previous observational and meta-analysis studies looking at regimens of combination of glucocorticoids and conventional immunosuppressants showed lower glucocorticoid dosing in remission induction phase was associated with higher relapse rates.[17,18] However, those studies did not include data of AAV patients treated with rituximab. Rituximab has a mechanism of action that is completely different from those of conventional immunosuppressants, and previous retrospective observational studies suggested the combination of low-dose glucocorticoids and rituximab could achieve re-remission in relapsing cases.[19] Thus, to resolve the unmet needs to reduce dose of glucocorticoids in remission induction therapy for AAV, we aim to evaluate whether rituximab can reduce a total amount of dose of glucocorticoids while maintaining the remission rate in this multicentre, open label, randomised controlled trial (LoVAS).

OBJECTIVES

We aim to examine the hypothesis that the low-dose glucocorticoid regimen is non-inferior in efficacy to the high-dose one when combined with rituximab in remission induction for AAV.

METHODS

Trial design

The LoVAS trial is an open-label, randomized trial comparing two arms that undergo remission induction treatment with rituximab plus low-dose glucocorticoids or rituximab plus high-dose glucocorticoids. After the induction treatment, patients in remission proceed promptly to maintenance treatment. The trial is designed and independently conducted by Chiba University Hospital. The ethics committee at each participating trial site approved the protocol and consent form. The trial will be conducted in full compliance with the articles of the Declaration of Helsinki. All analyses will be conducted by Chiba University, independent of the sponsor, according to the pre-specified statistical analysis plan. Executive committee members, and coauthors will review the data, revise the manuscript, and assume responsibility for trial adherence to the protocol and the accuracy and completeness of the data and analyses. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT checklist) was followed in designing the study protocol (see online supplementary appendix).

Eligibility criteria

Eligible patients are those who meet all of the following inclusion criteria and who do not have any listed exclusion criteria.

Inclusion criteria

1. Provision of written informed consent by patients themselves or their legally acceptable representative.
2. Age ≧ 20 years at the time of consent.
3. New diagnosis of ANCA-associated vasculitis (MPA, GPA, or renal-limited vasculitis) according to the definition of the 2012 Chapel Hill Conference (**Table 1**).[20]
4. Positive test for either MPO-ANCA or PR3-ANCA with ELISA, CLEIA, or FEIA method.

Exclusion criteria

1. Previous treatment for ANCA-associated vasculitis prior to providing consent to participate in this trial
2. Glomerulonephritis with estimated glomerular filtration rate (eGFR)<15ml/min or pulmonary alveolar hemorrhage that requires oxygen inhalation of 2L/min or more
3. Any other systemic autoimmune diseases as a co-morbidity (Note 1)
4. Human Immunodeficiency virus (HIV) infection, Hepatitis B virus (HBV)/Hepatitis C virus (HCV) infection or history thereof (Note 2)
5. Females who are pregnant, breast feeding, or at risk of pregnancy and not using a medically acceptable form of contraception
6. A history of malignancy within the past 5 years
7. A history of tuberculosis within the past 1 year
8. A history of severe allergic reactions or anaphylaxis to monoclonal antibodies
9. A co-morbidity that may require use of glucocorticoids, immunosuppressive agents, biopharmaceutical, plasma exchange, or high-dose gamma-globulin therapy (Note 3)
10. Treatment with a B-cell-targeting biologic agents (e.g. rituximab, belimumab) within the past 6 months
11. Conditions that, in the investigator's opinion, are unsuited for safe conduct of this trial

(Note 1) This does not apply to those with rheumatoid arthritis, scleroderma, or Sjogren's syndrome, that are with no severe symptom and not requiring glucocorticoid therapy.

(Note 2) In cases that patients are positive for HBV antibodies but negative for HBV-DNA, trial participation is allowed under HBV-DNA monitoring, considering that the Japanese local guideline for HBV allows rituximab to be administered to such patients.

(Note 3) Patients with well-controlled bronchial asthma not requiring oral glucocorticoids can participate in the study (inhaled steroids are allowed to use).

Table 1. Chapel Hill Consensus Conference definitions for ANCA-associated vasculitis

ANCA-associated vasculitis	**Necrotizing vasculitis, with few or no immune deposits. Small vessels (i.e., capillaries, venules, arterioles, and small arteries) are predominantly affected. Necrotizing arteritis of small/medium arteries may accompany. It is associated with MPO-/PR3-ANCA, but ANCA are not always found in all patients.**
MPA	Necrotizing vasculitis, with few or no immune deposits. Small vessels (i.e., capillaries, venules, arterioles, and small arteries) are predominantly affected. Necrotizing arteritis of small/medium arteries may accompany. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis also often occurs. Granulomatous inflammation does not occur.
GPA	Necrotizing granulomatous inflammation primarily affecting the upper and lower respiratory tract, and necrotizing vasculitis predominantly affecting small and medium vessels (capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is usually found.

Recruitment

This trial was registered at the UMIN clinical registry and ClinicalTrials.gov registry in July 2014. Recruitment into the trial started in October 2014 and will end in September 2017, or until a total of 140 participants is recruited. This study is being conducted at 34 rheumatology or nephrology centres in Japan.

Sample size calculation

Based on the RITUXVAS trial[14] and the Cambridge University cohort[19], we assumed that 80% of the patients in both treatment groups would achieve remission at 6 months. We specified a non-inferiority margin of −20 percentage points for the difference in remission rates and a one-sided alpha level of 0.025. Assuming a 10% dropout rate, we calculated that we would need to enroll 70 patients in each group for an 80% statistical power to demonstrate non-inferiority.

Allocation

Registration and allocation for an eligible patient will be performed by investigators using the DATATRAK Electronic Data Capture system (DATATRAK ONE version 14.1.0). Eligible patients who provide written informed consent will be randomized to either low-dose or high-dose glucocorticoid groups at a ratio of 1:1 using a minimization method.[21, 22] Referring to the previous trials,[13,14] age at entry (<65 years versus ≥65 years), renal function at entry (eGFR < 50 ml/min versus ≥ 50 ml/min) and ANCA subtypes (MPO-ANCA versus PR3-ANCA) were chosen as allocation adjustment factors.

