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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 controlled trial

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ABSTRACT

Introduction Antineutrophil cytoplasm antibody-associated vasculitis (AAV) is a form of systemic vasculitis. 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 to reduce side effects.

Methods and analysis This is a phase IV multicentre, 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 patients with AAV will be assessed for eligibility at 34 tertiary rheumatology/nephrology centres in Japan. One hundred and forty patients will be randomised (1:1) to receive low-dose prednisolone (0.5 mg/kg daily) plus rituximab (375 mg/m^2 weekly) or high-dose prednisolone (1 mg/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 first 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 University hospital Medical Information Network (UMIN) clinical registry (UMIN000014222) and ClinicalTrials.gov registry (NCT02198248). The Low-dose Glucocorticoid Vasculitis Induction Study (LoVAS) trial is currently ongoing and is due to finish in September 2019. The findings of this trial will be disseminated to participants through peer-reviewed publications and presented at national and international conferences in accordance with the Consolidated Standards of Reporting Trials (CONSORT) Statement.

Trial registration number UMIN000014222; 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 antineutrophil cytoplasm antibody-associated vasculitis (AAV). The low-dose glucocorticoids plus rituximab regimen in this trial has the 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 patients with AAV.
- 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 most severe forms of AAV, such as severe glomerulonephritis and severe alveolar haemorrhage, will be excluded from this trial.

INTRODUCTION

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is characterised 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 GPA (EGPA, Churg-Strauss). AAV is a life-threatening disease, and the mortality is 80% at 1 year in untreated patients.[1] Several randomised 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 patients with AAV, along with active vasculitis.[5 6] In addition, there are not only fatal side effects but also ones reducing patients' quality of life (QOL), 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 the 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-ANCA/PR3-ANCA; MPO, myeloperoxidase; PR3, proteinase3,[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 Rituximab for ANCA-associated Vasculitis (RAVE) and Rituximab versus Cyclophosphamide in ANCA-associated Renal Vasculitis (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 to reduce the 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 patients with AAV 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 (Low-dose Glucocorticoid Vasculitis Induction Study (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, randomised 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 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 prespecified 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, chemiluminescent enzyme immunoassay (CLEIA) or (fluorescence enzyme immunoassay) FEIA method.

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

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

ANCA, antineutrophil cytoplasm antibody; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase3.

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) <15 mL/min or pulmonary alveolar haemorrhage that requires oxygen inhalation of 2 L/min or more.
3. Any other systemic autoimmune diseases as a comorbidity (note 1).
4. HIV infection, hepatitis B virus (HBV)/hepatitis C virus 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 comorbidity 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 biological agents (eg, rituximab or 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 who 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).

Recruitment

This trial was registered at the University hospital Medical Information Network (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 are recruited. This study is being conducted at 34 rheumatology or nephrology centres in Japan.

Sample size calculation

On the basis of 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% 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 enrol 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 V.14.1.0). Eligible patients who provide written informed consent will be randomised to either low-dose or high-dose glucocorticoid groups at a ratio of 1:1 using a minimisation method.[21 22] Referring to the previous trials,[13 14] age at entry (<65 years vs ≥65 years), renal function at entry (eGFR <50 mL/min vs ≥50 mL/min) and ANCA subtypes (MPO-ANCA vs 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

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

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

Remission maintenance period (post-treatment observation period).

version 3 (BVAS)[23] scores has been known as a relatively hard endpoint.

Trial treatments

Remission induction period

Prednisolone must be initiated on the randomisation day or the following day. Initial doses of prednisolone are 0.5 mg/kg/day in the low-dose glucocorticoid group and 1.0 mg/kg/day in the high-dose glucocorticoid group. Prednisolone will be stopped at 5 months in the low-dose group, while dose of prednisolone will be reduced to 10 mg/body/day until 6 months in the high-dose group. The high-dose regimen is consistent with the current standard treatment.[15 16] 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 (C-reactive protein) CRP and ANCA values are not normalised, the principal investigator/coinvestigator can postpone the initiation of 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 (375 mg/m^2/week) 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.

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 version 3 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 and 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, dyslipidaemia, 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,[24] and health-related QOL using the Medical Outcomes Study 36-Item Short Form[25] 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 summarised in table 3.

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 will 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 V.9.3. Data will be stored for at least 5 years after study completion.

Table 3 Examination/observation schedule

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

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, IgG, IgA, IgM, C3, C4, complement titre, T-Cho, LDL-C, HDL-C, TG, blood glucose, HbA1c, MPO-/PR3-ANCA).
General urine test (glucose, protein, occult blood, sediment, urinary creatinine).
*Only at 12, 18 and 24 months.
†Screening blood test items.
‡Only at 12 and 24 months.
ALP, alkaline phosphatase; ALT, alanine transaminase; ANCA, anti-neutrophil cytoplasmic antibody; AST, aspartate transaminase; BUN, blood urea nitorogen; BVAS, Birmingham Vasculitis Activity Score; Cl, chlorine; CPK, creatine phosphokinase; CRP, C-reactive protein; GTP, glutamyl transpeptidase; HbA1c, haemoglobin A1c; K, potassium; HDL-C, high density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-C, low density lipoprotein cholesterol; MPO, myeloperoxidase; Na, sodium; PR3, proteinase3; SF-36, Medical Outcomes Study 36-Item Short Form; T-Cho, total cholesterol; TG, triglycerides; VDI, Vasculitis Damage Index.

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 electronic Case Report Form (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 χ^2 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% CI will be estimated using Wald statistics-based method. The non-inferiority will be considered statistically proven if the lower limit of two-tailed 95% CI 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 and 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 V.9.4, and are described in the statistical analysis plan, which will be fixed prior to database lock.

ETHICS AND DISSEMINATION

Protocol amendments

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 the 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 enrolment 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 randomised controlled 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 glucocorticoid 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 (eg, 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 glucocorticoid regimen.

There are some limitations in this study. Regional difference in patients with AAV between countries has been widely known.[26] 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 the high-dose regimen. We think that 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 patients with AAV.

There is another ongoing trial evaluating a lower-dose glucocorticoid regimen. The Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis (PEXIVAS) trial is a two-by-two factorial randomised trial evaluating adjunctive plasma exchange and two oral glucocorticoid regimens in combination with either cyclophosphamide or rituximab.[27] The subjects of the PEXIVAS trial have the most severe 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

As of 17 July 2017, LoVAS is actively recruiting in 33 centres with additional centres planned. A total of 75 of the planned 140 participants had been enrolled.

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Collaborators See online appendix.

Contributors All authors made 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.

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Competing interests HN reports receiving grant support from Chugai Pharmaceutical Corporation (Roche group).

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

Provenance and peer review Not commissioned; externally peer reviewed.

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