Protocol

An Open-label, Multicenter, Randomized Trial to Compare Low-dose versus High-dose Glucocorticoid Combined with Rituximab in Remission Induction Treatment for New-onset ANCA-associated Vasculitis

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August 24, 2014	Version 1.0
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March 24, 2017	Version 2.1
December 20, 2017	Version 2.2
June 20, 2018	Version 2.3
January 20, 2019	Version 2.4
September 1, 2019	Version 2.5

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0. Synopsis

Study Title	An Open-label, Multicenter, Randomized Trial to Compare Low-dose versus High-dose Glucocorticoid Combined with Rituximab in Remission Induction Treatment for New-onset ANCA-associated Vasculitis
Study Objective	To test the non-inferiority of low-dose glucocorticoid therapy combined with rituximab compared to high-dose glucocorticoid therapy combined with rituximab in remission induction treatment of patients with new-onset ANCA-associated vasculitis in terms of the proportion of participants who achieved remission at 6 months.
Study Design	Multicenter, open-label, non-inferiority, randomized trial comparing two arms
Phase	Phase IV
Investigational Agent RITUXAN®	Generic name: Rituximab Formulation: Intravenous infusion
Inclusion Criteria	Potential participants must meet all of the following criteria to be eligible for enrollment in the study: (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. (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, as a complication (3) Any other systemic autoimmune diseases as a co-morbidity (Note 1) (4) HIV infection, HBV/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 five years

	(7) A history of tuberculosis within the past one 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, biologic agents, 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 six 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).
Endpoints	(1) Primary endpoint 【Efficacy】 The proportion of participants who achieved remission at 6 months (2) Secondary endpoints 【Efficacy】 (1) Time required to achieve remission (2) Overall survival period, relapse-free interval, time to occurrence of ESRD, and time to the first serious adverse event (3) The proportion of death, relapse, ESRD, and occurrence of serious adverse events; and proportion of composite outcomes thereof (at 6 and 24 months; *at 6 months, proportions of death, ESRD, and serious adverse events only) (4) Proportions of minor and major relapses (5) The proportion of participants who achieved remission and discontinuation

	of glucocorticoid (6) Assessment of disease activity using Birmingham Vasculitis Activity Score (BVAS) ver3 (7) Assessment of irreversible damage using Vasculitis Damage Index (VDI) (8) Evaluation of health-related QOL using SF-36 (9) General assessment of patients using visualized analogue scale (VAS) (10) Cumulative dose of glucocorticoid 【Safety】 (1) The number of adverse events and serious adverse events and proportion of patients with adverse events and serious adverse events (2) Proportions of new-onset diabetes, hypertension, and dyslipidemia requiring treatment (3) The proportion of sleep disorder requiring treatment (4) The proportion of pathological fractures and bone density of the lumbar spine (5) The number of infections and proportion of patients with infections that required intravenous or oral administration of antibiotics (3) Exploratory endpoints (1) Immunoglobulin concentration (2) Whole blood B cell count (3) Changes in MPO-/PR3-ANCA values associated with treatment, treatment responses, and relapses
Study Procedures	Patients enrolled in the study receive the remission induction treatment comprising a total of four doses of 375 mg/m2 of rituximab once weekly along with glucocorticoids. For glucocorticoids, the participants are randomly allocated to either the high-dose group (conventional treatment group) or the low-dose group (novel treatment group) at a ratio of 1:1. For randomization, the patients are stratified according to ① age (<65 years vs ≥65 years), ② renal function (eGFR <50 ml/min vs ≥50 ml/min), and ③ANCA (MPO-ANCA vs PR3-ANCA). Setting the day of glucocorticoid commencement as day 1, the first dose of rituximab will be given between day 1 and day 7. The first dose of glucocorticoids

is to be given on the day of patient enrollment or the following day. However, with respect to glucocorticoids, administration of prednisolone 0.5 mg/kg/day between the day of screening and trial enrollment (up to 7 days) is allowed in accordance with the physician's discretion.

<Rituximab>

Rituximab as RITUXAN® is administered via intravenous infusion.

The first dose: Recommended starting administration rate is determined at 50 mg/hour, and then increase the rate by 50 mg/hour every 30 minutes. The administration rate can be increased up to 400 mg/hour.

The second and following doses: The rituximab infusion can be started at the rate of 100 mg/hour, and the rate can be increased by 100 mg/hour every 30 minutes, up to 400 mg/hour. 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.

<Glucocorticoids>

Oral Predonine® is used in principle (the same amount of water-soluble Predonine® may be given via intravenous infusion only when oral administration is difficult). Doses and tapering schedules for high- and low-dose groups are described as follows. The dose for the high-dose group is identical to that in the conventional standard treatment. 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 (5mg/body/day to drug off in 14 weeks) in the low-dose glucocorticoid regimen. Once the step has been initiated, prednisolone should be discontinued 14 weeks after the initiation of the step.

weeks	Low-dose group	High-dose group
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

Thereafter, both groups receive the remission maintenance therapy with 1g of rituximab once every six months (at 6, 12, and 18 months). However, if it is difficult to administer a dose of 1 g/body in a single day, it can be given as two doses of 0.5 g/body (the second dose should be administered within two weeks after the first dose). In such a case, the first dose should be given at 6, 12, and 18 months, and the second dose should be given within two weeks after the first dose. The glucocorticoid tapering regimen in the maintenance treatment phase is left to the discretion of the primary investigator or co-investigators in the high-dose group.

《Criteria for terminating the study – stopping rules》

The primary investigator or co-investigators discontinues the study when any of the following criteria are met.

(1) When an adverse event which falls under the dose reduction criteria occurred even after reducing the dose of the investigational agent to the minimum level, and the principal investigator or co-investigators find discontinuation necessary

(2) When an adverse event occurs and makes continuation of administration of the investigational agent difficult, and the principal investigator or co-investigators find discontinuation necessary

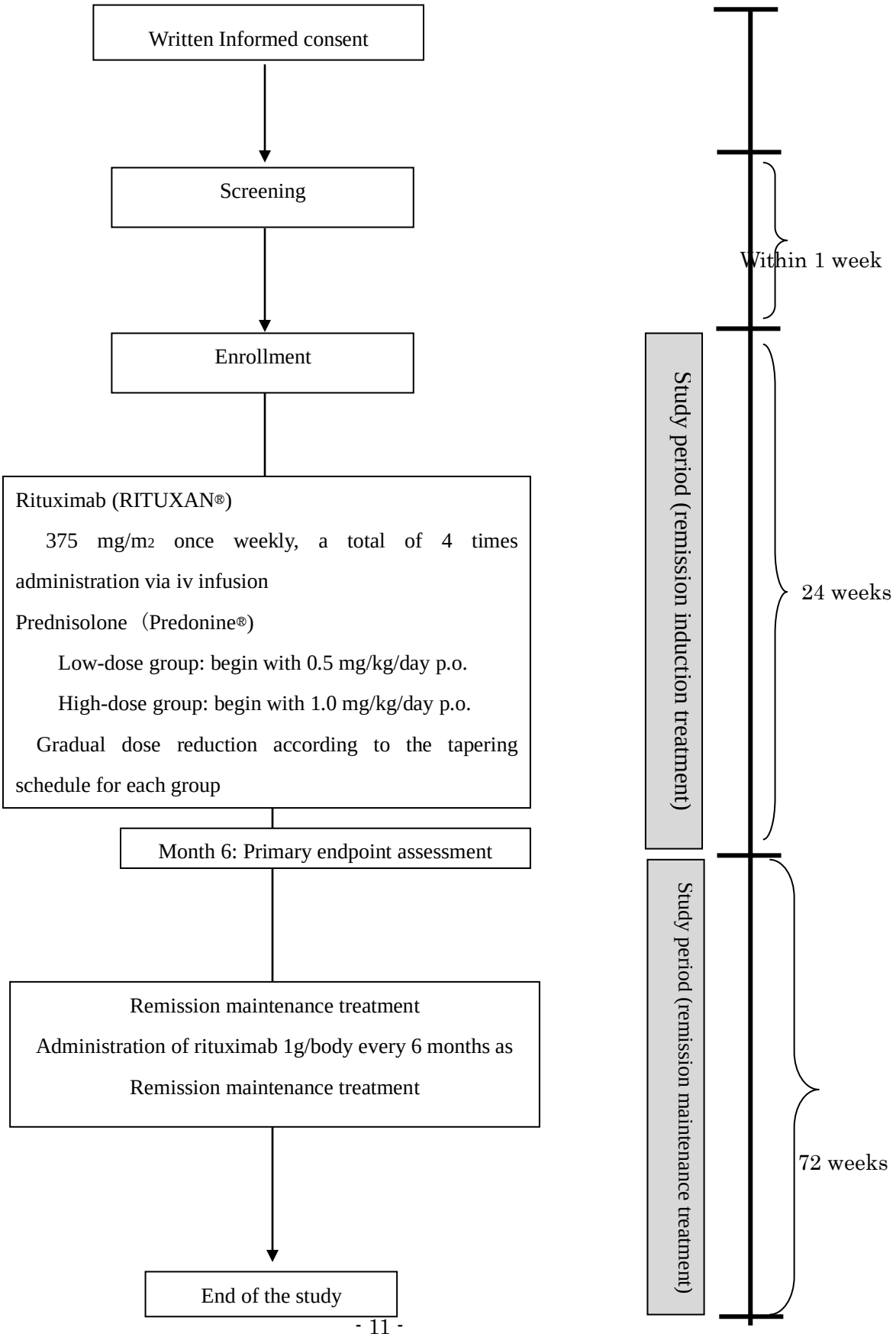
(3) When the patient requested discontinuation

(4) When the principal investigator or co-investigators found the investigational agent inappropriate to administer

(5) When the primary investigator or co-investigators found that discontinuation of the investigational agent is necessary.

(6) When the patient was found to be pregnant

	(7) When the principal investigator or co-investigators determined that the patient is unable to continue participating in the study The "date of discontinuation" shall be when the principal investigator or co-investigators decided to discontinue the study, rather than when the event causing the discontinuation occurred, except for (3).
Target Sample Size	140 subjects
Study Period	Study period: October 1, 2014 ― September 30, 2021
Ethical Considerations	This study shall be conducted in compliance with the ethical principles of the "Declaration of Helsinki" and the ethical guidelines on clinical research and in accordance with ICH-GCP and other relevant local regulatory requirements.
Institutional Review Board	Prior to study initiation, ethical, scientific, and medical validity of this study is reviewed by institutional review board (IRB). This study will be conducted after the approval is obtained from the IRB. If the conclusion of the IRB is "approval with modifications," the study will be conducted after the Protocol or other documents such as Case Report Form and Informed Consent Form are modified as requested. In addition, the IRB reviews if this study is appropriately conducted at least once a year on an on-going basis. With respect to safety reporting, the IRB shall promptly receive and review the reports on serious adverse events and any failures.