Blinding

This is an open label trial. The both treatment arms share the same regimen of administration of rituximab. In addition, it can be easily judged by subject's appearance, namely moon face due to high-dose glucocorticoid therapy, whether a subject is

randomised to low-dose or high-dose glucocorticoid groups. Thus, it was not feasible logistically or financially to blind the glucocorticoid intervention. Further, the trial primary endpoint of disease remission based on Birmingham Vasculitis Activity Score Version 3 (BVAS)[23] scores has been known as a relatively hard endpoint.

Trial treatments

Remission induction period

Prednisolone must be initiated on the randomization day or the following day. Initial doses of prednisolone are 0.5mg/kg/day in the low-dose glucocorticoid group and 1.0mg/kg/day in the high-dose glucocorticoid group respectively. Prednisolone will be stopped at 5 months in the low-dose group, while dose of prednisolone will be reduced to 10mg/body/day until 6 months in the high-dose group. The high-dose regimen is in consistent with the current standard treatment.[24,25] Prednisolone tapering schedules for low-dose and high-dose glucocorticoid regimens are shown in Table 2. Only in cases in which BVAS does not reach 0, or CRP and ANCA values are not normalized, the principal investigator/co-investigator can postpone the initiation of the prednisolone discontinuation step in the low-dose glucocorticoid regimen (5 >4 >3 >2 >1 >0 mg/body/day). Once the step has been initiated, prednisolone should be discontinued 14 weeks after the initiation of the step.

In combination with prednisolone, four doses of rituximab (375mg/m^2/w) will be administered via intravenous infusion in the both the treatment regimens. The first dose of rituximab must be administered between day 1 and day 7. To reduce infusion reactions, premedication with oral administration of acetaminophen and diphenhydramine and intravenous administration of 125 mg of methylprednisolone is mandatory at the time of initial administration of rituximab. Regarding the premedication for the second and subsequent administration of rituximab, it is not mandatory and left to each study site.

In the absence of contraindication, the concomitant use of the following medications is recommended; proton pump inhibitors for peptic ulcer prophylaxis, bisphosphonates, vitamin D preparations, and calcium preparations for osteoporosis prophylaxis, and trimethoprim-sulfamethoxazole combination for Pneumocystis pneumonia prophylaxis.

Table 2. Dose of prednisolone according to the low-dose and high-dose regimens

weeks	Low-dose regimen	High-dose regimen
1-2	0.5mg/kg/day	1.0mg/kg/day
3-4	0.25mg/kg/day	0.8mg/kg/day
5-6	7.5mg/body/day	0.7mg/kg/day
7-8	5mg/body/day	0.5mg/kg/day
9-10	4mg/body/day	0.4mg/kg/day
11-12	3mg/body/day	0.35mg/kg/day
13-16	2mg/body/day	15mg/body/day
17-20	1mg/body/day	12.5mg/body/day
21-24	0mg/body/day	10mg/body/day

Remission maintenance period (post-treatment observation period)

After the prednisolone discontinuation step, prednisolone is not administered in the low-dose group. Prednisolone tapering schedule during the remission maintenance period is left to each investigator with no specific restrictions in the high-dose group. Discontinuation of prednisolone is not necessary in the high-dose group.

For the remission maintenance therapy, 1 g/body of rituximab will be administered every 6 months (6, 12, and 18 months) in the both groups.

Outcomes

Primary endpoint

The primary endpoint is the remission rate at 6 months. Remission is defined as a state in which BVAS ver3 score is 0 (or ≤1, if all items are persistent) and the oral prednisolone dose is 10 mg/day or lower. This is the most widely used efficacy index in evaluation studies of remission induction therapies for AAV, and has been used as a primary endpoint in the majority of previous clinical trials for AAV.

Secondary endpoints

The secondary endpoints include time to remission, death, relapse, end stage renal disease and the first serious adverse event, proportion of death, relapse, end stage renal disease for efficacy. For safety profile, number of serious adverse events and proportion of participants with serious adverse events are evaluated. As glucocorticoid-related side effects, new-onset diabetes mellitus, hypertension, dyslipidemia, insomnia, bone fracture and infection are specifically evaluated. In addition, cumulative dose of prednisolone, disease activity using BVAS, disease and treatments damage using Vasculitis Damage Index (VDI),[26] and health-related QOL using the Medical Outcomes Study 36-Item Short Form (SF-36)[27] are also measured.

Data collection

Trial visits and examinations

The trial is divided into three periods: 1. screening; 2. remission induction period (6 months, including the primary endpoint assessment); and 3. remission maintenance period. The schedule for the study visits and data collection is summarized in **Table 3**.

Table 3. Examination/observation schedule

	Screening	Remission induction period					Remission maintenance period	At trial withdrawal
Time point	Within 1 week	At 0 month (day1)	At 1 months	At 2 months	At 4 months	At 6 months	At 9, 12, 18, 24 months At confirmation of relapse	
Informed consent	●							
BVAS		●	●	●	●	●	●	●
VDI		●				●	●[1)]	●
SF-36		●				●	●[1)]	●
Blood/urine tests	●[2)]	●	●	●	●	●	●	●
ECG, X-ray	●							
Bone density		●					●[3)]	●
Pregnancy test	←							→

[1)] Only at 12, 18, and 24 months

[2)] Screening blood test items

[3)] Only at 12 and 24 months

<Blood/urine tests>

Blood cell count including B cell count

Serum biochemical tests (total protein, albumin, electrolytes [Na, K, Cl], BUN, serum creatinine, CPK, total bilirubin, AST, ALT, ALP, LDH, γ-GTP, CRP, Ig-G, Ig-A, Ig-M, C3, C4, complement titer, T-Cho, LDL-C, HDL-C, TG, blood glucose, HbA1c, MPO-/PR3-ANCA)

General urine test (glucose, protein, occult blood, sediment, urinary creatinine)

Data management, monitoring and auditing

The trial data will be entered electronically according to Good Clinical Practice at the participating site where the data are originated. All entries in the system will be backed up by the relevant source data. The trial investigators will maintain individual records for each subject as source data, which include a log of informed consent, medical records, laboratory data and other records or notes, as appropriate. After study completion, the data will be locked and transferred to SAS. Data are stored for at least 5 years after study completion.

