



A phase I/IIa trial of atorvastatin in Japanese patients with acute Kawasaki disease with coronary artery aneurysm: Study protocol of a multicenter, single-arm, open-label trial

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ABSTRACT

Background: Kawasaki disease (KD) is a systemic vasculitis complicated with coronary artery abnormalities (CAAs). Intravenous immunoglobulin reduces the occurrence of CAAs, but significant number of KD patients with CAAs still exists. Thus, new approaches to prevent and attenuate CAAs are warranted. Atorvastatin has been shown to promote endothelial cell homeostasis and suppress vascular inflammation and has received enthusiasm as a potentially new candidate treatment for KD. In the United States, a phase I/IIa dose-escalation study of atorvastatin in KD patients with CAAs demonstrated the safety and pharmacokinetic data of atorvastatin. However, due to the uncertainty in the application of these results to other populations, we aim to examine the tolerability and generate pharmacokinetics data in Japanese KD patients.

Methods: This is a multicenter, single-arm, open-label, phase I/IIa study of atorvastatin in acute KD patients with CAAs in Japan. A minimum of 9 and a maximum of 18 KD patients (2 years–17 years old) will be recruited for a 3 + 3 dose-escalation study of a 6-week course of atorvastatin (0.125–0.5 mg/kg/day). The primary outcome will be safety of atorvastatin. The secondary outcomes will be pharmacokinetics of atorvastatin, activity of atorvastatin and echocardiographic assessment of CAAs. The activity of atorvastatin will include assessment of C-reactive protein or high sensitivity C-reactive protein and white blood cell levels.

Discussion: This study will provide evidence of the safety, tolerability, and pharmacokinetics of atorvastatin in Japanese KD patients and may lead new standard therapy for acute-phase KD associated with CAA complications.

Trial registration: Japan Registry of Clinical Trials (JRCTs031180057). Registered December 19, 2018, <https://jrct.niph.go.jp/en-latest-detail/jrct031180057>.

1. Introduction

Kawasaki disease (KD) is a systemic vasculitis complicated with coronary artery abnormalities (CAAs) [1]. The standard initial treatment is intravenous immunoglobulin (IVIG) plus aspirin (ASA). IVIG-resistant KD patients are treated with methylprednisolone pulse,

prednisolone, or infliximab added to IVIG. These approaches have reduced the occurrence of CAAs [2,3]. However, 8.9% of KD patients in Japan still experienced CAAs [4]. Therefore, new approaches to prevent or attenuate CAAs are warranted.

Statins are a class of drugs that lower the level of cholesterol in the blood by blocking hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). Studies have shown that statins have pleiotropic

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Abbreviations

24-OHC	24(S)-hydroxy- cholesterol	FOCE-IL:	first-order conditional estimation subroutine with interaction and perhaps Laplacian
AE	adverse event	HMG-CoA reductase	hydroxy-methylglutaryl-coenzyme A reductase
ALT	alanine aminotransferase	hsCRP	high sensitivity CRP
ASA	aspirin	IVIG	Intravenous immunoglobulin
AST	aspartate aminotransferase	KD	Kawasaki disease
AUC	area under the curve	LAD	left anterior descending coronary artery
BQL:	below quantifiable limit	MMP-9	matrix metalloproteinase 9
CAAs	coronary artery abnormalities	MTD	maximum tolerated dose
CK	creatin phosphokinase	PK	pharmacokinetics
CL:	clearance	PPS	Per Protocol Set
CRP	C-reactive protein	RCA	right coronary artery
CYP3A4	cytochrome P450 3A4	SAE	serious adverse events
DLT	dose-limiting toxicities	TC	total cholesterol
ELISA	enzyme linked immunosorbent assay	TGF	transforming growth factor
FAS	Full Analysis Set	TNF	tumor necrosis factor
FOCE-ELS	first-order conditional estimate-extended least squares	Vd	volume of distribution
		WBC	white blood cell

anti-inflammatory antioxidant, anti-coagulation and thrombolytic effects, promoting endothelial cell homeostasis and suppressing vascular inflammation [5,6]. Atorvastatin (Lipitor) suppresses matrix metalloproteinase 9 (MMP-9) activity and upregulates regulatory T cells [7, 8]. Other statins inhibit tumor necrosis factor (TNF)- α production, MMP-9 secretion and transforming growth factor (TGF)- β -induced myofibroblast *trans*-differentiation [9,10]. These mechanisms contribute to restoring cardiovascular homeostasis. Among the statins, atorvastatin is supposed to have the highest anti-inflammatory effect [11,12].