Written Informed consent
Screening
Enrollment
Rituximab (RITUXAN®)
375 mg/m2 once weekly, a total of 4 times administration via iv infusion
Prednisolone（Predonine®)
Low-dose group: begin with 0.5 mg/kg/day p.o.
High-dose group: begin with 1.0 mg/kg/day p.o.
Gradual dose reduction according to the tapering schedule for each group
Month 6: Primary endpoint assessment
Remission maintenance treatment
Administration of rituximab 1g/body every 6 months as Remission maintenance treatment
End of the study
Within 1 week
Study period (remission induction treatment)
24 weeks
Study period (remission maintenance treatment)
72 weeks

Glossary of Abbreviations and Terms

Abbreviation	English	Japanese
ANCA	Antineutrophil cytoplasmic antibody	抗好中球細胞質抗体
AST（GOT）	Aspartate aminotransferase （Glutamic oxaloacetic transaminase）	アスパラギン酸アミノトランスフェラーゼ（グルタミン酸オキザロ酢酸トランスアミナーゼ）
ALT（GPT）	Alanine aminotransferase（Glutamic pyruvic transaminase）	アラニンアミノトランスフェラーゼ（グルタミン酸ピルビン酸トランスアミナーゼ）
BUN	Blood urea nitrogen	血液尿素窒素
BVAS	Birmingham Vasculitis Activity Score	血管炎の活動性指標のひとつ
CLEIA	Chemiluminescent enzyme immunoassay	化学発光酵素免疫測定法
CPK	Creatine phosphokinase	クレアチンフォスフォキナーゼ
CRP	C-reactive protein	C 反応性蛋白
CT	Computed tomography scanning	コンピュータ断層撮影
CTCAE	Common Terminology Criteria for Adverse Events	有害事象　共通用語規準
ELISA	Enzyme-Linked Immuno Sorbent Assay	酵素結合免疫吸着法
ESRD	End-stage renal disease	末期腎不全
FEIA	Fluorescence enzyme immunoassay	蛍光酵素免疫測定法
GCP	Good Clinical Practice	医薬品の臨床試験の実施の基準
eGFR	Estimated glomerular filtration rate	推算糸球体濾過量
GPA	Granulomatosis with polyangiitis	多発血管炎性肉芽腫症
γ-GTP	γ-Glutamyltranspeptidase	γーグルタミルトランスペプチダーゼ
HBV	Hepatitis B virus	B 型肝炎ウイルス
HCV	Hepatitis C virus	C 型肝炎ウイルス
HDL-C	High-density lipoprotein cholesterol	高密度リポタンパク質コレステロール
HIV	Human immunodeficiency virus	ヒト免疫不全ウイルス
Ig	Immunoglobulin	免疫グロブリン
IV-CY	IV-cyclophosphamide	シクロフォスファミド・パルス療法

LDH	Lactate Dehydrogenase	乳酸脱水素酵素
LDL-C	Low-density lipoprotein cholesterol	低密度リポタンパク質コレステロール
MPA	Microscopic polyangiitis	顕微鏡的多発血管炎
QOL	Quality of life	生活の質
T-Cho	Total cholesterol	総コレステロール
TG	Triglyceride	中性脂肪
VAS	Visualized analogue scale	視覚的評価スケール
VDI	Vasculitis Damage Index	血管炎の不可逆障害指標

Standards and Definitions to be Used in This Study

Remission

A state in which Birmingham Vasculitis Activity Score (BVAS) ver3 is 0 (or ≤1, if all items are low-invasive/ persistent) and the oral prednisolone dose is 10 mg/day or lower

Relapse

Relapses are divided into major and minor. Relapses described without major/minor distinction include both types.

（1） Major relapse

Relapses that investigators decide that administration of prednisolone of more than 20 mg/day, an escalation dose of immunosuppressive agent, and/or treatment with other additional immunosuppressive agent are necessary, due to the new emergence or recurrence of BVAS ver3 items which indicate severe condition.

（2） Minor relapse

New emergence or recurrence not meeting criteria for major relapses as assessed with BVAS ver3

End-stage renal disease (ESRD)

Dialysis for 6 weeks or more is required, and there is no chance of recovery.

B cell depletion

B cells in the peripheral blood are below the site's detection limit with flow cytometry.

B cell recovery

B cells in the peripheral blood return to a level detectable with flow cytometry.

1. Introduction

1.1 Background of disease being studied

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is a disease that is characterized by small vessel vasculitis and the presence of ANCA, and composed of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA; previously known as Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome). Life and renal prognosis are often poor in patients with ANCA-associated vasculitis, with five-year survival rate of approximately 75%, and of those, approximately 20% patients reportedly experience progression to end-stage renal disease (ESRD) [1].

1.2 Standard therapy for disease being studied

The concomitant use of high-dose glucocorticoids and cyclophosphamide pulse therapy (IV-CY), which is a current standard remission induction treatment, has achieved a high remission rate of 80-90% [2-4]. However, this therapy is associated with a variety of side effects, particularly those attributable to high-dose glucocorticoids, including infections, osteoporosis/aseptic necrosis, hypertension/diabetes/dyslipidemia, cataract/glaucoma, gastric/duodenal ulcer, muscle weakness, menstrual disorder, steroid psychosis, insomnia, and moon-shaped face. Among these side effects, infections are strongly associated with deaths of patients with ANCA-associated vasculitis. In Japan, MPA, which frequently occurs most often in the elderly, account for the majority of ANCA-associated vasculitis, resulting in high mortality from infections compared to other countries, which accounts for approximately half of deaths [13]. Moreover, side effects that are not related to death also affect decreased patients' quality of life and growth in medical costs. Therefore, a new standard treatment with reduced side effects is awaited to be developed.

1.3 Background of this study

1.3.1 B cell-targeted therapy

For treatment of ANCA-associated vasculitis, rituximab, an anti-CD20 monoclonal antibody that specifically depletes B cells, has been investigated in other countries for following reasons; ① infiltration of B cells are found in inflammatory foci, ② B cell activation is associated with the disease activity, and ③ cyclophosphamide, an immunosuppressive agent which is relatively specific to B cells, shows reasonable efficacy [5-6]. In two clinical trials published in 2010; RAVE trial (the United States) and RITUXVAS trial (Europe); the concomitant treatment of high-dose glucocorticoids and rituximab showed a remission induction rate equivalent to the combination of high-dose glucocorticoids and IV-CY in patients with new-onset ANCA-associated vasculitis [7-8]. The analysis of the relapsing cases in the RAVE trial

indicated that rituximab showed superior remission induction rate compared with IV-CY. As opposed to the initial expectation, that is, the rituximab group will show better safety results, the combination of high-dose glucocorticoids and rituximab was comparable with the combination of high-dose glucocorticoids and IV-CY also in terms of safety. For this reason, the indication of rituximab as remission induction treatment is currently limited to use for patients with relapses or those for whom the use of cyclophosphamide is undesirable. Two hypotheses may explain why the two regimens were comparable in safety in RAVE and RITUXVAS trials; ① rituximab and cyclophosphamide have equivalent risks, and ② statistical differences between the two groups were difficult to detect because high-dose glucocorticoids are associated with a majority of side effects in both groups. Given general perception of rituximab with high safety standards (except at the initiation of administration) based on previous reports [9-10], the hypothesis ② may be more likely to be true, and thus the glucocorticoid dose reduction is essential to improve safety.

1.3.2 Glucocorticoid dose reduction

RAVE and RITUXVAS trials suggested that the glucocorticoid dose reduction is required to develop a new treatment to reduce infection and other side effects. For immunosuppressive agents other than rituximab, previous studies have shown that the glucocorticoid dose reduction is associated with a reduced remission rate and an increased relapse rate [11-12], suggesting that the concomitant use with low-dose glucocorticoids is difficult. However, the efficacy of rituximab has not been examined in combination with low-dose glucocorticoids. As mechanism of action of rituximab on ANCA-associated vasculitis is substantially different from mechanisms of conventional immunosuppressive agents, rituximab is considered a valid option to achieve the glucocorticoid dose reduction in remission induction treatment. In fact, Smith et al. have reported that their observational study showed good remission re-induction rates (93-96%) with the concomitant use of rituximab and low-dose glucocorticoids in ANCA-associated vasculitis patients with major relapses [14].

1.3.3 Background of this study plan

In Japan, a public knowledge-based application was approved in June 2013 on the basis of results of RAVE and RITUXVAS trials, and insurance coverage of rituximab for MPA and GPA was approved. In addition, academic societies (Japan College of Rheumatology and Japanese Society of Nephrology) and the intractable vasculitis study group of the Ministry of Health, Labour and Welfare have released the joint statement on the use of RITUXAN for ANCA-associated vasculitis, in which the actual indications are specifically restricted as it should be considered "only when existing treatments, cyclophosphamide, produce insufficient effects, existing treatments are contraindicated, or in the patient have multiple

relapses." These indications were based on clinical trials conducted in other countries, and are largely similar to the indications in other countries. Therefore, although the use of RITUXAN for new-onset ANCA-associated vasculitis is within the insurance coverage, its use in daily medical practice is limited by relevant academic societies.

The objective of the present study is to verify whether rituximab can reduce a total amount of glucocorticoid dose while maintaining the remission induction rate in remission induction treatment for ANCA-associated vasculitis. By providing high-quality evidence, we hope that the current treatment guidelines developed by the Ministry of Health, Labour and Welfare study group will be revised, and ultimately, low-dose glucocorticoid therapy combined with rituximab can be used in daily medical practice.

2. Objectives

The objective is to verify whether rituximab can reduce a total amount of glucocorticoid dose in remission induction treatment of patients with new-onset ANCA-associated vasculitis. More specifically, this study aims to demonstrate the non-inferiority of concomitant use of low-dose glucocorticoid and rituximab compared to concomitant use of high-dose glucocorticoid and rituximab in terms of the efficacy in remission induction treatment of patients with new-onset ANCA-associated vasculitis.

2.1 Primary endpoint

【Efficacy】

The proportion of participants who achieved remission at 6 months

2.2 Secondary endpoints

【Efficacy】

Time required to achieve remission

Overall survival period, relapse-free interval, time to ESRD, time to occurrence of the first serious adverse event

The proportion of death, relapse, ESRD, and patients with serious adverse events; and proportion of composite outcomes thereof (at 6 and 24 months; *at 6 months, proportions of death, ESRD, and serious adverse events only)

Proportions of major and minor relapses

Assessment of disease activity using Birmingham Vasculitis Activity Score (BVAS) ver3

Assessment of irreversible damage using Vasculitis Damage Index (VDI) [19]

Evaluation of health-related QOL using SF-36

General assessment of patients using visualized analogue scale (VAS)

Cumulative dose of glucocorticoid

【Safety】

The number of adverse events and serious adverse events and proportion of patients with adverse events and serious adverse events

Proportions of new-onset diabetes, hypertension, and dyslipidemia requiring treatment

The proportion of sleep disorder requiring treatment

The proportion of pathological fractures and bone density of the lumbar spine

The number of infections and proportion of patients with infections that required intravenous or oral administration of antibiotics