Independent monitors will visit the sites to review the records, compare them with source documents, and observe and discuss the conduct of the trial with the investigators and site coordinator. The monitors are responsible for monitoring adherence to the protocol and guidelines, as well as ensuring completion of the eCRF and other documentation.

The study will be audited or inspected by the contract research organisation. In case of an audit, the investigators must make all study documentation available to the auditor. If an audit or inspection occurs, the investigators at the study site must discuss the findings and any relevant issues.

STATISTICAL METHODS

Statistical analyses and reporting of this trial will be conducted in accordance with the Consolidated Standards of Reporting Trials statement guidelines. All efficacy analyses will be primarily based on the full analysis set, which includes all patients who have received at least one dose of the trial treatment.

For the baseline variables, summary statistics will be constructed using frequencies and proportions for categorical data, and means and SDs for continuous variables. Patient characteristics will be compared using Pearson's chi-square test or Fisher's exact

test for categorical outcomes, and Wilcoxon rank-sum test for continuous variables, as appropriate.

For the primary analysis to evaluate treatment efficacy, the risk difference in the remission induction rate at 6 months between the rituximab plus low-dose glucocorticoid group and rituximab plus high-dose glucocorticoid group and its 95% confidence interval will be estimated using Wald statistics-based method. The non-inferiority is considered statistically proven if the lower limit of two-tailed 95% confidence interval of the risk difference exceeds -0.2. As a sensitivity analysis, adjusted risk differences will be estimated by the Mantel-Haenszel method. Adjustment factors to be used are allocation factors (age at the time of consent, eGFR, ANCA). The secondary analysis will be performed in the same manner as the primary analysis.

All comparisons have been planned, and all p values will be two-sided. P values <0.05 will be considered statistically significant. All statistical analyses will be performed using SAS version 9.4, and are described in the statistical analysis plan, which will be fixed prior to database lock.

ETHICS AND DISSEMINATION

Research ethics approval and protocol amendments

The protocol was approved by the Institutional Review Board (IRB) of each hospital before the start of the trial. Substantial amendments of the study protocol must be approved by IRB. The trial was registered at the UMIN clinical registry (UMIN000014222) and ClinicalTrials.gov registry (NCT02198248).

Informed consent

All participants will receive adequate information about the nature, purpose, possible risks and benefits of the trial, and on alternative therapeutic choices using an informed

consent approved by IRB. A participant must be given ample time and opportunity to ask questions and to consider participation in the trial. A completed informed consent is required for enrollment in the trial. The investigators must maintain the original signed consent form and a copy of the signed consent form.

Confidentiality

To assure confidentiality, trial participants will be allocated a unique trial identification number throughout the trial.

Dissemination plan

Data from all centres will be analysed together and published as soon as possible. Individual investigators will not publish data concerning their patients before publishing the trial final report. The trial results of remission induction (6 months) and remission maintenance (24 months) phases will be separately presented at scientific meetings and separately published in a peer-reviewed journal according to the trial protocol.

DISCUSSION

The previous randomized control trials for AAV have improved prognosis of this disease. The current standard therapies, high-dose glucocorticoids with cyclophosphamide or rituximab, have achieved high remission rate of 80-90%. However, there are still remaining issues such as glucocorticoids toxicity, severe conditions like alveolar haemorrhage or relapse prevention. The LoVAS trial aims to establish a new remission induction regimen with low-dose glucocorticoids and rituximab which enables to reduce the side effects.

Current guidelines recommend a combination of high-dose glucocorticoids and either cyclophosphamide or rituximab for remission induction of AAV.[15,16] Both the combination therapies showed the similar efficacy and safety,[13,14] therefore cyclophosphamide is

preferable to rituximab due to the high cost of rituximab except some specific instances (e.g. patients who wish to preserve their reproductive potential). However, positioning of rituximab will change from an alternative of cyclophosphamide to a single standard if this trial reveals an additional merit of rituximab allowing the low-dose glucocorticoids regimen.

There are some limitations in this study. Regional difference in AAV patients between have been widely known. [28] In Japan, MPA is a major form of AAV, while GPA is very rare (annual incidence; 18.2 and 2.1 per million). In most Caucasian countries, GPA is more frequent than MPA. The difference of MPA/GPA balance might be a problem when interpreting the trial results for non-Japanese patients. However, remission rates (the primary endpoint in this study) were similar between MPA and GPA patients in most previous trials. Long-term relapse rate (the secondary endpoint in this study) was higher in GPA than in MPA.

The second limitation is that this trial excludes the most life/organ-threatening forms of AAV, namely AAV presenting severe glomerulonephritis or alveolar haemorrhage. The low-dose glucocorticoid regimen can show a similar response rate with the high-dose regimen, but it might work more slowly than dose the high-dose regimen. We think the possibility of slower treatment response is not acceptable in AAV patient with severe glomerulonephritis or alveolar haemorrhage. However, the subject in this trial can cover a wide range of AAV forms, and the trial results can be applied to the majority of AAV patients.

Despite these possible limitations, the LoVAS trial is the first to examine the potential of rituximab to reduce corticosteroid dose in remission induction of AAV. The results will contribute to establish a safer treatment strategy, which is still a big remaining issue in the treatment of AAV.

Trial Status

The LoVAS trial first received ethical approval from the Institutional Review Board of Chiba University Hospital on February 18, 2014 (reference number G25051). As of July 17, 2017, LoVAS is actively recruiting in 33 centers with additional centers planned. A total of 75 of the planned 140 participants had been enrolled.