Pathogenesis of the anti-inflammatory effects of statins for KD vasculitis examined using an animal model of KD. Atorvastatin inhibits lymphocyte proliferation in response to superantigen stimulation and production of interleukin (IL)-2, TNF- α and MMP-9, which improves coronary outcomes [13–17]. These *in vitro* studies suggest atorvastatin may be a reasonable candidate as a new treatment for KD.

In clinical settings, Niedra et al. [18] reported on a Canadian case series of 20 patients with giant CAAs in which an atorvastatin was safe. In the US, Tremoulet et al. [19] conducted a phase I/IIa dose-escalation study of atorvastatin (0.125–0.75 mg/kg/day) in KD patients with CAAs. This study indicated that up to 0.75 mg/kg/day of atorvastatin was safe. The study also showed differences in pharmacokinetics (PK) characteristics between KD patients and adults; the C_{max} and the areas under the curve (AUC) for atorvastatin and its metabolite, ortho-hydroxyatorvastatin, increased depending on the weight-based dose of atorvastatin and were higher in the study patients than in adults, suggesting a slower metabolic process in children.

While promising, it is still uncertain that results of the US study can be applied to Asian patients. The AUC of atorvastatin is influenced by genetic variation of cytochrome P450 3A4 (CYP3A4) and polymorphisms of *SLCOB1*, a transporter gene [20]. According to the drug information of Lipitor, the maximum dose for adults in Japan is lower than that in the US. Therefore, careful evaluation of the safety and PK of atorvastatin is needed in Japanese KD children.

The incidence rate of KD in Japan is the highest in the world and there is urgency in identifying new treatment approaches in Japan, such as the use of atorvastatin, but there is no available data on its safety and PK in Japanese KD patients. We planned a phase I/IIa dose-escalation study of atorvastatin in the treatment of acute KD patients with CAAs in Japan with the objective of generating high-quality evidence related to the tolerability and PK of this promising drug.

2. Methods**2.1. Trial design**

This is a multicenter, single-arm, open-label, phase I/IIa dose-escalation study of atorvastatin for patients with acute KD with CAAs in Japan. 14 hospitals in Japan are registered.

2.2. Inclusion criteria

This is a phase I/IIa study using a 3 + 3 dose-escalation design. Depending on the dose level at which the maximum tolerated dose (MTD) is reached, a minimum of 9 or a maximum of 18 patients will be enrolled. We recruited participants from May 1, 2019 to April 30, 2022. Patients who fulfill all criteria described below are eligible for the study.

1. Patients who are 2–17 years old diagnosed with classic KD within 20 days after the fever onset. (Classic KD; presenting at least five of the following six principal symptoms: (i) fever persisting ≥ 5 days; (ii) bilateral conjunctival congestion; (iii) changes in lips and oral cavity; (iv) polymorphous exanthema; (v) changes in peripheral extremities; and (vi) acute non-purulent cervical lymphadenopathy. [21])
2. Patients with left anterior descending coronary artery (LAD) or right coronary artery (RCA) Z-score ≥ 2.5 or an aneurysm (≥ 1.5 x the adjacent segment) of one of the coronary arteries in the echocardiogram evaluation.
3. Patients whose parent or legal guardian will provide written informed consent and patients who will also provide informed assent or consent by themselves in case that they are aged 7 and above.

2.3. Exclusion criteria

Patients who fall under any of the following categories will be excluded from the study.

1. Use of statins, fibrates, or niacins within 90 days prior to the enrollment.
2. History of any severe chronic disease (e.g. congenital heart diseases, autoimmune diseases, chromosomal disorders or neurodegenerative diseases), except for bronchial asthma, atopic dermatitis, autism spectrum disorder or controlled acute disease.
3. Creatine phosphokinase (CK) ≥ 500 IU/L at the screening laboratory test.

4. Total cholesterol (TC) level ≤ 99 mg/dL at the screening laboratory test.
5. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 76 IU/at the screening laboratory test.
6. Intake of CYP3A4 inhibitors (i.e. cyclosporine, clarithromycin or doxycycline) within 7 days prior to the enrollment.
7. History of allergy to atorvastatin.
8. Being pregnant or lactating, or having a possibility of being pregnant.
9. Patient's parent or legal guardian do not fully understand the study explanation in Japanese.
10. Not considered suitable for this study by the investigators for any other reasons.