【Exploratory】

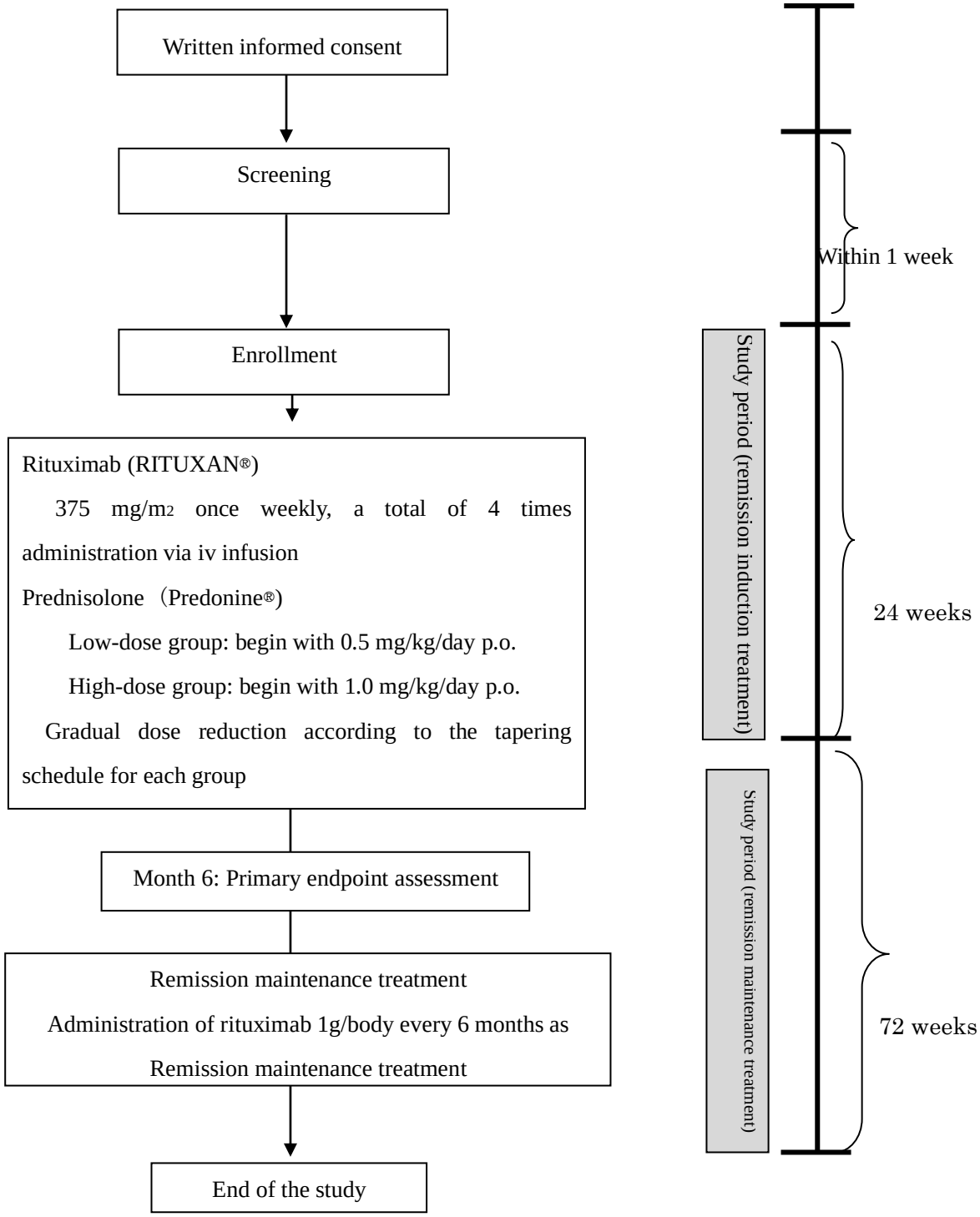
Immunoglobulin concentration

Whole blood B cell count

Changes in MPO-/PR3-ANCA values associated with treatment, treatment responses, and relapses

3. Study Design

This is an open-label, randomized trial comparing two arms that undergo remission induction treatment with rituximab + low-dose glucocorticoids or rituximab + high-dose glucocorticoids. After the trial, patients in remission proceed promptly to maintenance treatment.


Written informed consent
Screening
Enrollment
Rituximab (RITUXAN®)
375 mg/m2 once weekly, a total of 4 times administration via iv infusion
Prednisolone（Predonine®)
Low-dose group: begin with 0.5 mg/kg/day p.o.
High-dose group: begin with 1.0 mg/kg/day p.o.
Gradual dose reduction according to the tapering schedule for each group
Month 6: Primary endpoint assessment
Remission maintenance treatment
Administration of rituximab 1g/body every 6 months as Remission maintenance treatment
End of the study
Within 1 week
Study period (remission induction treatment)
24 weeks
Study period (remission maintenance treatment)
72 weeks

Rationale for study design

This study is a multicenter, open-label, randomized controlled trial. To verify whether concomitant use of rituximab allows to reduce the glucocorticoid dose in remission induction treatment, the efficacy and safety of the remission induction treatment with rituximab + low-dose glucocorticoids are assessed using the remission induction treatment with rituximab + high-dose glucocorticoids as a control regimen. To test the hypothesis that the dose reduction of glucocorticoids is possible, this study aims to demonstrate the non-inferiority of the low-dose glucocorticoids group in efficacy.

It should be noted that the rituximab + high-dose glucocorticoids regimen to be used for the control group has been demonstrated to have the efficacy and safety equivalent to current standard regimen of cyclophosphamide + high-dose glucocorticoids by the results of previous clinical trials.

The study duration of 24 months and the primary endpoint of the remission induction rate at 6 months are the most widely used efficacy indices in clinical trials of remission induction treatments for vasculitis.

3.1 Target sample size and study period

Target sample size: 140 subjects

【Rationale】

To demonstrate the non-inferiority in remission induction rate, the necessary number of study subjects calculated with the following conditions is 63 in each arm:

$\alpha = 0.025$, $1 - \beta = 0.8$

① Remission induction rate with rituximab + high-dose glucocorticoids = 0.80

② Remission induction rate with rituximab + low-dose glucocorticoids = 0.80

Non-inferiority margin = -0.2

Ratio 1:1.

With a predicted withdrawal rate of 10%, the target sample size was set as 70 subjects in each arm, a total of 140 subjects. The induction rates ① and ② are based on RITUXVAS study [8] and the Cambridge University cohort, respectively [14]. The non-inferiority margin was set in reference to the margin used in RAVE study, which was a non-inferiority study of rituximab [7].

Study period: October 1, 2014 – September 30, 2021

Patient enrollment period: October 1, 2014 – September 30, 2019

4. Selection and Enrollment of Study Population

Patients who meet all of the following inclusion criteria and none of the exclusion criteria are considered eligible.

4.1 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 (microscopic polyangiitis, granulomatosis with polyangiitis, or renal-limited vasculitis) according to the definition of the 2012 Chapel Hill Conference [15].

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

【Rationale】

(1) This criterion was included to conduct the trial in compliance with ethical principles, such as the Declaration of Helsinki. In addition, subjects are required to be 20 years of age or older to ensure a certain level of judgement ability, as disease notification is necessary, considering the poor prognosis of the disease being studied.

(2), (3) Based on previous clinical trials concerning the target disease in this study, the most frequently used inclusion criteria were chosen.

4.2 Exclusion criteria

(1) Previous treatment for ANCA-associated vasculitis prior to providing consent to participate in this study

(2) Glomerulonephritis with eGFR <15 ml/min or pulmonary alveolar hemorrhage that requires oxygen inhalation of 2L/min or more, as a complication

(3) Any other systemic autoimmune diseases as a co-morbidity (Note 1)

(4) HIV infection, HBV/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, biologic agents, 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

【Rationale】

(1) For the same reason as (1) in the inclusion criteria.

(2) These are severe conditions requiring plasma exchange in addition to the conventional treatment; therefore, patients with these conditions were excluded, as this study is not planned to perform plasma exchange.

(3) This criterion was set as it can affect the assessment of the treatment effect.

(4) – (10) These were set to ensure the safety of subjects, in reference to the package insert of rituximab and criteria used in clinical trials using other biologic agents.

(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 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).

4.3 Informed consent procedure

Prior to initiation of the study, principal investigator or co-investigators provide a clear explanation to potential participants using the informed consent form approved by the IRB, and obtain voluntary written consent to participate in the study. When obtaining the consent, potential participants should be given sufficient time to determine, whether or not to participate in the trial, and opportunities to ask questions, which should be fully, answered.

The principal investigator or co-investigators who provided the explanation and study subjects who received the explanation should put their name and affix a seal, or give their signatures with the date to the consent form. If subjects cannot perform this procedure due to, for example, progression of the primary disease, the written consent may be obtained from their legally acceptable representatives, with informed consent of the subject. When study cooperators provided a supplementary explanation, the cooperators shall also put their name/affix a seal or give their signature with the date to the form. A copy of the consent form and information materials used in the informed consent procedure should be given to the subject, and

the original consent form shall be retained in the trial site.

The principal investigator, co-investigators, or study cooperators ask the subjects who provided the consent whether they are currently visiting any other departments or hospitals. If they are visiting other hospitals or departments, attending physicians at those medical settings must be informed of the subject participation in this trial, after obtaining the consent from the subject.

4.4 Provision of updating information to study subjects

Principal investigator or co-investigators shall immediately explain important information that is newly obtained and may affect subject's intention to participate, and confirm the subject's intention to continue the trial participation. The principal investigator or co-investigators shall record the date of explanation, the person who provided the explanation, content of the explanation, the intention of continuation, and the date of confirmation in documents such as subject's medical records.

In addition, the principal investigator revises the informed consent form where appropriate. If there are subjects who have already been receiving the study treatment at the time of the revision, the changed contents shall be explained to those subjects, and a new consent must be obtained for the continuation of the participation.

4.5 Registration

A central registration system in a case registration center (Data Management office of clinical research center, Chiba University Hospital) will be used to register study sites and subjects. Procedures for site and case registration are as follows;

① Site registration

1) After obtaining approval from IRB or other relevant committee(s), the principal investigator will fax a copy of the notification letter(s) of approval and a request form of site registration to the case registration center.

2) The case registration center will register the site(s) and forward a notification letter of site registration completion to the principal investigator.

② Case registration

1) The principal investigator or co-investigators obtain written consent from study subjects, and confirm that the subject meets the inclusion criteria and does not correspond to exclusion criteria through screening tests. Subjects determined to be "eligible" will be registered. Case registration is carried out on the website.

2) The principal investigator or co-investigators accesses to a designated URL to confirm eligibility determination that requires entering necessary information, and allocation results. When the subject's eligibility is confirmed, study treatment will be initiated in accordance with the allocation.
The principal investigator or co-investigators should not administer the investigational medicinal product (rituximab) until the subject's registration is completed.

4.5.1 Instructions for registration

(1) Registration is not allowed after the initiation of protocol treatment without exception.
(2) Once the patient was registered, the registration is not cancelled (i.e., not deleted from the database), except when there was a consent withdrawal that include refusal of the research use of data. In case of duplicated registration, information entered at the initial registration (registration number, allocated group) is always used.
(3) When registration error or duplication is found, contact the case registration center immediately.
(4) Each study site is responsible for calculation of the body surface area and the drug dose. The information of the body surface area and the drug dose from the case registration center at the time of registration is only for double-checking of the values that attending physicians calculated. Make sure that calculations are also done and verified at the site. If the study site hospital's information system uses a different calculating formula for body surface area from the one used in the case registration center (Dubois formula: body surface area (m^2) = body weight (kg) 0.425 x height (cm) 0.725 x 71.84 ÷ 10,000), there will be a difference in the calculated dose between hospital information system and the JCOG-adopted equation. In such a case, the principal investigator of the study site will decide which dose to use.

4.6 Allocation

At the time of registration, the case registration center randomly assigns a treatment arm.

【Rationale】
Allocation adjustment factors chosen for this study are the factors found to have significant effect on the prognosis of ANCA-associated vasculitis by previous studies. Indeed, these factors have been used as allocation factors in many clinical trials on vasculitis [7,8].

In random allocation, the minimization method using ① age at the time of informed consent (<65 years vs ≥65 years), ② renal function (eGFR < 50 ml/min vs ≥ 50 ml/min), ③ ANCA (MPO-ANCA vs PR3-ANCA; cases of double positive will be allocated based on the subtype with a higher measured value)

as allocation adjustment factors is used to avoid significant bias. Researchers at participating sites will not be informed of detailed procedures for random allocation.

4.7 Pregnancy

To ensure patients' safety, the principal investigator must report pregnancy of the study subjects (including a case of pregnancy test positive) to the coordinating investigator and the provider of investigational medicinal product. Subjects found to be pregnant are subject to follow-up on pregnancy, and outcomes (e.g., spontaneous or artificial abortion, childbirth details, congenital defects, congenital abnormalities, and maternal or neonatal complication) must be confirmed.

5. Study medications

For detailed information and handling of study medications, also see package insert. Study medications to be used in this trial are as follows.