Declarations of interest Dr. Nakajima reports receiving grant support from Chugai Pharmaceutical Corporation (Roche group). Chugai Pharmaceutical Corporation was not involved in the planning of the protocol or in the conduct of the trial. No other potential conflict of interest relevant to this article was reported.

Dissemination policy The findings of this trial will be presented at national and international conferences and will be disseminated through peer-reviewed publications in accordance with the CONSORT Statement.

Author contributions All authors made a significant contribution to the conception and design of the study protocol. SF designed the original concept and wrote the study protocol and manuscript. The protocol and manuscript was critically reviewed by TS, TU, YK, KA, KK, DN, MH, HH, KI and HN. YS wrote the statistical analysis plan. SF is the coordinating investigator and HN is the chief investigator of this study. All authors gave approval for the publication.

Funding This trial was funded by intramural competitive grant of Chiba University Hospital for clinical research.

Ethics approval The protocol was approved by IRB of each participating hospital.

Provenance and peer review Not commissioned; internally peer reviewed

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P.1
	2b	All items from the World Health Organization Trial Registration Data Set	See the website of ClinicalTrials.gov. (NCT02198248).
Protocol version	3	Date and version identifier	P.1
Funding	4	Sources and types of financial, material, and other support	P.52
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P.53
	5b	Name and contact information for the trial sponsor	P.53
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P.52

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P.53-P.54
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P.15-P.17
	6b	Explanation for choice of comparators	P.15-P.17
Objectives	7	Specific objectives or hypotheses	P.5_& P.17
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P.5_& P.18-P.20_
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	See Appendix.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P.5-P.6_& P.21-P.22
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P.7-P.10 & P.26-P.29
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P.29-P.30
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P.40 & P.44 & P.49
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P.30

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P.6-P.7_& P.17-P.18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P.10 & P. 20
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P.10 & P.20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	No specific strategy is planned, and not addressed in the manuscript.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P.24-P.25
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P.23-P.24
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P.24
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A_(open label)

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A_(open label)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P.45-P.46
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P.46
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P45.-P.46
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P.40-P.42
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P.40-P.42
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P.40-P.42
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P.49
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P.45 & Interim analysis is not planned.

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P.35-P.38
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P.51
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P.47
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P.44-P.45_&_P.47-P.49
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P.22-P.23
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P.45
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P.52
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P.41-P.42 & P.53. This is a self-sponsored trial by the physicians,_and there is no limit to access the data.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	P.51

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P.52
	31b	Authorship eligibility guidelines and any intended use of professional writers	P.52
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	P.22
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Low-dose Glucocorticoids Plus Rituximab versus High-dose Glucocorticoids Plus Rituximab for Remission Induction in ANCA-associated Vasculitis (LoVAS): Protocol for a Multicentre, Open Label, Randomised Control Trial

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Low-dose Glucocorticoids Plus Rituximab versus High-dose Glucocorticoids Plus Rituximab for Remission Induction in ANCA-associated Vasculitis (LoVAS): Protocol for a Multicentre, Open Label, Randomised Control Trial

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ABSTRACT

Introduction: Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a form of systemic vasculitides. The current standard induction therapy with the combination of high-dose glucocorticoids and cyclophosphamide or rituximab has high remission rates of 80-90%. However, it is also associated with various side effects including death due to infection or cardiovascular disease. There is an unmet medical need of a new therapy reducing side effects.

Methods and analysis: This is a phase IV multi-centre, open label, randomised controlled trial that aims to evaluate the efficacy and safety of a new remission induction regimen with the combination of low-dose glucocorticoids and rituximab. Newly diagnosed AAV patients will be assessed for eligibility at 34 tertiary rheumatology/nephrology centres in Japan. One hundred forty patients will be randomized (1:1) to receive low-dose prednisolone (0.5mg/kg daily) plus rituximab (375mg/m^2 weekly) or high-dose prednisolone (1mg/kg daily) plus rituximab. The trial consists of remission induction and maintenance phases. The primary endpoint of the study is the remission rate at 6 months (induction phase). Relapse and long-term safety profile will also be assessed until 24 months (maintenance phase).

Ethics and dissemination: The protocol was firstly approved by the Institutional Review Board of Chiba University Hospital (reference number: G25051), and then approved by each participating site. The trial was registered at the UMIN clinical registry (UMIN000014222) and ClinicalTrials.gov registry (NCT02198248). The LoVAS trial is currently ongoing and is due to finish in September 2019. The findings of this trial will be disseminated through peer-reviewed publications and conference presentations and also be disseminated to participants.

Trial registration number: UMIN000014222 and NCT02198248

Strengths and limitations of this study

- To establish a new remission induction regimen with fewer adverse events is now one of the biggest remaining issues in the field of AAV. The low-dose glucocorticoids plus rituximab regimen in this trial has potential to resolve it.
- There are no other trials using the rituximab-based remission induction regimen followed by the rituximab-based maintenance regimen for newly diagnosed AAV patients.
- Electronic data capture system on-site monitoring and audit in accordance with Good Clinical Practice will increase reliability of the results of this trial.
- This is an open label trial, though the primary endpoint is a relatively hard endpoint.
- The severest forms of AAV, such as severe glomerulonephritis and severe alveolar haemorrhage, will be excluded from this trial.

INTRODUCTION

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is characterized by a small to medium-size vasculitis and the presence of ANCA. AAV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss). AAV is a life-threatening disease and the mortality is 80% at 1 year in untreated patients.[1] Several randomized controlled trials in the past 20 years have led to the current standard therapy of the combination of high-dose glucocorticoids and cyclophosphamide for remission induction of AAV.[2-4] This combination therapy has high remission rates of 80-90% and has reduced mortality to 25% at 5 years. However, it is also associated with various side effects. Infections and cardiovascular diseases due to the treatment are main causes of death in AAV patients, along with active vasculitis.[5,6] In addition, there are not only fatal side effects but also ones reducing patients' quality of life, such as osteoporosis, peptic ulcer, myopathy, and cataract. Thus, new therapies with lower toxicity are needed.