2.4. Intervention

Based on guidelines for medical treatment of acute KD [22], all patients will receive IVIG (2 g/kg/day) with ASA (30–50 mg/kg/day). Prednisolone or methylprednisolone pulse therapy can be added to the standard therapy in patients with the Kobayashi risk score of five points or higher which represents a high risk of no response to the initial treatment with intravenous immunoglobulin. Patients who have coronary artery Z-score ≥ 2.5 or an aneurysm (≥ 1.5 x the adjacent segment) within the first 20 days after the fever onset will receive atorvastatin once a day orally for 6 weeks (Fig. 1). For patients who are unable to swallow tablets, tablets will be crushed. Adherence of atorvastatin will be confirmed at the 2- and 6-week visits.

This study uses a 3 + 3 dose-escalation design in which a minimum of 3 patients will be enrolled into each cohort group of 3 dose levels (Step1: 0.125 mg/kg/day, Step 2: 0.25 mg/kg/day, Step3:0.5 mg/kg/day) (Table 1). A phase I/IIa trial of atorvastatin in patients with acute KD with CAAs in the US showed 0.75 mg/kg/day of atorvastatin as MTD [19]. In Japan, maximum dose of atorvastatin in adults is 40 mg/day, which is less than the maximum adult dose in the US (80 mg/day). Based on this information, we determined a maximum dose for this study to be 0.5 mg/kg/day (maximum dose of 40 mg/day).

Dose escalation depends on the number of patients with a dose-limiting toxicity (DLT) at a given dose level. Three patients will be given the first dose. If none of the 3 patients showed DLT after 6 weeks of the therapy, the next 3 patients will be enrolled for the next higher dose; if 1 of 3 patients have a DLT, then an additional 3 patients will be

Table 1
Dose escalation protocol.

Dose Cohort	Dose Level	Number of patients
Step 1	0.125 mg/kg/day	3–6
Step 2	0.25 mg/kg/day	3–6
Step 3	0.5 mg/kg/day	3–6
TOTAL		9–18

enrolled at that dose level, and further dose escalation will depend on the number of DLTs among those 6 patients in the cohort of this dosage. If 2 or fewer of the 6 patients have a DLT, the next 3 patients will be given the next higher dose. However, if 3 or more patients in this cohort have a DLT, we will consider this dose level as surpassing the MTD and stop the dose-escalation, signaling the end of the trial; if 2 of 3 patients in a cohort group have a DLT at any dose level, dose-escalation will cease and the trial will be ended.

The MTD is defined as the highest dose of atorvastatin examined at which a maximum of 2 or fewer of the 6 patients in the same cohort experience a DLT during the 6 weeks of the treatment. If dose-escalation reaches the highest dose level set for this study (0.5 mg/kg/day) without patients experiencing DLT, this dose will be considered the MTD.

DLT will be defined as any of the following at the 2- or 6- week time point:

- ALT or AST is elevated by 20% or more compared to entry level and above 76 IU/dl.

Table 2
Upper limit of normal CK.

	CK (IU/L) male	CK (IU/L) female
0 month	310	310
1–2 months	315	315
3–5 months	321	321
6–11 months	321	321
1 year	299	295
2 years	293	290
3–5 years	270	270
6–11 years	230	230
12–14 years	270	210
15–19 years	275	180