5.1 Investigational medicinal product (rituximab)

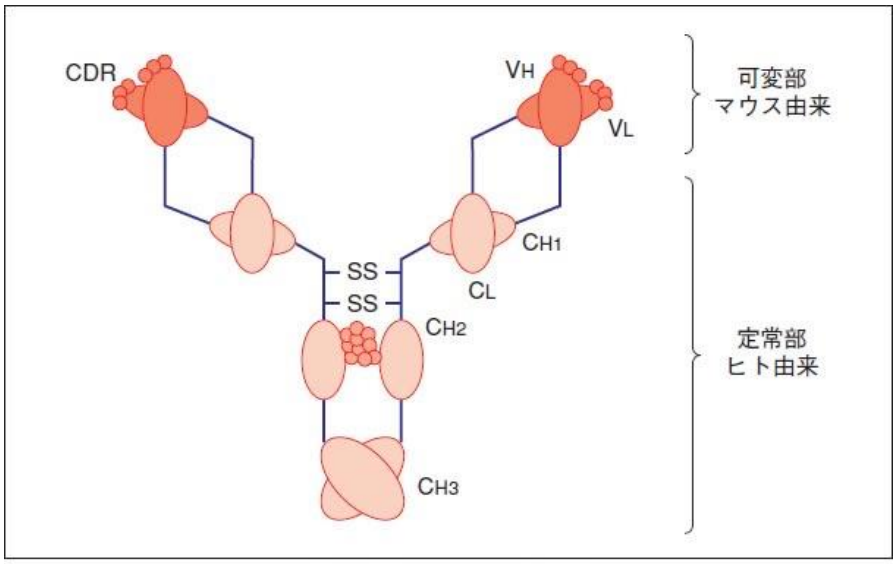
Generic name	rituximab
Trade name	RITUXAN injection 10 mg/ml
Structural formula	An IgG1κ antibody (1328 amino acid residues) comprising mouse-derived light chain and heavy chain variable domains, and human-derived γ1 heavy chain and κ light chain constant domains  **図1 リツキシマブの構造** 抗CD20マウスモノクローナル抗体の可変領域とヒトIgGの定常領域が融合されている

	Figure 1 Structure of rituximab Variable domains of an anti-CD20 moue monoclonal antibody are fused with constant domains of a human IgG. Mouse-derived variable domains Human-derived constant domains
Dosage form	Intravenous infusion
Storage conditions	Store in a cool place (2°C-8°C) while avoiding freezing
Shelf life	30 months

5.2 Storage of study medications

Investigational medicinal products should be stored in a cool place (2°C-8°C) while avoiding freezing.

6. Study Procedures

Patients participating in the study will receive administration of 375 mg/m2 of rituximab once weekly × 4 times along with glucocorticoids, as remission induction treatment. Participants are randomly assigned to either the high-dose glucocorticoid group (conventional treatment group) or low-dose glucocorticoid group (novel treatment group) at 1:1 ratio. At the time of randomization, study subjects are stratified according to age, renal function, and ANCA subtype.

Defining the day of glucocorticoid commencement as day 1, the first dose of rituximab will be given between day 1 and day 7. The first dose of glucocorticoids is to be given on the day of patient enrollment or the following day. However, with respect to glucocorticoids, administration of prednisolone 0.5 mg/kg/day is allowed during the period from screening to patient enrollment (up to 7 days) depending on physicians' discretion.

6.1 Dosage, dosage regimen, and administration schedule (rituximab)

Rituximab 375 mg/m2 (cut off after the decimal point; calculated based on the body height and weight at the time of screening) as RITUXAN® will be administered via intravenous infusion once weekly × 4 times.

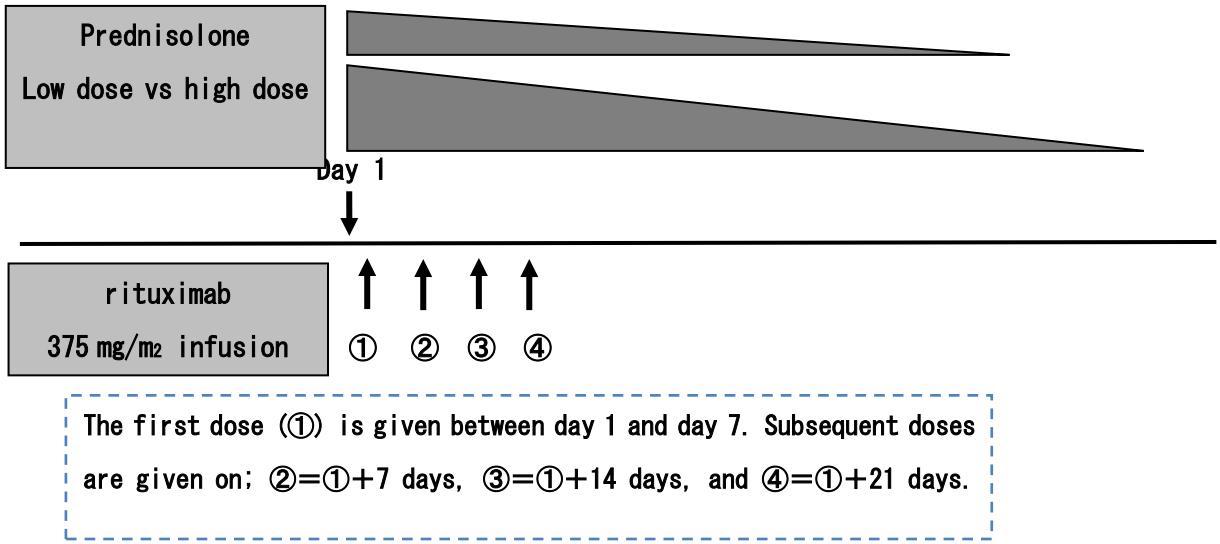
First administration: Administration rate at the beginning is recommended to be at 50 mg/hour and then can be increased by 50 mg/hour every 30 minutes, up to 400 mg/hour.

Subsequent administration: The rituximab infusion can be started at the rate of 100 mg/hour, and increased by 100 mg/hour every 30 minutes, up to 400 mg/hour. 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.

【Rationale】

This administration regimen is identical to the one used in previous clinical trials, and the efficacy and safety have already been confirmed [8]. The dosing regimen is also identical to the one used in Japan, although the standard indication is for relapsing/refractory cases.



6.2 Dosage, dosage regimen, and administration schedule (glucocorticoids)

Glucocorticoid is orally administered as Predonine® (the same dose of water-soluble Predonine® can be given via intravenous infusion only when oral administration is difficult). Administration starts on day 1; however, administration of prednisolone 0.5 mg/kg/day is allowed during the period from screening to patient enrollment (up to 7 days) depending on attending physicians' discretion. Doses and tapering schedules from day 1 for both groups are shown in the table below. The dose for the high-dose group is identical to the conventional standard treatment. 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 (5mg/body/day to drug off in 14 weeks) in the low-dose glucocorticoid regimen. Once the step has been initiated, prednisolone should be discontinued 14 weeks after the initiation of the step.

weeks	Low-dose group	High-dose group
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

Prednisolone doses for the low-dose group in weeks 1-4 and for the high-dose group in weeks 1-12 shall be rounded up in increments of 5 mg.

Actual example;

weeks	BW: 40kg (Low dose)	BW: 60kg (Low dose)	BW: 80kg (Low dose)	BW: 60kg (High dose)
1-2	20 mg/day	30 mg/day	40 mg/day	60 mg/day
3-4	10 mg/day	15 mg/day	20 mg/day	50 mg/day
5-6	7.5 mg/day	7.5 mg/day	7.5 mg/day	45 mg/day
7-8	5 mg/day	5 mg/day	5 mg/day	30 mg/day
9-10	4 mg/day	4 mg/day	4 mg/day	25 mg/day
11-12	3 mg/day	3 mg/day	3 mg/day	20 mg/day
13-16	2 mg/day	2 mg/day	2 mg/day	15 mg/day
17-20	1 mg/day	1 mg/day	1 mg/day	12.5 mg/day
21-24	0 mg/day	0 mg/day	0 mg/day	10 mg/day
cumulative dose	707 mg/24 weeks	987 mg/24 weeks	1197 mg/24 weeks	4200 mg/24 weeks

6.3 Maintenance treatment

For remission maintenance treatment during the post-treatment observation period, 1 g/body of rituximab will be administered every 6 months (6, 12, and 18 months). However, if it is difficult to administer a dose of 1 g/body in a single day, it can be administered as two doses of 0.5 g/body (the second dose is

administered within two weeks after the first infusion). In such a case, the first dose should be given at 6, 12, and 18 months, and the second dose should be given within two weeks after the first dose. The rituximab infusion can be started at a rate of 100 mg/hour, and the rate can be increased by 100 mg/hour every 30 minutes, up to 400 mg/hour. The choice of the premedication method is left to each study site. The glucocorticoid tapering regimen is left to the discretion of the principal investigator or co-investigators with no specific restrictions in the high-dose group.

【Rationale】

The results of previous clinical trials (RAVE and RITUXVAS trials) have suggested that the relapse rate is higher with only one course of rituximab treatment, resulting in requiring some form of remission maintenance treatment. In the Cambridge University cohort, which is one of the largest cohort of ANCA-associated vasculitis patients treated with rituximab, remission maintenance treatment with administration of 1 g/body rituximab every 6 months has been demonstrated to be effective in those who accomplished remission introduction with rituximab combination therapy, although the results have not validated by.

6.4 Criteria for terminating the study – stopping rules

The principal investigator or co-investigators discontinue the study when any of the following criteria are met.

(1) When an adverse event, which falls under the dose reduction criteria, occurred even after reducing the dose of the investigational medicinal product to the minimum level and the principal investigator or co-investigators find discontinuation necessary

(2) When an adverse event occurs and makes continuation of administration of the investigational agent difficult, and the principal investigator or co-investigators find discontinuation necessary

(3) When the patient requested discontinuation

(4) When the principal investigator or co-investigators find the investigational medicinal product inappropriate to administer

(5) When the principal investigator or co-investigators find that discontinuation of the investigational medicinal product is necessary

(6) When the patient was found to be pregnant

(7) When the principal investigator or co-investigators determined that the patient is unable to continue participating in the study

The "date of discontinuation" shall be when the principal investigator or co-investigators decided to discontinue the study, rather than when the event causing the discontinuation occurred, except for (3).

6.5 Concomitant medications

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 for Pneumocystis pneumonia prophylaxis. In addition, premedication is administered at the time of rituximab administration (see **6.1**).

6.6 Restrictions

There are no daily life restrictions required for participants of this study. However, an appropriate use of contraception methods for 12 months after the final dose of rituximab. Participants are also recommended to avoid vaccination with live vaccine while receiving rituximab.

7. Clinical assessments, Laboratory evaluations, and Schedule

7.1 Screening

After patient's written consent was obtained, the following clinical assessments and laboratory evaluations are performed.

・Patient background (subject identification code, age at the time of consent, year and month of birth, sex, body height, diagnosis, date of diagnosis, medical history, complication)

・Body weight

・Vital signs (blood pressure, pulse, body temperature)

・Chest X-ray

・Electrocardiography (ECG)

・Blood tests:

Serum creatinine level; MPO-ANCA and PR3-ANCA measured by ELISA, CLEIA, or FEIA; HIV antibodies; HBs antigen/antibodies; HBc antibodies; and HCV antibodies

・Pregnancy test[1)]

・Observation of adverse events

・Presence or absence of prednisolone administration during the period from screening to patient enrollment, and the dosage if it was used

Note that following data obtained within 2 weeks before the consent can be used; chest X-ray, ECG,

MPO-/PR3-ANCA, HIV antibodies, HBS antigen/antibodies, HBc antibodies, and HCV antibodies.

1) A urine pregnancy test will be performed (hCG ≥25 IU/L).