In the pathogenesis of AAV, importance of B cells has been widely known. The presence of B cells at sites of inflammation,[7,8] correlation between B cell activation and disease activity in GPA,[9] the efficacy of cyclophosphamide which is a relatively B cell-specific immunosuppressant,[10] and the presence of pathogenic autoantibodies, MPO-/PR3-ANCA,[11,12] were previously reported. Those facts led to a rationale for B cell-targeted therapy in AAV. Rituximab is an anti-CD20 monoclonal antibody depleting B cells. Two randomised controlled trials, the RAVE and RITUXVAS trials, evaluated efficacy of rituximab in remission induction of AAV, and the results were published in 2010.[13,14] They demonstrated similar remission rate between the rituximab and cyclophosphamide groups in combination with high-dose glucocorticoids. The subgroup analysis regarding only relapsing patients in the RAVE trial demonstrated higher remission rate in the rituximab group than in the cyclophosphamide group, though the

RAVE trial was not designed for this purpose and not powered to detect the difference in the subgroup. Contrary to the trial investigators' expectation, these trials reported similar safety profiles between the rituximab and cyclophosphamide groups. This fact suggested that high-dose glucocorticoids were the main contributor to adverse events in these regimens for AAV. Since the results of the RAVE and RITUXVAS trials have been reported, rituximab with high-dose glucocorticoids has been established as another standard therapy for remission induction of AAV. [15,16]

There is an unmet medical need of a new therapy reducing adverse events in AAV. Lowering dose of glucocorticoids is a possibility to resolve the need. Previous observational and meta-analysis studies looking at regimens of combination of glucocorticoids and conventional immunosuppressants showed lower glucocorticoid dosing in remission induction phase was associated with higher relapse rates.[17,18] However, those studies did not include data of AAV patients treated with rituximab. Rituximab has a mechanism of action that is completely different from those of conventional immunosuppressants, and previous retrospective observational studies have suggested the combination of low-dose glucocorticoids and rituximab can induce re-remission in relapsing cases.[19] Thus, to resolve the unmet needs to reduce dose of glucocorticoids in remission induction therapy for AAV, we aim to evaluate whether rituximab can reduce a total amount of dose of glucocorticoids while maintaining the remission rate in this multicentre, open label, randomised controlled trial (LoVAS).

OBJECTIVES

We aim to examine the hypothesis that the low-dose glucocorticoid regimen is non-inferior in efficacy to the high-dose one when combined with rituximab in remission induction for AAV.

METHODS

Trial design

The LoVAS trial is an open-label, randomized trial comparing two arms that undergo remission induction treatment with rituximab plus low-dose glucocorticoids or rituximab plus high-dose glucocorticoids. After the induction treatment, patients in remission will proceed promptly to maintenance treatment. The trial was designed and will independently be conducted by Chiba University Hospital. The ethics committee at each participating trial site has approved the protocol and consent form. The trial will be conducted in full compliance with the articles of the Declaration of Helsinki. All analyses will be conducted by Chiba University, independent of the sponsor, according to the pre-specified statistical analysis plan. Executive committee members, and coauthors will review the data, revise the manuscript, and assume responsibility for trial adherence to the protocol and the accuracy and completeness of the data and analyses. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT checklist) was followed in designing the study protocol (see online supplementary appendix).

Eligibility criteria

Eligible patients are those who meet all of the following inclusion criteria and who do not have any listed exclusion criteria.

Inclusion criteria

1. Provision of written informed consent by patients themselves or their legally acceptable representative.
2. Age ≧ 20 years at the time of consent.
3. New diagnosis of ANCA-associated vasculitis (MPA, GPA, or renal-limited vasculitis) according to the definition of the 2012 Chapel Hill Conference (**Table 1**).[20]

4. Positive test for either MPO-ANCA or PR3-ANCA with ELISA, CLEIA, or FEIA method.

Exclusion criteria

1. Previous treatment for ANCA-associated vasculitis prior to providing consent to participate in this trial
2. Glomerulonephritis with estimated glomerular filtration rate (eGFR)<15ml/min or pulmonary alveolar hemorrhage that requires oxygen inhalation of 2L/min or more
3. Any other systemic autoimmune diseases as a co-morbidity (Note 1)
4. Human Immunodeficiency virus (HIV) infection, Hepatitis B virus (HBV)/Hepatitis C virus (HCV) infection or history thereof (Note 2)
5. Females who are pregnant, breast feeding, or at risk of pregnancy and not using a medically acceptable form of contraception
6. A history of malignancy within the past 5 years
7. A history of tuberculosis within the past 1 year
8. A history of severe allergic reactions or anaphylaxis to monoclonal antibodies
9. A co-morbidity that may require use of glucocorticoids, immunosuppressive agents, biopharmaceutical, plasma exchange, or high-dose gamma-globulin therapy (Note 3)
10. Treatment with a B-cell-targeting biologic agents (e.g. rituximab, belimumab) within the past 6 months
11. Conditions that, in the investigator's opinion, are unsuited for safe conduct of this trial

(Note 1) This does not apply to those with rheumatoid arthritis, scleroderma, or Sjogren's syndrome, that are with no severe symptom and not requiring glucocorticoid therapy.

(Note 2) In cases that patients are positive for HBV antibodies but negative for HBV-DNA, trial participation is allowed under HBV-DNA monitoring, considering that the Japanese local guideline for HBV allows rituximab to be administered to such patients.

(Note 3) Patients with well-controlled bronchial asthma not requiring oral glucocorticoids can participate in the study (inhaled steroids are allowed to use).