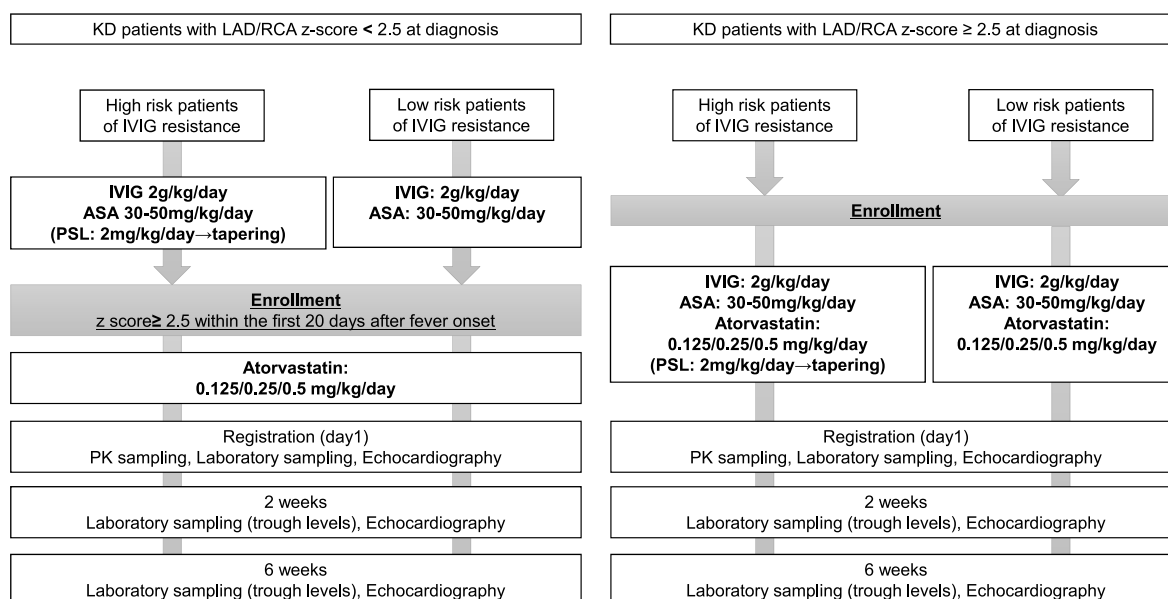


Fig. 1. Schematic depiction of the trial design.

- CK elevation >10 times of the upper limit of normal (Table 2) or symptoms of muscle pain due to myositis [23].
- A decrease in total cholesterol (TC) level that is reduced by 10% or more compared to entry level and below 99 mg/dl.

All patients will be monitored for DLT occurrence for up to 6 weeks from the time of enrollment. A patient who experiences a DLT will discontinue atorvastatin immediately and will be monitored for symptoms and abnormal measurements. Patients will be followed until resolution of the DLT or for 6 weeks, whichever is later.

2.5. Outcomes

The primary outcome is safety of atorvastatin in Japanese KD patients with CAA.

The secondary outcomes are as follows:

1. Pharmacokinetics of atorvastatin
2. Activity of atorvastatin
 - a. Biomarkers and measures of inflammation: Levels of C-reactive protein (CRP) or high sensitivity CRP (hsCRP) and white blood cells (WBC).
3. Echocardiographic assessment (Z-score) of CAAs (LAD, proximal part of RCA)

2.6. Data collection and management

The following data will be collected before the first administration of atorvastatin.

- Demographic data: patient’s age at KD onset, sex, family history, past history, ethnicity
- Physical data: height, weight, body temperature
- Clinical data: physical findings confirming the KD case definition, the date of diagnosis, start of treatment and study entry
- Laboratory data: complete blood count, CRP or hsCRP, total protein, albumin, total bilirubin, AST, ALT, lactate dehydrogenase, gamma-glutamyl transpeptidase, CK, TC, low-density lipoprotein, high-density lipoprotein, triglyceride, blood urea nitrogen, creatinine, sodium, potassium, chlorine
- Echocardiogram: internal lumen diameters and Z-scores of proximal RCA and proximal LAD. Z-score curve is derived from the lambda-

mu-sigma (LMS) method [24], and the Z-score will be calculated by Z score calculator Version 4.0.

- Concomitant therapy

The laboratory tests and the echocardiogram will be performed within 24 h from, and 2 and 6 weeks after, the first administration of atorvastatin. Time series PK specimen collection (1, 4, and 12 h or 2, 6, and 24 h) will be performed at the first dose and only trough level will be measured at 2 weeks and 6 weeks. We will also measure the plasma concentrations of the brain-specific cholesterol metabolite, 24(S)-hydroxy- cholesterol (24-OHC) at 2 weeks and 6 weeks because there may be an effect of atorvastatin treatment on the brain (Tables 3–5).

- Laboratory data: complete blood count, CRP or hsCRP, total protein, albumin, total bilirubin, AST, ALT, lactate dehydrogenase, gamma-glutamyl transpeptidase, CK, TC, low-density lipoprotein, high-density lipoprotein, triglyceride, blood urea nitrogen, creatinine, sodium, potassium, chlorine.
- Echocardiogram: internal lumen diameters and Z-scores of proximal RCA and proximal LAD
- PK assessment: blood samples are drawn according to two schedules (Schedule 1 and Schedule 2) (Table 4). Data centers will alternately assign participants to Schedule 1 and Schedule 2 in the order of registration. Samples are collected at 2, 6, and 24 h for Schedule 1 and at 1, 4, and 12 h for Schedule 2 after the first dose. The blood sample for trough level is collected right before taking atorvastatin at 2 and 6 weeks after the enrollment for both schedules (Table 5).
- 24-OHC: measured at 2 weeks and 6 weeks.
- Patient adherence
- Adverse events
- Concomitant therapy