7.2 Clinical assessments and laboratory evaluations during the study period

During the study period, the following clinical assessment and laboratory evaluations are performed as specified for each evaluation time point (at 0, 1, 2, 4, 6, 9, 12, 18, and 24 months, and when a relapse is confirmed; * 0 month = day 1± 3 days, 1 month = day 30 ± 7 days, 2 months = day 60 ± 15 days, 4 months = day 120 ± 15 days, 6 months = day 180 ± 15 days, 9 months = day 270 ± 30 days, 12 months = day 360 ± 30 days, 18 months = day 540 ± 30 days, 24 months = day 720 ± 30 days). During the maintenance treatment period (from month 6 to month 18), interval of hospital visits should not exceed 3 months at a maximum.

・Confirmation of medication adherence

・Confirmation of concomitant medications

・Presence or absence of additional treatment for ANCA-associated vasculitis not included in study protocol

・Observation of adverse events

・Body weight

・Vital signs (blood pressure, pulse, body temperature)

・Blood tests:

<Blood cell count> Red blood cells, hemoglobin, platelets, white blood cells, differential leukocyte counts, number of B cells

<Serum biochemical examinations> Total protein, albumin, electrolytes [Na, K, Cl], BUN, serum creatinine level, CPK, total bilirubin level, 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, and MPO-ANCA and PR3-ANCA measured by ELISA (or CLEIA, FEIA)

Note that MPO-ANCA and PR3-ANCA data at the time of screening can be used as substitutes for data at 0 months.

・Urinary examinations: General urine tests (glucose, protein, occult blood), urinary sediment, urinary creatinine

・BVAS ver3

・VDI (at 0, 6, 12, 18, and 24 months only)

・SF-36 (at 0, 6, 12, 18, and 24 months only)

・VAS

・Bone density of the lumbar spine (at 0, 12, and 24 months; images taken during day 1–28 are acceptable as 0-month data.)

・Pregnancy test1)

・Confirmation of survival, ESRD, remission or relapse

1) A urine pregnancy test will be performed (hCG ≥25 IU/L).

7.3 Clinical assessments and laboratory evaluations at completion or discontinuation of the study

The following tests are performed as specified at the end of the study or when the study is discontinued.

・Confirmation of medication adherence

・Confirmation of concomitant medications

・Presence or absence of additional treatment for ANCA-associated vasculitis not included in study protocol

・Observation of adverse events

・Body weight

・Vital signs (blood pressure, pulse, body temperature)

・Blood tests:

<Blood cell count> Red blood cells, hemoglobin, platelets, white blood cells, differential leukocyte counts, number of B cells

<Serum biochemical examinations> Total protein, albumin, electrolytes [Na, K, Cl], BUN, serum creatinine level, CPK, total bilirubin level, 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, and MPO-ANCA and PR3-ANCA measured by ELISA (or CLEIA, FEIA)

・Urinary examinations: General urine tests (glucose, protein, occult blood), urinary sediment, urinary creatinine

・BVAS ver3

・VDI

・SF-36

・VAS

・Bone density of the lumbar spine (at 0, 12, and 24 months; images taken during day 1–28 are acceptable as 0-month data.)

・Pregnancy test1)

・Confirmation of survival, ESRD, remission or relapse

1) A urine pregnancy test will be performed (hCG ≥25 IU/L).

7.4 Pregnancy test (only for women of childbearing potential)

Female patients of childbearing potential undergo pregnancy tests (urinary tests: hCG ≥25 IU/L) at the following time points. The principal investigator or co-investigators confirm that the pregnancy test is negative during the period from consent to initiation of administration of the study medication. When a false positive or positive result is obtained, the test should be repeated in accordance with the package insert of the extracorporeal diagnostic agent, and report the result to a gynecologist. The principal investigator or co-investigators also confirms that the pregnancy test results are negative at the end of the study and when the study is discontinued.

(1) Before starting the study medication

(2) At the end of the study or when the study is discontinued

(3) 4 weeks after the completion or discontinuation of the study

7.4.1 Definition of women of childbearing potential

Women who do not meet any of the following criteria

(1) Women who have reached natural menopause (45 years of age or older and no menstruation experienced for 1 year or more)

(2) Women who have undergone hysterectomy

(3) Women who have undergone bilateral oophorectomy

7.5 Tests and observation items for efficacy assessment

7.5.1 Proportion of participants who achieved remission (at 6 months)

The proportion of study subjects who achieved remission at 6 months will be evaluated.

7.5.2 Time to remission, overall survival period, relapse-free period, time to ESRD, and time to the first serious adverse event

The number of days from randomization to each of abovementioned events will be evaluated.

7.5.3 Occurrence rate of death, relapse, ESRD, serious adverse events, and composite outcome of those (at 6 and 24 months; * at 6 months, occurrence rate of death, ESRD, and serious adverse events only)

The number of occurrence and proportion of those events are used for evaluation.

7.5.4 Occurrence rate of minor and major relapses (at 24 months)

The number of occurrence and proportion of minor and major relapses are used for evaluation.

7.5.5 Disease activity assessment (at 6 and 24 months)

BVAS ver3 is used for assessments.

7.5.6 Irreversible disorder assessment (at 24 months)

VDI is used for assessments.

7.5.7 Cumulative glucocorticoid dose (at 6 and 24 months)

Cumulative glucocorticoid doses from the beginning of study participation to 6 and 24 months are evaluated.

7.5.8 Patient general assessment (at 6 and 24 months)

VAS is used for assessments.

7.5.9 Patient QOL assessment (at 6 and 24 months)

SF-36 is used for assessments.

7.6 Tests and observation items for safety assessment

7.6.1 Determination of adverse events

An adverse event refers to any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in patients administered a study medication, regardless of whether it has a causal relationship with the trial medication.

As a general rule, an adverse event is itemized and graded using the Common Terminology Criteria for Adverse Events (CTCAE ver 4.0). Adverse events defined in this study include events occurred during a period from patient's consent to commencement of study medication.

7.6.2 Serious adverse events

A serious adverse event refers to an adverse event that meets any of the following criteria [16].

(1) Death

(2) Life-threatening

(3) Resulting in disability

(4) Risks leading to disability

(5) Requiring inpatient hospitalization or prolongation of existing hospitalization

(6) Serious condition according to the above (1) - (5)

(7) Congenital diseases or anomaly in a later generation

7.6.3 Non-serious adverse events

Non-serious adverse events are adverse events other than those that have been determined to be "serious," and the judgment shall be made by the principal investigator or co-investigators.

7.6.4 Reversibility of adverse events and causal relationships with glucocorticoids

Recovery of adverse event means recovery to a condition where the adverse event no longer exists or to the pre-treatment grade. The judgement of causality between an adverse event and trial medication/glucocorticoids will be performed based on the subject's general condition, complications, concomitant medications/treatments, and temporal relationships. The causality judgement shall be either "deniable" or "undeniable."

7.6.5 Safety assessments specific to this trial

Among glucocorticoid-related side effects, the number of occurrence and proportion of new conditions that require treatment will be individually assessed separately from general safety assessments. Such conditions include; diabetes, hypertension, dyslipidemia, sleep disorders, pathological fractures, and infections. In addition, bone density of the lumbar spine will be measured to evaluate steroidal osteoporosis (at 0, 12, 24 months).

8. Management and Report in Case of Adverse Events

8.1 Definition of adverse event

An adverse event refers to any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs after the trial participation, regardless of whether it has a causal relationship with the trial medication. Adverse events occurred by the completion date of the trial medication administration will be observed until 4 weeks after the final administration. When the adverse event persists, the observation should be continued beyond 4 weeks until recovery, wherever possible. Even if an adverse event occurs after the completion of trial medication administration, follow-up observation shall be continued wherever possible in case the causal relationship with the trial medication cannot be denied. However, this is not applied in following cases; symptoms have become chronic due to exacerbation of primary disease or complications, or follow-up observation is difficult due to transferring to another hospital or commencement of a post-trial treatment.

8.2 Assessment and report of adverse events

When an adverse event occurred, the principal investigator and co-investigators investigate the event and describe it on a case report form, which should include the following details. If the study medication is discontinued or the adverse event requires a treatment, the subject shall be informed of it.

(1) Name of adverse event

(2) Date of occurrence

(3) Outcome (recovering/resolving, recovered/resolved, not recovered/not resolved, fatal)

(4) Action taken regarding the trial medication: Dose increased, dose reduced, dose not changed, medication interrupted, medication discontinued

(5) Concomitant treatment: Details of any concomitant treatments that was being performed at the time or immediately before the event occurred

(6) Severity: Severity shall be judged based on CTCAE v4.0 Japanese Translation JCOG version.

(7) Seriousness classification: Serious adverse events are defined as adverse events that cause death; life-threatening condition; disabilities; a condition potentially leading to disabilities; requires hospitalization or prolongation of existing hospitalization, any other serious conditions according the forgoing examples, and causes congenital diseases or anomalies in a later generation.

8.3 Emergency report and management of adverse events

8.3.1 Scope of adverse events to be reported

Adverse events that the principal investigator or co-investigators are obligated to report to the coordinating investigator or others are the adverse events classified as serious. No mandatory reporting is required for adverse events occurred after completion of the observation period.

8.3.2 Actions to be taken in case of occurrence of serious adverse events

(1) When a serious adverse event occurred, the principal investigator or co-investigators perform appropriate procedures, regardless of causal relationship with the study medication, and engage in investigation of the causes.

(2) The principal investigators of each site are required to report the adverse event information to the Coordinating Office, the head and IRB of each site. Reports to be submitted are the first report (an emergency report and an adverse event report form which is filled in as much as possible, are submitted via either e-mail, telephone, or FAX) and the second report (a detailed report, the adverse event report form which is fully completed, and an adverse event detailed report form, are submitted via either e-mail, telephone, FAX, or in person). For a lethal adverse event, the principal investigator or co-investigators should submit the first report within 72 hours after the event was identified. The second report should be submitted within 15 days.

(3) The trial coordinating office and the coordinating investigator report the event information as promptly as possible to the principal investigators of study sites other than the one where the adverse event occurred. Depending the urgency, reporting over telephone is acceptable; however,

a written report should follow as soon as possible (via either e-mail, FAX, mail, or in person). The principal investigators of each site report the event to the head of own institution.

The coordinating investigator/committee determine the extent of urgency, significance, impact, etc. of the reported event, and take measures such as temporary suspension of patient enrollment and emergency contact to the participating site to inform necessary information.

8.4 Review by Efficacy and Safety Assessment Committee

If judgement of the appropriateness of continuing enrollment or the necessity of any protocol revision is required, the Efficacy and Safety Assessment Committee reviews the report contents, and makes recommendations in writing to the coordinating investigator, coordinating committee, and the case registration center.

8.5 Anticipated adverse effects

In the package insert of RITUXAN®, the following major side effects are described: infusion reaction, exacerbation of hepatitis caused by hepatitis B virus (frequency unknown), liver dysfunction (<5%), mucocutaneous ocular syndrome (frequency unknown), leukopenia (≥10%), thrombocytopenia (<5%), infection (frequency unknown), progressive multifocal leukoencephalopathy (frequency unknown), interstitial pneumonia (frequency unknown), cardiac disorder (frequency unknown), renal disorder (frequency unknown), gastrointestinal perforation (frequency unknown), and reversible posterior leukoencephalopathy syndrome (frequency unknown).

Major side effects described in the package insert of Predonine® are: infection, secondary adrenal cortex dysfunction, diabetes, gastrointestinal ulceration, gastrointestinal perforation, gastrointestinal bleeding, pancreatitis, dysthymia, depression, convulsion, osteoporosis, aseptic osteonecrosis, myopathy, glaucoma, cataract, central serous chorioretinopathy, thrombosis, myocardial infarction, cerebral infarction, aneurysm, epidural lipoma, and tendon rupture (none of these are subject to frequency survey).