Table 1. Chapel Hill Consensus Conference definitions for ANCA-associated vasculitis

ANCA-associated vasculitis	**Necrotizing vasculitis, with few or no immune deposits. Small vessels (i.e., capillaries, venules, arterioles, and small arteries) are predominantly affected. Necrotizing arteritis of small/medium arteries may accompany. It is associated with MPO-/PR3-ANCA, but ANCA are not always found in all patients.**
MPA	Necrotizing vasculitis, with few or no immune deposits. Small vessels (i.e., capillaries, venules, arterioles, and small arteries) are predominantly affected. Necrotizing arteritis of small/medium arteries may accompany. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis also often occurs. Granulomatous inflammation does not occur.
GPA	Necrotizing granulomatous inflammation primarily affecting the upper and lower respiratory tract, and necrotizing vasculitis predominantly affecting small and medium vessels (capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is usually found.

Recruitment

This trial was registered at the UMIN clinical registry and ClinicalTrials.gov registry in July 2014. Recruitment into the trial started in October 2014 and will end in September 2017, or until a total of 140 participants is recruited. This study is being conducted at 34 rheumatology or nephrology centres in Japan.

Sample size calculation

Based on the RITUXVAS trial[14] and the Cambridge University cohort[19], we assumed that 80% of the patients in both treatment groups would achieve remission at 6 months. We specified a non-inferiority margin of −20 percentage points for the difference in remission rates and a one-sided alpha level of 0.025. Assuming a 10% dropout rate, we calculated that we would need to enroll 70 patients in each group for an 80% statistical power to demonstrate non-inferiority.

Allocation

Registration and allocation for an eligible patient will be performed by investigators using the DATATRAK Electronic Data Capture system (DATATRAK ONE version 14.1.0). Eligible patients who provide written informed consent will be randomized to either low-dose or high-dose glucocorticoid groups at a ratio of 1:1 using a minimization method.[21, 22] Referring to the previous trials,[13,14] age at entry (<65 years versus ≥65 years), renal function at entry (eGFR < 50 ml/min versus ≥ 50 ml/min) and ANCA subtypes (MPO-ANCA versus PR3-ANCA) were chosen as allocation adjustment factors.

Blinding

This is an open label trial. Both treatment arms share the same regimen of administration of rituximab. In addition, it can be easily judged by subject's appearance, namely moon face due to high-dose glucocorticoid therapy, whether a subject is randomised to

low-dose or high-dose glucocorticoid groups. Thus, it was not feasible logistically or financially to blind the glucocorticoid intervention. Further, the trial primary endpoint of disease remission based on Birmingham Vasculitis Activity Score Version 3 (BVAS)[23] scores has been known as a relatively hard endpoint.

Trial treatments

Remission induction period

Prednisolone must be initiated on the randomization day or the following day. Initial doses of prednisolone are 0.5mg/kg/day in the low-dose glucocorticoid group and 1.0mg/kg/day in the high-dose glucocorticoid group respectively. Prednisolone will be stopped at 5 months in the low-dose group, while dose of prednisolone will be reduced to 10mg/body/day until 6 months in the high-dose group. The high-dose regimen is consistent with the current standard treatment.[24,25] Prednisolone tapering schedules for low-dose and high-dose glucocorticoid regimens are shown in Table 2. Only in cases in which BVAS does not reach 0, or CRP and ANCA values are not normalized, the principal investigator/co-investigator can postpone the initiation of the prednisolone discontinuation step in the low-dose glucocorticoid regimen (5 >4 >3 >2 >1 >0 mg/body/day). Once the discontinuation step has been initiated, prednisolone should be discontinued 14 weeks after the initiation of the step.

In combination with prednisolone, four doses of rituximab (375mg/m^2/w) will be administered via intravenous infusion in both treatment regimens. The first dose of rituximab must be administered between day 1 and day 7. To reduce infusion reactions, premedication with oral administration of acetaminophen and diphenhydramine and intravenous administration of 125 mg of methylprednisolone is mandatory at the time of initial administration of rituximab. Regarding the premedication for the second and subsequent administration of rituximab, it is not mandatory and left to each study site.

In the absence of contraindication, the concomitant use of the following medications is recommended; proton pump inhibitors for peptic ulcer prophylaxis, bisphosphonates, vitamin D preparations, and calcium preparations for osteoporosis prophylaxis, and trimethoprim-sulfamethoxazole combination for Pneumocystis pneumonia prophylaxis.

Table 2. Dose of prednisolone according to the low-dose and high-dose regimens

weeks	Low-dose regimen	High-dose regimen
1-2	0.5mg/kg/day	1.0mg/kg/day
3-4	0.25mg/kg/day	0.8mg/kg/day
5-6	7.5mg/body/day	0.7mg/kg/day
7-8	5mg/body/day	0.5mg/kg/day
9-10	4mg/body/day	0.4mg/kg/day
11-12	3mg/body/day	0.35mg/kg/day
13-16	2mg/body/day	15mg/body/day
17-20	1mg/body/day	12.5mg/body/day
21-24	0mg/body/day	10mg/body/day

Remission maintenance period (post-treatment observation period)

After the prednisolone discontinuation step, prednisolone is not administered in the low-dose group. Prednisolone tapering schedule during the remission maintenance period is left to each investigator with no specific restrictions in the high-dose group. Discontinuation of prednisolone is not necessary in the high-dose group.

For the remission maintenance therapy, 1 g/body of rituximab will be administered every 6 months (6, 12, and 18 months) in both groups.

Outcomes

Primary endpoint

The primary endpoint is the remission rate at 6 months. Remission is defined as a state in which BVAS ver3 score is 0 (or ≤1, if all items are persistent) and the oral prednisolone dose is 10 mg/day or lower. This is the most widely used efficacy index in evaluation studies of remission induction therapies for AAV, and has been used as a primary endpoint in the majority of previous clinical trials for AAV.

Secondary endpoints

The secondary endpoints include time to remission, death, relapse, end stage renal disease and the first serious adverse event, proportion of death, relapse, end stage renal disease for efficacy. For safety profile, number of serious adverse events and proportion of participants with serious adverse events will be evaluated. As glucocorticoid-related side effects, new-onset diabetes mellitus, hypertension, dyslipidemia, insomnia, bone fracture and infection will be specifically evaluated. In addition, cumulative dose of prednisolone, disease activity using BVAS, disease and treatments damage using Vasculitis Damage Index (VDI),[26] and health-related QOL using the Medical Outcomes Study 36-Item Short Form (SF-36)[27] will also be measured.