For the laboratory test, a total of 2 ml of whole blood will be drawn and equally divided into two tubes with and without anticoagulant (EDTA) for plasma and serum segregation, respectively. For plasma segregation, the EDTA-treated tube will be centrifuged for about 15 min at 1000–2000×g and the supernatant will be immediately transfer to a clean tube using a pipette. For serum segregation, we will leave the tube at room temperature for about 15 min to allow the blood to clot which will be removed by centrifuging at 1000–2000×g for 10 min. For the PK study, about 1 ml of whole blood will be collected in a heparin sodium treated tube. The same procedures as the plasma segregation for the laboratory test will be performed. These procedures will allow us to

Table 3
Schedule of data collection and monitoring.

	The day of Diagnosis	2 days after IVIG	enrolled day (Day 1)	PK analysis	2 weeks	6 weeks
Acceptable period	The day of Diagnosis	1–3 days after IVIG	Day1	Day 1–2	Day 12–16	Day 35–49
Informed consent			O			
Administration of atorvastatin						
Demographic data			O			
Clinical data			O		(O)	(O)
Monitoring adverse events			O		O	O
Laboratory data						
CBC	(O)	(O)	O ^a		O	O
Serum Chemistry	(O)	(O)	O ^a		O	O
PK sample				O		
Trough level					O	O
Echocardiogram	(O)	(O)	O		O	O
Sample preservation						
PK sample: (plasma (heparin sodium) 0.5 ml)				O		
Serum (0.5 ml)	(O)	(O)	O ^a		O	O
Plasma (EDTA) (0.5 ml)	(O)	(O)	O ^a		O	O

(O): clinical information or samples will be recorded if they can be accessed.

*PK study will be performed according to schedule 1 or schedule 2. Data center will determine the dose level and PK schedule on the enrollment.

^a Laboratory test and sample preservation will be allowed within 2 days prior to enrollment.

Table 4
Schedules of PK sampling.

	PK study					
	1 h	2 h	4 h	6 h	12 h	24 h
Acceptable period	30–90 min	90–150 min	180–300 min	300–420 min	600–840 min	1260–1620 min
Schedule 1		O		O		O
Schedule 2	O		O		O	

Table 5
Schedule of sampling trough level.

	Trough level	
	2 weeks	6 weeks
	Acceptable period	Day 12–16
Schedule 1	O	O
Schedule 2	O	O

collect 0.5 ml of plasma or serum. We will store the samples at -80°C for 5 years after this study is completed or discontinued.

Atorvastatin and ortho-hydroxy atorvastatin blood concentration measurements will be performed by LC/MS at Q2 Solutions in the United States (the same assay as the atorvastatin study performed in the US [19]). 24-OHC will be measured by enzyme linked immunosorbent assay (ELISA) (the same assay as the US study [19]).

2.7. Statistical methods

The Full Analysis Set (FAS) consists of all patients enrolled in this trial except for the following patients:

- Patients who will not be treated with the protocol treatment
- Patients whose data will not be collected after the protocol treatment starts
- Patients who are designated to be ineligible after enrollment

A Per Protocol Set (PPS) consists of the population without serious protocol violations in the FAS. A safety analysis set consists of patients who will be treated with the protocol treatment at least once.

Regarding discrete variables of patient's demographics (e.g. sex, past history), we will calculate proportions for each category. Regarding continuous variables (e.g. age, height, weight), we will provide descriptive statistics (e.g. mean, standard deviation, median, interquartile range, maximum, minimum).

Population-based PK analyses will be attempted despite limitations in sample size. NONMEM 7.3 (Icon, Dublin, Ireland) or Phoenix NLME (Certara USA, Inc) will be used to perform non-linear mixed effects modeling. We will generate individual patient parameter estimates for volume of distribution (Vd) and clearance (CL) using the maximum a posteriori Bayesian analysis for each patient's data applying the final population model and the POSTHOC subroutine.