For other anticipated adverse effects, please refer package inserts of rituximab and prednisolone. As a reference, side effects identified in the RAVE trial (Remission induction treatment with the combined use of rituximab + high-dose glucocorticoids in ANCA-associated vasculitis) conducted in the United States are listed below.

< Aggregate calculation of 99 patients with ANCA-associated vasculitis in RAVE trial>

Side effect	Frequency

Infection	7/99 patients (7 %)
Leukopenia (Grade ≥3)	3/99 patients (3 %)
Thrombocytopenia (Grade ≥3)	3/99 patients (3 %)
Venous thrombosis	6/99 patients (6 %)
Infusion reaction	1/99 patients (1%)

9. Endpoints

9.1 Primary endpoint

【Efficacy】

Remission induction rate (at 6 months) $= \frac{\text{Number of patients who achieved remission (at 6 months)}}{\text{Total number of patients}}$

【Rationale】

This is the most widely used efficacy index in evaluation studies of remission induction treatments for vasculitis, and has been used as a primary endpoint in the majority of similar clinical trials.

9.2 Secondary endpoints

【Efficacy】

① Time to remission

② Overall survival period, relapse-free period, time to ESRD, time to the first serious adverse event
These endpoints are defined as a length of time from the time of randomization to the occurrence of respective events, and patients who did not experience the event will be counted as censored. Definitions of event and date censored for each endpoint are shown in a table below.

Endpoint	**Event (whichever is earlier if more than one)**	**Date censored**	**Competing risk**
Time to remission	Remission	The last day of confirmed absence of remission	Death
Overall survival period	Any death	The last day of confirmed survival	None
Relapse-free survival period	Any death, relapse	The last day of confirmed absence of relapse	None
Time to ESRD	ESRD	The last day of confirmed	Death

		absence of ESRD	
Time to the first serious adverse event	First serious adverse event (including death and hospitalization)	The last day of confirmed absence of serious adverse event	None

③ The proportion of death, relapse, ESRD, or serious adverse events, and proportion of a composite outcome thereof (at 6 and 24 months; *at 6 months, proportions of death, ESRD, and serious adverse events only)

④ Proportions of minor and major relapses (at 24 months)

⑤ The proportion of participants who achieved remission and glucocorticoid cessation

⑥ Assessment of disease activity using BVAS ver3 (at 6 and 24 months)

⑦ Irreversible damage measured using VDI (at 24 months)

⑧ Evaluation of health-related QOL using SF-36 (at 6 and 24 months)

⑨ Patient general assessment with a VAS (at 6 and 24 months)

⑩ Cumulative glucocorticoid dose (at 6 and 24 months)

【Safety】

① The number of occurrence and proportion of adverse events and serious adverse events that occurred (at 6 and 24 months)

② Proportions of new-onset diabetes, hypertension, and dyslipidemia requiring treatment (at 6 and 24 months)

③ Proportion of sleep disorder requiring treatment (at 6 and 24 months)

④ Proportion of pathological fractures and bone density of the lumbar spine (at 24 months)

⑤ The number of occurrence and proportion of infections (intravenous or oral antibiotics are used) (at 6 and 24 months)

【Rationale】

Among the efficacy-related items, ① is to supplement the primary endpoint, ② - ④ are typical non-remission efficacy endpoints. The composite outcome was included to assess the efficacy-safety balance. ⑤, ⑥, ⑦, ⑧ are indices of the disease activity, irreversible damage caused by the disease, patient QOL [18], and overall patient evaluation, respectively. ⑨ is considered necessary to prove the hypothesis of this study.

Among the safety-related items, we think that ① is required for general safety evaluation of a clinical study. ② - ⑤ are items to reflect adverse effects of glucocorticoids, which represent a major focus of this

study.

9.3 Exploratory endpoints

① Immunoglobulin concentration

② Whole blood B cell count

③ Changes in MPO-/PR3-ANCA values associated with treatment, treatment responses, and relapses

Endpoint	**Event (whichever is earlier if more than one)**	**Date censored**	**Competing risk**
Time to B cell recovery	B cell recovery	The last day of confirmed absence of B cell recovery	Death

【Rationale】

We think that these exploratory endpoints are candidate biomarkers, of which ① serves as an index of side effects, and ② and ③ serve as efficacy indices.

10. Statistical Matters

10.1 Analysis sets

10.1.1 Full Analysis Set (FAS)

The full analysis set (FAS) comprises all subjects enrolled in this study that received at least one dose of a study medication after randomization and visited hospital at least once during the treatment period, from which efficacy data are available. However, subjects are excluded if baseline data cannot be obtained. Subjects are also excluded if there is any serious protocol violation (e.g., consent has not been obtained, patient enrolled outside the contract period).

10.1.2 Per Protocol Set (PPS)

This comprises the remainder of FAS after excluding subjects with any of the following major violations of provisions of the protocol, such as study procedures and concomitant medications.

Violation of inclusion criteria

Violation of exclusion criteria

Less than 75% adherence to the study medication

10.1.3 Safety analysis set

All subjects enrolled in this trial who received at least one dose of a trial medication will be included in analyses. The subjects are divided into groups according to the trial medication that they actually received.

10.2 Target sample size and underlying rationale

Up to 140 cases

【Rationale】

To demonstrate the non-inferiority in remission induction rate, the necessary number of cases calculated with the following conditions is 63 in each arm:

α = 0.025 (one-tailed), $1 - \beta = 0.8$

①Remission induction rate with rituximab + high-dose glucocorticoids = 0.80

②Remission induction rate with rituximab + low-dose glucocorticoids = 0.80

Non-inferiority margin=-0.2

Allocation ratio, 1:1.

With a predicted withdrawal rate of 10%, the target sample size was set as 70 in each arm, a total of 140 cases. The induction rates ① and ② are based on RITUXVAS study [8] and the Cambridge University cohort, respectively [14].

10.3 Case handling

As a general rule, the coordinating investigator determines how to handle registered cases. When a new problem has arisen, the statistical analysis supervisor or the Efficacy and Safety Assessment Committee discuss and decide how to handle it as needed.

10.4 Data handling

During data tabulation and analysis, the coordinating investigator determines how to handle the data as a general rule. However, when a question has arisen, the coordinating investigator consults the statistical analysis supervisor or the Efficacy and Safety Assessment Committee before making a decision.

Missing laboratory test data will be supplemented as needed. For more information, see the Statistical Analysis Plan.

10.5 Statistical analysis items and analytical plan

Efficacy and safety analyses including the primary endpoint will be conducted after all subjects have completed the study medication in the remission induction phase and the data have been fixed (data at 6

months). Thereafter, the data for the remission maintenance phase (at 24 months) are also analyzed to assess the efficacy and safety in a longer term. In all efficacy assessments, the analysis in the full analysis set (FAS) is the primary analysis, and the analysis in the Per Protocol Set (PPS) is done for the purpose of reference. Safety Analysis Set will be used for safety-related analyses.

Major analytical methods are described below. Further details of analyses will be described in the Statistical Analysis Plan, which will be prepared before the data fixation.

10.5.1 Subject background

Distribution and descriptive statistics of the subject background data in each analysis set will be calculated for each treatment arm. For nominal variables and ordinal variables, the frequency and proportion of categories will be shown for each arm. For continuous variables, descriptive statistics (number of cases, mean value, standard deviation, minimum value, median value, and maximum value) will be calculated for each group. In intergroup comparisons, Pearson's chi-square test will be used for nominal variables, unless cells with an expected frequency less than 5 accounts for 20% or more where Fisher's exact test will be used, Wilcoxon rank-sum test will be used for ordinal variables, and t test will be used for continuous variables. The significance level to be used is 5% (two-sided).

10.5.2 Endpoints

10.5.2.1 Primary endpoint analyses

The primary objective of this trial is to test the non-inferiority of low-dose glucocorticoid therapy combined with rituximab compared to high-dose glucocorticoid therapy combined with rituximab in remission induction treatment of new-onset ANCA-associated vasculitis patients in terms of the proportion of participants who achieved remission at 6 months.

Therefore, the evaluation in the primary analysis will be based on a risk difference in the remission induction rate at 6 months between the rituximab + low-dose glucocorticoid group and rituximab + high-dose glucocorticoid group (proportion of participants who achieved remission in the low-dose group - proportion of participants who achieved remission in the high-dose group). The non-inferiority is considered statistically proven if the lower limit of two-tailed 95% confidence interval of the risk difference exceeds -0.2. In addition, the P value for non-inferiority hypothesis testing (H_0: proportion of participants who achieved remission in the low-dose group - proportion of participants who achieved remission in the high-dose group $\leq$ -0.2 v.s. H_1: proportion of participants who achieved remission in the low-dose group - proportion of participants who achieved remission in the high-dose group > -0.2) will be determined. Wald statistics-based methods will be used for estimation of risk difference intervals and calculation of P values.

Further, 95% confidence intervals of adjusted risk differences will be determined as a means of sensitivity analysis. Adjustment factors to be used are allocation factors (age at the time of consent, eGFR, ANCA). The two-tailed 95% confidence interval of the Mantel-Haenszel risk difference reported by Sato (1989) will be used for interval estimation for adjusted risk differences.

10.5.2.2 Secondary efficacy endpoint analyses

The secondary efficacy endpoint data will be analyzed for the purpose of discussions that supplement the results from the primary analyses. The adjustment of multiplicity will not be performed in the analyses on the secondary efficacy endpoints. The significance level in the hypothesis test will be 5% (two-sided), and confidence intervals to be calculated are two-tailed 95% confidence intervals.

Among the secondary endpoints, duration of remission, overall survival, relapse-free survival, time to ESRD, and time to the first serious adverse event are measured from the time of randomization as the starting point, and survival time analysis and competing risk analysis will be performed on lengths of time to respective events.

For proportions of death, relapse, ESRD, and serious adverse events, and proportions of the composite outcome thereof, proportions of occurrence of events at each time point and two-tailed 95% confidence intervals will be calculated.

For BVAS ver3, VDI, SF-36, and VAS, their changes over time will be presented using descriptive statistics (number of cases, mean value, standard deviation, minimum value, median value, and maximum value), and compared between the groups by the analysis of variance model.

Glucocorticoid dose changes over time will be presented using descriptive statistics for each group, and cumulated amounts will be compared between groups with Wilcoxon rank-sum test.

10.5.2.3 Secondary safety endpoint analyses

This study is a non-inferiority trial, in which adverse effects of glucocorticoids are expected to be reduced in the low-dose group. The adjustment of multiplicity will not be performed in the analyses on the secondary safety endpoints. The significance level in the hypothesis test will be 5% (two-sided), and confidence intervals to be calculated are two-tailed 95% confidence intervals.

The number of cases in which adverse events and serious adverse events occurred and proportions of those with and without occurrence, etc. are aggregated in a group-by-group manner, and Pearson's chi-square test will be used for intergroup comparisons (or Fisher's exact test, when cells with an expected frequency less than 5 account for 20% or more).

For occurrence of new-onset diabetes requiring treatment, hypertension, dyslipidemia, sleep disorder

requiring treatment, pathological fractures, and infections (intravenous or oral antibiotics are used), the number of cases and proportions of cases with and without occurrence in each group are determined, and Pearson's chi-square test will be used for intergroup comparisons (or Fisher's exact test, when cells with an expected frequency less than 5 account for 20% or more).

For bone density of the lumbar spine, the data will be aggregated using summary statistics for each group, and compared between the groups by the analysis of variance model.

10.5.3 Exploratory analyses

For eGFR, IgG, and B cell count, their changes over time will be described with summary statistics for each group, and compared between the groups by the analysis of variance model. eGFR values will be calculated with the MDRD equation [17] (to be corrected with the coefficient for Japanese), and patients receiving dialysis will be assumed to have eGFR = 0 ml/min/1.73m$_2$.