Data collection

Trial visits and examinations

The trial is divided into three periods: 1. screening; 2. remission induction period (6 months, including the primary endpoint assessment); and 3. remission maintenance period. The schedule for the study visits and data collection is summarized in **Table 3**.

Table 3. Examination/observation schedule

	Screening	Remission induction period					Remission maintenance period	At trial withdrawal
Time point	Within 1 week	At 0 month (day1)	At 1 months	At 2 months	At 4 months	At 6 months	At 9, 12, 18, 24 months At confirmation of relapse	
Informed consent	●							
BVAS		●	●	●	●	●	●	●
VDI		●				●	●[1)]	●
SF-36		●				●	●[1)]	●
Blood/urine tests	●[2)]	●	●	●	●	●	●	●
ECG, X-ray	●							
Bone density		●					●[3)]	●
Pregnancy test	←							→

[1)] Only at 12, 18, and 24 months

[2)] Screening blood test items

[3)] Only at 12 and 24 months

<Blood/urine tests>

Blood cell count including B cell count

Serum biochemical tests (total protein, albumin, electrolytes [Na, K, Cl], BUN, serum creatinine, CPK, total bilirubin, AST, ALT, ALP, LDH, γ-GTP, CRP, Ig-G, Ig-A, Ig-M, C3, C4, complement titer, T-Cho, LDL-C, HDL-C, TG, blood glucose, HbA1c, MPO-/PR3-ANCA)

General urine test (glucose, protein, occult blood, sediment, urinary creatinine)

Data management, monitoring and auditing

The trial data will be entered electronically according to Good Clinical Practice at the participating site where the data are originated. All entries in the system will be backed up by the relevant source data. The trial investigators will maintain individual records for each subject as source data, which include a log of informed consent, medical records, laboratory data and other records or notes, as appropriate. After study completion, the data will be locked and transferred to SAS. Data will be stored for at least 5 years after study completion.

Independent monitors will visit the sites to review the records, compare them with source documents, and observe and discuss the conduct of the trial with the investigators and site coordinator. The monitors are responsible for monitoring adherence to the protocol and guidelines, as well as ensuring completion of the eCRF and other documentation.

The study will be audited or inspected by the contract research organisation. In case of an audit, the investigators must make all study documentation available to the auditor. If an audit or inspection occurs, the investigators at the study site must discuss the findings and any relevant issues.

STATISTICAL METHODS

Statistical analyses and reporting of this trial will be conducted in accordance with the Consolidated Standards of Reporting Trials statement guidelines. All efficacy analyses will be primarily based on the full analysis set, which includes all patients who have received at least one dose of the trial treatment.

For the baseline variables, summary statistics will be constructed using frequencies and proportions for categorical data, and means and SDs for continuous variables. Patient characteristics will be compared using Pearson's chi-square test or Fisher's exact

test for categorical outcomes, and Wilcoxon rank-sum test for continuous variables, as appropriate.

For the primary analysis to evaluate treatment efficacy, the risk difference in the remission induction rate at 6 months between the rituximab plus low-dose glucocorticoid group and rituximab plus high-dose glucocorticoid group and its 95% confidence interval will be estimated using Wald statistics-based method. The non-inferiority will be considered statistically proven if the lower limit of two-tailed 95% confidence interval of the risk difference exceeds -0.2. As a sensitivity analysis, adjusted risk differences will be estimated by the Mantel-Haenszel method. Adjustment factors to be used are allocation factors (age at the time of consent, eGFR, ANCA). The secondary analysis will be performed in the same manner as the primary analysis.

All comparisons have been planned, and all p values will be two-sided. P values <0.05 will be considered statistically significant. All statistical analyses will be performed using SAS version 9.4, and are described in the statistical analysis plan, which will be fixed prior to database lock.

ETHICS AND DISSEMINATION

Research ethics approval and protocol amendments

The protocol was firstly approved by the Institutional Review Board (IRB) of Chiba University Hospital (reference number: G25051) and then approved by each participating site before the start of the trial. Substantial amendments of the study protocol must be approved by IRB. The trial has been registered at the UMIN clinical registry (UMIN000014222) and ClinicalTrials.gov registry (NCT02198248).

Informed consent

All participants will receive adequate information about the nature, purpose, possible

risks and benefits of the trial, and on alternative therapeutic choices using an informed consent approved by IRB. A participant must be given ample time and opportunity to ask questions and to consider participation in the trial. A completed informed consent is required for enrollment in the trial. The investigators must maintain the original signed consent form and a copy of the signed consent form.

Confidentiality

To assure confidentiality, trial participants will be allocated a unique trial identification number throughout the trial.

Dissemination plan

Data from all centres will be analysed together and published as soon as possible. Individual investigators will not publish data concerning their patients before publishing the trial final report. The trial results of remission induction (6 months) and remission maintenance (24 months) phases will be separately presented at scientific meetings and separately published in a peer-reviewed journal according to the trial protocol.

DISCUSSION

The previous randomized control trials for AAV have improved prognosis of this disease. The current standard therapies, high-dose glucocorticoids with cyclophosphamide or rituximab, have achieved high remission rate of 80-90%. However, there are still remaining issues such as glucocorticoids toxicity, severe conditions like alveolar haemorrhage or relapse prevention. The LoVAS trial aims to establish a new remission induction regimen with low-dose glucocorticoids and rituximab which enables to reduce the side effects.

Current guidelines recommend a combination of high-dose glucocorticoids and either cyclophosphamide or rituximab for remission induction of AAV.[15,16] These combination

therapies showed the similar efficacy and safety,[13,14] therefore cyclophosphamide is preferable to rituximab due to the high cost of rituximab except some specific instances (e.g. patients who wish to preserve their reproductive potential). However, positioning of rituximab will change from an alternative of cyclophosphamide to a single standard if this trial reveals an additional merit of rituximab allowing the low-dose glucocorticoids regimen.