Covariates for Vd and CL will be assessed to the extent possible with age, weight, ALT, and CRP included. The uncertainty in the final model will be evaluated using a bootstrap analysis of 1000 virtual patients to calculate the 95% confidence intervals for the population estimates [25]. The model will be supposed reliable if the parameter estimates are within the 95% confidence intervals. If a reliable model will not be obtained because of small patient numbers, the PK profile will be simply described by plotting the observed concentrations of each dosing and PK sampling group.

2.8. Criteria for discontinuing or modifying allocated interventions

The intervention will be discontinued when:

1. The patient or his/her parent or legal guardian asks for withdrawal from the study.
2. Exacerbation or recurrence of the primary disease makes the intervention difficult to continue.
3. The investigators judge it as necessary to discontinue the intervention because of an adverse event(s).
4. Patient dies during the intervention.
5. Exacerbation of the chronic disease or complications make the intervention difficult to continue.
6. The patient is found to be ineligible for the study (e.g. misdiagnosis) after enrollment.
7. Attending the hospital is difficult because of patient's relocation.
8. The Efficiency and Safety Monitoring Committee orders the discontinuance of the intervention because of the adverse events.

The investigators judge discontinuance of the intervention because of any other reasons.

2.9. Adverse event reporting and harms

As for safety evaluations, all adverse events will be monitored and evaluated. Adverse events refer to any unfavorable or unintended change in a sign (i.e. abnormal laboratory), symptom or disease temporally associated with the study treatment, whether or not it is considered to be related to the study product. All adverse events will be graded according to NCI-CTCAE (the National Cancer Institute Common Terminology Criteria for Adverse Events) version 4.0. All serious adverse events (SAEs) must be reported to all investigators and discussed. When adverse events occur, patients will receive appropriate treatment and the cost will be supported by the National Health Insurance. For patients who are experiencing ongoing unresolved adverse events at the time of 6 weeks after enrollment, the observation period will be extended until the treatment is completed.

3. Discussion

This study will provide evidence of the safety, tolerability, and PK characteristics of atorvastatin in Japanese KD patients with CAAs. Furthermore, this study may provide helpful insight about its effectiveness for the prevention and attenuation of CAAs.

This study may have limited statistical power to determine the effectiveness of atorvastatin. However, we will pursue thorough sample size considerations for the next phase III study based on the result of this current evaluation. If the phase III study demonstrates the efficiency of atorvastatin, we will be able to develop a new standard therapy for acute-phase KD experiencing complications with CAAs. This treatment can be expected to reduce the number of KD patients with CAAs, leading to improved quality of life of patients and their family and the reduction of medical expenses.

4. Declarations

4.1. Ethics approval and consent to participate

The study will be conducted according to the principles of the World Medical Association (WMA) Declaration of Helsinki and Clinical Trials Act (Act No. 16 of April 14, 2017). This study was approved by the

Certificated Review Board.

All patients will receive adequate information about the nature, purpose, possible risks and benefits of the study, and alternative therapeutic choices using an informed consent protocol approved by the Certificated Review Board. In this study, patient's parent or legal guardian will sign a consent form. A patient aged 16 years and above will also sign the consent form. Patients aged 7–15 years will be provided information about the study and will sign an assent form. In case that a patient between age 7 and 12 years gives assent orally, the patient's parent or legal guardian will be allowed to indicate the patient's assent on the consent form.

4.2. Consent for publication

Results of the trial will belong to the National Center for Child Health and Development in Japan and will be submitted to a scientific journal as a report after the final analysis. The principal investigator will decide the first author of the report and co-authors following the guidelines of the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals. All authors will read and approve the final manuscript.

4.3. Competing interests

The authors declare no conflicts of interest.

Trial status

This protocol is version 1.5 (amended on April 14, 2020). Enrolment commenced as of May 01, 2019 and will end by April 30, 2022. Total study period will be May 01, 2019 to April 30, 2022.

Credit author statement

Yo Murata: Writing - Original Draft Reina Isayama: Project Administration, Writing - review & editing Shoko Imai: Project Administration, Writing - review & editing Kensuke Shoji: Methodology, Writing - review & editing Mizuho Youndzi: Data curation, Writing - review & editing Mami Okada: Data curation, Writing - review & editing Masashi Mikami: Methodology, Formal analysis, Writing - review & editing Shinobu Kobayashi: Data curation, Writing - review & editing Kevin Y. Urayama: Methodology, Writing - review & editing Tohru Kobayashi: Conceptualization, Investigation, Funding acquisition, Supervision, Methodology, Project administration, Writing - review & editing. All authors read and approved the final manuscript.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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