For B cells being depleted/recovered, MPO-/PR3-ANCA remaining positive/turning to negative, and prednisolone discontinuation/continuation, the number of cases and proportion will be determined for each group, and Pearson's chi-square test will be used for intergroup comparisons (or Fisher's exact test, when cells with an expected frequency less than 5 account for 20% or more).

For time to B cell recovery, an analysis of competing risks will be performed.

11. Adherence to and Deviation from Protocol

(1) The principal investigator or co-investigators should document any procedure deviating from the Protocol regardless of the reason for the deviation.

(2) For any deviation from the Protocol that occurred for a medically compelling reason, such as avoidance of an imminent danger to the subject, the investigator should describe details and the reason of the deviation in the Status Report of this study, and submit the report to the head of the institution every fiscal year.

12. Modifications to Protocol and Case Report Form

12.1 Revision of protocol and case report form

(1) When the principal investigator finds it necessary to revise the Protocol and Case Report Form, the investigator shall promptly submit the revised Protocol and Case Report Form to the head of the institution and obtain the approval promptly from the IRB through the head of the institution.

(2) The same procedure shall be followed when instructions by the head of the institution based on opinions of the IRB are acceptable to the investigator and the Protocol and Case Report Form are to

be revised accordingly.

13. Termination, halt, or completion of the study

13.1 Criteria for terminating or halting the study

1) The principal investigator examines the appropriateness of the trial continuation when:
   1. Critical information has been obtained on the quality, safety, or efficacy of the study medication;
   2. Recruitment of study subjects are difficult, and the achievement of target case number is deemed to be difficult.
   3. The IRB issued an instruction to modify the Protocol, and the instructed modifications are deemed to be difficult to accept.
2) The study will be terminated when the IRB issued a recommendation or instruction of termination.
3) The coordinating investigator examines the abovementioned matters to decide whether the study should be continued.
4) When the investigator decided to terminate or halt the study, the investigator should report the decision and underlying reasons promptly in writing to the head of the institution.

13.2 Study completion

After the completion of the study, the principal investigator shall submit a written notice of the study completion and a written report summarizing the results from the study to the head of the institution.

14 Data Handling and Storage of Records

Detailed data management procedures are described in the Data Management Plan.

14.1 Data collection

All the data related to this trial will be transcribed to the Case Report Form (CRF) after anonymization. Clinical study data on CRFs are extracted from source documents, and must be consistent with the contents of the source documents. The principal investigator or co-investigators should prepare CRFs using a software compatible with requirements of 21 CFR Part 11, GCP ministerial ordinances, and ER/ES guidelines. When any modification, correction, or addition is made to the CRF contents, the principal investigator or co-investigators should use the software that was used to create the CRF, and all changes should be recorded as electronic information. It should be noted that any CRF prepared by a co-investigator or CRF containing data that have been transcribed from the source documents (source data) by a study

collaborator is subject to content verification by the principal investigator before submission to ensure the absence of any problem. The principal investigator ultimately provides the institution with electronic CRFs (copy) in an electronic medium (e.g., CD-R). The principal investigator ensures the readability and storage stability of the electronic CRFs (copy).

14.2 Retention and submission of source documents and other records

The principal investigators of each site keep essential documents related to the implementation of the trial (duplicate copies of application documents, notifications from the hospital director, duplicate copies of various application forms and reports, list of subject identification codes, informed consent forms, duplicate copies of case report forms, and other documents and records that are necessary to ensure the reliability of the data), and retains them for at least five years after the end of the study.

In this study, source documents (source data) refer to the following documents and the like.

(1) Records of subjects' consents and information provided to subjects
(2) Records, which are the basis of CRF contents, such as medical records, nursing records, clinical laboratory test data, and imaging films. Note that data stored in electronic medical records are also regarded as source documents.
(3) Records related to administration of the study medications.
(4) Trial-related documents or records pertinent to tests required for GCP

Among the data documented in the CRF, the source documents (source data) for the following items are descriptions in CRF themselves. However, if they are also described in medical records or the like, said medical records or the like are deemed to be the source documents (source data).

(1) Purpose of concomitant medication/treatment
(2) Adverse event information on grade, outcomes (including follow-up results), severity, and judgment and rationale for causal relationships between the study medication and glucocorticoids
(3) Reasons for subjects to have discontinued trial participation
(4) Principal investigator's or co-investigator's comments
(5) BVAS and VDI

15 Ethical matters

15.1 Ethical matters

This study shall be conducted in compliance with ethical principles based on the Declaration of Helsinki and ethical guidelines for clinical research and in accordance with ICH-GCP and other relevant local regulatory requirements.

15.2 Adherence to the protocol

Researchers participating in this study adhere to the Protocol as long as patients' safety and human rights are endangered.

15.3 Approval from the Institutional Review Board

15.3.1 Approval at the start of study participation

To participate in this trial, each institution must approve that the trial will be conducted using this Protocol and the information document for patients. When the approval is obtained, the site coordinator at each institution sends a duplicate copy of the approval document to the case registration center (DM Office, Clinical Research Center, Chiba University Hospital). The principal investigator of the site retains the original approval document, and the case registration center retains the duplicate copy (see 4.5① for sending procedure). Each institution can modify the information document for patients independently, without deviating from the scope of requirements for the clinical trials, and use it after the institutional approval. However, institutions are not allowed to introduce any institution-specific modification to contents of the Protocol. The common Protocol must be used by all participating institutions. When any modification of the contents is required, an amendment or revision will be made to the common Protocol used by all institutions. Therefore, when a modification of the protocol text is requested by an institution, the site coordinator consults the Trial Coordinating Office. When the information document is modified in response to an instruction or the like of the institution, the modified document should be sent to the Trial Coordinating Office. The Trial Coordinating Office can request the institution to reconsider the modification request (deletion or content change) through the principal investigator of the site, if such modifications are considered inappropriate.

15.3.2 Annual renewal of the institutional approval

The review/approval of this Protocol and the patient information document by each institution may or may not be subject to annual renewal according to the rule of each institution. Even if they have undergone annual renewal, the Trial Coordinating Office does not require the renewed approval be sent from each applicable institution.

15.4 Protocol modifications

The Protocol is revised according to the following procedure.

(1) When the coordinating investigator finds a revision necessary, the coordinating investigator

provides the principal investigator with a proposed Protocol revision and other necessary materials and information.

(2) The coordinating investigator allows adequate time for the principal investigator to fully examine the proposed Protocol revision and other materials/information provided as described in the preceding paragraph and consult with the coordinating investigator.

(3) Immediately after consultation with the coordinating investigator, the principal investigator submits a revised version of the Protocol to the head of the institution and quickly obtains an approval from the IRB, etc. through the head of the institution.

(4) The same procedure shall be followed when an instruction from the head of institution based on an opinion of the IRB is acceptable to the coordinating investigator and the Protocol is revised accordingly.

15.4.1 Categories of protocol content modifications

In this trial, protocol content modifications approved by the Protocol Review Committee are divided into two categories, i.e., amendments and revisions. Further, additions of supplementary descriptions that fall into neither of the above two categories of protocol content modifications are separately categorized as memorandums. These are defined and handled as follows.

(1) Amendment A partial modification of the Protocol that potentially poses an increased risk on patients participating in the trial or substantially affects the primary endpoint of the trial. In case of an amendment, patient enrollment will be halted temporarily and an approval of contents amended will be obtained from each institution.

(2) Revision Protocol modification with no possibility of posing an increased risk on patients participating in the trial or substantially affecting the primary endpoint of the trial. A protocol modification of this type requires an approval from each institution. The choice between standard and expedite review formats is left to the discretion of each institution. In case of a revision, patient enrollment will not be halted as a general rule.

(3) Memorandum A supplementary description of the Protocol, rather than a modification of Protocol contents, to be distributed to concerned parties of the trial from the coordinating investigator/Coordinating Committee for various purposes such as reducing variations in text interpretation and calling attention to specific matters. Document format does not matter.

15.4.2 Institutional approval of amended/revised Protocol

When an amendment has been made to this Protocol or the information document for patients during the trial, the amended Protocol and information document must be approved by each institution. If the amendment is approved, the site coordinator of each institution sends a copy of the approval document to the Case Registration Center (DM Office, Clinical Research Center, Chiba University Hospital). The original approval document should be retained by the principal investigator of the site, and a duplicate copy should be retained by the Case Registration Center (see 4.5① for sending procedure). An approval is required from each institution also when a revision is made. The choice between standard and expedite review formats is left to the discretion of each institution.

As the information document states that the patient should be informed promptly of any change in the trial contents, the attending physicians should provide the enrolled patient with an adequate explanation (about changes in the protocol treatment, follow-up, etc. after the revision) in case of an amendment or revision.

16. Monitoring and Auditing

16.1 Monitoring

Monitoring is carried out in accordance with the monitoring procedure manual. Since monitoring aims at improving scientific and ethical aspects of the trial by feedback of problems and does not intend to detect problems of the trial sites, the Coordinating Committee, the coordinating investigator, and the principal investigator of the site share information about problems identified through monitoring activities with researchers of participating sites and make efforts to improve them.

16.1.1 Items subject to monitoring

① Enrollment status: number of patients enrolled

② Eligibility: Ineligible patients/potentially ineligible patients

④ Pretreatment background factors

⑤ Status of protocol treatment (ongoing/completed), reasons for discontinuation/completion

⑤ Protocol deviations

⑥ Serious adverse events

⑦ Adverse events

⑧ Overall survival

⑨ Other problems on progress and safety of the study

16.1.2 Eligibility (eligible/ineligible)

All enrolled patients are classified as one of the following eligibility categories according to the definitions described below. For monitoring, patients who are potentially ineligible are listed in the "Eligibility Review" section of the monitoring report by the monitoring subcontractor (CX Medical Japan Co., Ltd.), and examined in CRF review by the Coordinating Committee, and finally determined to be either 1), 2), 9), or 99) by the approval from the coordinating investigator before the primary analysis.

Only those determined to be 1) eligible are "eligible patients"; those determined to be 2) post hoc ineligible, 9) ineligible at enrollment, or 99) defaulting enrollment are collectively "ineligible patients."

1）Eligible　Information occurring before enrollment satisfies all inclusion criteria according to methods and criteria defined in the Protocol.

2）Post hoc ineligible　Information occurring after enrollment does not satisfy either of the inclusion criteria, or information occurring before enrollment does not satisfy either of the inclusion criteria because the method or criterion used was different from what is defined in the Protocol.

9）Ineligible at enrollment　With the method (performed on all patients) and criteria as specified in the Protocol, information occurring before enrollment does not satisfy either of the inclusion criteria. Patients whose information occurring before enrolment were found to be incorrect after enrollment are also included.

99）Defaulting enrollment　A patient who was known not to meet inclusion criteria but enrolled deliberately (falsely). This is a false report, and treated as a serious problem.

16.1.3 Protocol deviations/violations

Protocol deviations are defined as treatments, such as drug administration, laboratory tests, and efficacy/safety assessments that were not conducted in accordance with the provisions of the Protocol. For monitoring, deviations beyond a certain acceptable range specifically determined for individual trials by the monitoring subcontractor (CX Medical Japan Co., Ltd.) and the coordinating investigator/Coordinating Committee before or after the commencement of the trial are listed as "possible deviations" in the monitoring report, and classified into one of the following through a review by the Coordinating Committee.

1）Violation　A deviation from protocol provisions that is caused by the attending physician/site, is clinically inappropriate, and meets more than one of the following items is defined as a "violation."

① Endpoint assessments in the trial will be substantially affected.

② Intentional or systematic

③ Dangerous or extensive

As a general rule, any violations shall be individually described when the trial results are published as articles.

2） Deviation A deviation that is not included in either 1) a violation or 3) within acceptable range.