There are some limitations in this study. Regional difference in AAV patients between countries has been widely known.[28] In Japan, MPA is a major form of AAV, while GPA is very rare (annual incidence; 18.2 and 2.1 per million, respectively). In most Caucasian countries, GPA is more frequent than MPA. The difference of MPA/GPA balance might be a problem when interpreting the trial results for non-Japanese patients. However, remission rates (the primary endpoint in this study) were similar between MPA and GPA patients in most previous trials. Regarding long-term relapse rate (the secondary endpoint in this study), most trials have reported higher relapse rate in GPA than in MPA, and the regional difference might influence it.

The second limitation is that this trial excludes the most life/organ-threatening forms of AAV, namely AAV presenting severe glomerulonephritis or alveolar haemorrhage. The low-dose glucocorticoid regimen can show a similar response rate with the high-dose regimen, but it might work more slowly than dose the high-dose regimen. We think the possibility of slower treatment response is not acceptable in AAV patients with severe glomerulonephritis or alveolar haemorrhage. However, the subjects in this trial can cover a wide range of AAV forms, and the trial results can be applied to the majority of AAV patients.

There is another ongoing trial evaluating a lower-dose glucocorticoids regimen. The PEXIVAS trial is a two-by-two factorial randomized trial evaluating adjunctive plasma exchange and two oral glucocorticoid regimens in combination with either

cyclophosphamide or rituximab.[29] The subjects of the PEXIVAS trial are the severest form of AAV (severe glomerulonephritis and/or alveolar haemorrhage), whereas the LoVAS trial covers moderate to severe AAV. Accordingly, glucocorticoid reduction is milder in the PEXIVAS trial than the LoVAS trial. Thus, the LoVAS and PEXIVAS trials can compensate for each other.

Despite those possible limitations, the LoVAS trial is the first to examine the potential of rituximab to reduce corticosteroid dose in remission induction of AAV along with the PEXIVAS trial. The results will contribute to establish a safer treatment strategy, which is still a big remaining issue in the treatment of AAV.

Trial Status

The LoVAS trial first received ethical approval from the Institutional Review Board of Chiba University Hospital on February 18, 2014 (reference number: G25051). As of July 17, 2017, LoVAS is actively recruiting in 33 centres with additional centres planned. A total of 75 of the planned 140 participants had been enrolled.

Declarations of interest Dr. Nakajima reports receiving grant support from Chugai Pharmaceutical Corporation (Roche group). Chugai Pharmaceutical Corporation was not involved in the planning of the protocol or in the conduct of the trial. No other potential conflict of interest relevant to this article was reported.

Dissemination policy The findings of this trial will be presented at national and international conferences and will be disseminated through peer-reviewed publications in accordance with the CONSORT Statement.

Author contributions All authors made a significant contribution to the conception and design of the study protocol. SF designed the original concept and wrote the study

protocol and manuscript. The protocol and manuscript was critically reviewed by TS, TU, YK, KA, KK, DN, MH, HH, KI and HN. YS wrote the statistical analysis plan. SF is the coordinating investigator and HN is the chief investigator of this study. All authors gave approval for the publication.

Funding This trial was funded by intramural competitive grant of Chiba University Hospital for clinical research.

Ethics approval The protocol was firstly approved by IRB of Chiba University Hospital (reference number: G25051), and then approved by each participating site.

Provenance and peer review Not commissioned; internally peer reviewed

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P.1
	2b	All items from the World Health Organization Trial Registration Data Set	See the website of ClinicalTrials.gov. (NCT02198248).
Protocol version	3	Date and version identifier	P.1
Funding	4	Sources and types of financial, material, and other support	P.52
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P.53
	5b	Name and contact information for the trial sponsor	P.53
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P.52

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P.53-P.54
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P.15-P.17
	6b	Explanation for choice of comparators	P.15-P.17
Objectives	7	Specific objectives or hypotheses	P.5_& P.17
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P.5_& P.18-P.20_
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	See Appendix.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P.5-P.6_& P.21-P.22
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P.7-P.10 & P.26-P.29
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P.29-P.30
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P.40 & P.44 & P.49
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P.30

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P.6-P.7_& P.17-P.18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P.10 & P. 20
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P.10 & P.20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	No specific strategy is planned, and not addressed in the manuscript.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P.24-P.25
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P.23-P.24
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P.24
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A_(open label)

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A_(open label)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P.45-P.46
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P.46
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P45.-P.46
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P.40-P.42
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P.40-P.42
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P.40-P.42
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P.49
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P.45 & Interim analysis is not planned.

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P.35-P.38
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P.51
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P.47
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P.44-P.45_&_P.47-P.49
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P.22-P.23
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P.45
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P.52
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P.41-P.42 & P.53. This is a self-sponsored trial by the physicians,_and there is no limit to access the data.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	P.51

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P.52
	31b	Authorship eligibility guidelines and any intended use of professional writers	P.52
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	P.22
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Correction: *Low-dose glucocorticoids plus rituximab versus high-dose glucocorticoids plus rituximab for remission induction in ANCA-associated vasculitis (LoVAS): protocol for a multicentre, open-label, randomised controlled trial*

Furuta S, Sugiyama T, Umibe T on behalf of the LoVAS Trial study investigators, *et al*. Low-dose glucocorticoids plus rituximab versus high-dose glucocorticoids plus rituximab for remission induction in ANCA-associated vasculitis (LoVAS): protocol for a multicentre, open-label, randomised controlled trial. *BMJ Open* 2017;7:e018748. doi: 10.1136/bmjopen-2017-018748

The author name 'Daiki Nakaomi' should be spelled 'Daiki Nakagomi'.

BMJ Open 2018;**8**:e018748corr1. doi:10.1136/bmjopen-2017-018748corr1