Deviations are classified into one of the following at the time of monitoring report review.

① Deviation (undesirable)

② Deviation (compelling; e.g., postponed due to year-end and new-year holidays, instrument failure)

③ Deviation (clinically reasonable)

3） Within acceptable range A deviation from the protocol within an acceptable range defined by the coordinating investigator/Coordinating Committee and the monitoring subcontractor (CX Medical Japan Co. Ltd.) before or after the commencement of the trial. Deviations within the pre-determined acceptable range will not be described in monitoring reports.

16.2 Quality assurance

To assure that the trial procedures and data creation, recording, and reporting are conducted appropriately in compliance with the Protocol and GCP, an auditor (INCREASE Co., Ltd.) independent of any organizations involved in the trial including that in charge of monitoring conducts on-site auditing at institutions and ensures that quality control is performed appropriately.

17. Heath Damage Compensation and Insurance

If a health damage occurred in a subject as a result of participating in this trial, the institution takes necessary and appropriate actions, such as providing a medical care system for treatment of the damage. The health damages will be treated under subjects' health insurance. The study medication in this trial is not covered by the Relief System for Sufferers from Adverse Drug Reactions in Japan, and no compensation insurance will be subscribed.

The principal investigator and co-investigators subscribe physician liability insurance in preparation for liability due to the medical practice. In addition, the institution also purchases hospital liability insurance, etc.

18. Patients' Expenses

Since this study is conducted as an investigator-initiated clinical trial, all costs for medications and various examinations, such as blood/urine tests, ECG, and chest X-ray shall be borne by patients within Japanese insurance medical care system.

19. Publication Policy

Our plan is to first publish analysis results including the primary endpoint (analysis at 6-month point) and then separately publish results of longer-term efficacy and safety observations (analysis at 24-month point). The publication media shall be English-language journals. In addition, the data will be published as articles even if the results are not the ones that were originally expected in spite of proper implementation of the study.

As a general rule, the first author of the main article to publish the study results (the article to publish the primary endpoint results for the first time) shall be the coordinating investigator. Other co-authors will comprise researchers selected from each site based on the amount of contributions, will be listed in the descending order of the number of patients enrolled. A person who was in charge of statistical analyses (at the time of analyses for publication) will also be added as a co-author. The final author shall be one of the co-authors who made the greatest contribution to the trial. The coordinating investigator decides whether or not to include members of the research support division of the Coordinating Committee depending on contributions. Authors of articles other than the main article (articles on secondary endpoints, secondary analysis, etc.) will be determined after approval from the coordinating investigator.

20. Research Funding and Conflict of Interest

This trial is planned to be conducted fairly by the principal investigator and co-investigators with a competition-based intramural research grant from the Chiba University Hospital. After obtaining an approval from the Conflict of Interest Committee of the Chiba University Hospital, the fairness of interests pertinent to this trial shall be maintained by appropriately managing conflicts of interests and regularly reporting the trial progress to the Conflict of Interest Committee in accordance with the "conflict of interest policy for clinical research" of the Chiba University Hospital. In addition, each participating site obtains an approval from own Conflict of Interest Committee, and shall comply with the provisions of the Committee.

21. Study Team

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Participating sites/Investigators

See attachment

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23. Appendices

23.1 Examination/observation schedule

	Screening	Remission induction period					Remission maintenance period	At trial withdrawal
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, 24 months At confirmation of relapse5)	
Informed consent	●							
Case registration	●							
Patient background check	●							
Concomitant medication check	←	—	—	—	—	—	—	→
Medication adherence check			●	●	●	●	●	●
Subjective/objective symptom check		●	●	●	●	●	●	●
Adverse event observation	←	—	—	—	—	—	—	→
BVAS		●	●	●	●	●	●	●
VDI		●				●	●1)	●
SF-36		●				●	●1)	●
VAS		●	●	●	●	●	●	●
Body weight	●	●	●	●	●	●	●	●
Blood pressure/pulse/body temperature	●	●	●	●	●	●	●	●
Blood/urine tests	●2)	●	●	●	●	●	●	●
ECG, X-ray	●							
Bone density		●4)					●3)	●
Pregnancy test	←	—	—	—	—	—	—	→

Remission/relapse check		←					→	

Day1=The day to start glucocorticoid administration, 1 month = day 30 ± 7 days, 2 months = day 60 ± 15 days, 4 months = day 120 ± 15 days, 6 months = day 180 ± 15 days, 9 months = day 270 ± 30 days, 12 months = day 360 ± 30 days, 18 months = day 540 ± 30 days, 24 months = day 720 ± 30 days))

Note that existing data on chest X-ray, ECG, MPO-/PR3-ANCA, HIV antibodies, HBs antigen/HBs antibodies/HBc antibodies, and HCV antibodies may be used as screening data, as long as they were obtained within 2 weeks before consent.

1) Only at 12, 18, and 24 months

2) Screening blood test items

3) Only at 12 and 24 months

4) To be taken between Day 1 and Day 28

5) When a relapse was confirmed in a Protocol-required visit, only tests specified for the visit are required. However, specified tests for a point of relapse confirmation must be performed when a relapse was found in a non-required visit.

<Blood/urine tests>

Blood cell count (red blood cells, hemoglobin, platelet, white blood cells, differential leukocyte count, B cell count)

Serum biochemical tests (total protein, albumin, electrolytes [Na, K, Cl], BUN, serum creatinine level, 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)

Note that MPO-ANCA and PR3-ANCA at screening may be used as month 0 data.

23.2 BVAS ver3

Table 1　BVAS2003

	なし	活動性病変		なし	活動性病変
1．一般状態	□		6．心血管	□	
筋肉痛		○	脈の欠如		○
関節痛あるいは関節炎		○	弁膜疾患		○
38.0℃以上の発熱		○	心外膜炎		○
2kg以上の体重減少		○	虚血性の胸痛		○
2．皮膚	□		心筋症		○
硬塞		○	うっ血性心不全		○
紫斑		○	7．腹部	□	
潰瘍		○	腹膜炎		○
壊疽		○	血性下痢便		○
他の皮膚血管炎		○	虚血性の腹痛		○
3．粘膜／眼	□		8．腎	□	
口腔潰瘍／肉芽腫		○	高血圧		○
陰部潰瘍		○	蛋白尿＞1＋		○
付属器炎		○	血尿＞10rbc/hpf		○
著明な眼球突出		○	血清クレアチニン125～249 μmol/l		○
上強膜炎		○	血清クレアチニン250～499 μmol/l		○
結膜炎／眼瞼炎／角膜炎		○	血清クレアチニン≧500 μmol/l		○
霧視		○	30％超の血清クレアチニン値の上昇あるいは		○
突然の視力喪失		○	25％超のクレアチニンクリアランスの低下		
ぶどう膜炎		○	9．神経	□	
網膜血管炎／網膜血栓／網膜滲出／網膜出血		○	頭痛		○
4．耳鼻咽喉	□		髄膜炎		○
血性鼻汁／鼻垢／潰瘍かつ／または肉芽腫		○	器質的病変に基づく認知障害		○
副鼻腔病変		○	痙攣（高血圧性脳症ではない）		○
声門下狭窄		○	脳卒中		○
伝音性難聴		○	脊髄病変		○
感音性難聴		○	脳神経麻痺		○
5．胸部	□		感覚末梢神経障害		○
喉鳴		○	運動性多発単神経炎		○
結節または空洞		○	10．その他	□	
胸水貯留／胸膜炎		○			
浸潤影		○	持続性血管炎病態限定		
気管支内病変		○	上記のすべての症候が，新規／悪化		
多量の血痰／肺胞出血		○	ではなく，低侵襲／持続性のとき		
呼吸不全		○	のみチェック		

□：病変が活動性病態によると考えられる場合のみ，チェックする[慢性障害と考えられる場合はvasculitis damage index(VDI)を使用する]．臓器に異常がない場合は，それぞれの臓器項目の「なし」にチェックする．○：記録されているすべての病変が，くすぶり型／低侵襲型／断続型で，新規／悪化の症候がない場合は，右下端の四角にチェックする．

23.3 Vascular Damage Index (VDI)

	あり	なし		あり	なし
I. 筋骨格		□	VII. 消化器		□
1. 明らかな筋萎縮，筋力低下	○		1. 腸管梗塞／腸管切除後	○	
2. 変形または骨びらんを伴った関節炎	○		2. 腸間膜動脈循環不全／膵炎	○	
3. 骨粗鬆症／脊椎圧迫骨折	○		3. 慢性腹膜炎	○	
4. 無菌性骨壊死	○		4. 食道狭窄／上部消化管の手術	○	
5. 骨髄炎	○		VIII. 末梢循環		□
II. 皮膚症状		□	1. 1肢における脈の欠損	○	
1. 脱毛			2. 1肢における2回目の脈の欠損	○	
2. 皮膚潰瘍	○		3. 2肢以上の脈の欠損	○	
3. 口腔潰瘍	○		4. 大血管の狭窄	○	
III. 耳鼻咽喉		□	5. 3カ月超続く間欠性跛行	○	
1. 難聴	○		6. 静脈血栓症	○	
2. 鼻閉／慢性鼻汁分泌	○		7. 小さな部位の組織欠損	○	
3. 鞍鼻／鼻中隔穿孔	○		8. 大きな部位の組織欠損	○	
4. 慢性副鼻腔炎／X線による骨破壊所見	○		9. 2回目の大きな部位の組織欠損	○	
5. 声門狭窄(未手術)	○		IX. 眼		□
6. 声門狭窄(手術後)	○		1. 白内障	○	
IV. 呼吸器		□	2. 網膜病変	○	
1. 肺高血圧	○		3. 視神経萎縮	○	
2. 肺線維症	○		4. 視力低下・複視	○	
3. 胸膜線維化	○		5. 1眼の失明	○	
4. 肺梗塞	○		6. もう1眼の失明	○	
5. 慢性気管支喘息	○		7. 眼窩の破壊	○	
6. 慢性呼吸不全	○		X. 精神神経		□
7. 呼吸機能異常	○		1. 認知障害	○	
V. 循環器		□	2. 主要精神障害	○	
1. 狭心症／冠動脈バイパス術後	○		3. 痙攣	○	
2. 陳旧性心筋梗塞	○		4. 脳血管障害	○	
3. 2度目の心筋梗塞			5. 2回目の脳血管障害	○	
4. 心筋症	○		6. 脳神経障害	○	
5. 心弁膜異常	○		7. 末梢神経障害	○	
6. 3カ月以上続く心外膜炎 あるいは心外膜切除後	○		8. 横断性脊髄障害	○	
			XI. その他		□
7. 高血圧；拡張期血圧95mmHg または降圧薬内服	○		1. 性腺障害	○	
			2. 骨髄障害	○	
VI. 腎		□	3. 糖尿病	○	
1. 予測または実測の 糸球体濾過率(GFR)が50%以下	○		4. 薬剤性膀胱炎	○	
			5. 悪性腫瘍	○	
2. 蛋白尿0.5g／日以上	○		XII. その他	○	
3. 腎不全末期	○		合計		

VDIは血管炎初発時から生じている臓器障害の記録集である．血管炎症例では血管炎が進展する前にしばしば合併症を伴うことが多いが，その合併症については加点をしない．活動性病変については，Birmingham vasculitis activity score (BVAS)を用いて記録する．血管炎初発時より3カ月以上経過し，かつ，初発時より臓器障害が進展あるいは悪化していない限りは，VDI点数は通常0点となる．

23.4 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.

23.5 VAS scale

"To what extent has your quality of life been reduced due to the disease you have (ANCA-associated vasculitis)?"

Not reduced Significantly reduced

"To what extent has your quality of life been reduced due to the medication you are receiving for treatment?"

Not reduced Significantly reduced

Appendix: List of sites and investigators

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