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RESEARCH ARTICLE

Serum progranulin level is a novel tool for monitoring disease activity of dermatomyositis with antimelanoma differentiation-associated protein 5 antibodies

Asami Fujii MD | Yuki H. Mizutani MD, PhD | Miho Kawamura MD | Kanako Matusyama MD, PhD | Yoko Mizutani MD, PhD | En Shu MD, PhD | Mariko Seishima MD, PhD

Department of Dermatology, Gifu University Graduate School of Medicine, Gifu, Japan

Correspondence
Mariko Seishima, MD, PhD, Department of Dermatology, Gifu University Graduate School of Medicine, 1-1 Yanaido, Gifu 501-1194, Japan.
Email: marikoseishima@yahoo.co.jp

Abstract

Objectives: Dermatomyositis (DM) is an autoimmune disease that presents with a wide variety of clinical manifestations. Patients with DM or clinically amyopathic dermatomyositis (CADM) with antimelanoma differentiation-associated protein 5 (anti-MDA5) antibodies are frequently associated with interstitial pneumonia, especially rapidly progressive interstitial lung disease. Progranulin (PGRN) is an autocrine growth factor involved in inflammation. Elevated serum PGRN levels have been reported in the patients with systemic lupus erythematosus and rheumatoid arthritis. However, they have not been precisely studied in DM/CADM. We assessed PGRN levels as a potential biomarker for DM/CADM with anti-MDA5 antibodies.

Methods: Twenty-four DM/CADM patients with anti-MDA5 antibodies, 12 patients without anti-MDA5 antibodies, and eight healthy volunteers were enrolled. We measured serum PGRN levels and compared them between the anti-MDA5 antibody-positive and antibody-negative groups. They were also measured before and after the start of treatment in anti-MDA5 antibody-positive patients. We examined the correlations between serum PGRN levels and laboratory data such as serum KL-6 and ferritin levels.

Results: Patients with DM/CADM, especially those with anti-MDA5 antibodies, had significantly higher serum PGRN levels than healthy individuals. They decreased after the start of treatment. Serum PGRN levels were positively correlated with serum KL-6 and ferritin levels, and anti-MDA5 antibody titers.

Conclusions: This is the first study to show that PGRN levels were significantly elevated in the sera of DM/CADM patients, particularly in those with anti-MDA5 antibodies. PGRN may be a useful biomarker of disease activity. However, further studies are required to reveal the mechanisms of PGRN in DM/CADM more precisely.

KEYWORDS
anti-MDA5 antibodies, collagen diseases, dermatomyositis, interstitial lung disease, progranulin

1 | INTRODUCTION

Dermatomyositis (DM) is a systemic autoimmune and inflammatory disease that involves not only the muscle and skin, but also several other organs, such as the lungs and joints. Clinically amyopathic DM (CADM) is a distinct subtype of DM that causes the same cutaneous symptoms as classic DM, but with little or no evidence of muscular manifestations.[1,2] Disease-specific autoantibodies, known as myositis-specific autoantibodies, are strongly associated with distinct clinical phenotypes and are used to classify patients into groups with more homogenous clinical features. These include antibodies against melanoma differentiation-associated protein 5 (MDA5; anti-CADM 140 antibody),[2–5] aminoacyl-tRNA synthetases,[6,7] Mi-2 protein,[8] transcriptional intermediary factor-1 (TIF1; anti-155/140 antibody),[9,10] and NXP-2.[11]

Patients with anti-MDA5 antibodies have a high rate of concomitant interstitial lung disease (ILD), especially at risk for rapidly progressive interstitial lung disease (RP-ILD),[3–5,12–14] and usually do not show muscular symptoms. In DM or CADM (DM/CADM) with anti-MDA5 antibodies, three different phenotypes have recently been reported: RP-ILD group with a very high mortality rate, pure dermato-rheumatologic symptom (such as arthralgia) group with a good prognosis, and severe skin vasculopathy group with frequent signs of myositis associated with an intermediate prognosis.[15] Several biomarkers of disease activity have been reported, such as serum ferritin,[13,16] interferon-α,[17] and interleukin (IL)-15[18] levels and anti-MDA5 antibody titers[2] in anti-MDA5 antibody-positive DM/CADM patients.

Progranulin (PGRN) is an autocrine growth factor involved in embryonic development, tissue repair, tumorigenesis, and inflammation.[19,20] PGRN has been shown to directly bind to TNF receptors and block TNF-α signaling, thereby reducing the development of arthritis in mice.[19] Elevated serum PGRN levels are associated with systemic lupus erythematosus (SLE)[21] and rheumatoid arthritis.[22] However, PGRN levels have not been studied precisely in DM/CADM.[23] In this study, we assessed the PGRN levels as a potential biomarker in DM/CADM patients with anti-MDA5 antibodies.

2 | METHODS

2.1 | Patients

We examined adult Japanese patients with DM/CADM who visited the Department of Dermatology, Gifu University Hospital between 2017 and 2019. The diagnosis of DM/CADM was based on the criteria of Bohan and Peter,[24,25] and Sontheimer,[26] and 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria.[27] Twenty-four patients (18 females and six males; aged 17-86 years) with anti-MDA5 antibodies, 12 patients (six females and six males; aged 33-76 years) with non-MDA5 antibodies (anti-TIF1 antibody: 6, anti-Mi-2 antibody: 6), and eight healthy volunteers (four females and four males; aged 33-62 years) were included.

2.2 | Clinical characteristics, treatments, and clinical courses

We compared the skin lesions (Gottron's papules/sign, heliotrope rash, mechanics' hands, palmar papules/erythema, ulcer, calcinosis, periungual hemorrhage, and Raynaud's phenomenon; Figure 1) and general symptoms (fever, muscular symptoms, ILD, and arthropathy) between the anti-MDA5 antibody-positive and antibody-negative groups and followed at least 6 months after the start of treatment. Treatment outcomes and death rates within 6 months were compared.

2.3 | Laboratory data

We measured the levels of KL-6, C-reactive protein (CRP), erythrocyte sedimentation rate at 1 h (ESR), ferritin, and lactate dehydrogenase (LD) before and after the start of treatment, at approximately 1-month interval.

2.4 | Measurement of serum levels of PGRN

Serum PGRN concentrations were measured by enzyme-linked immunosorbent assay (ELISA; CircuLex Human Progranulin ELISA Kit, MBL) in duplicate according to the manufacturer's instructions and assessed using a spectrophotometer (Epoch, BioTek Instruments). The sera and ELISA Kits were stored at −80°C before use. The PGRN levels were measured before and after the start of the treatment at approximately 1-month interval.

2.5 | Statistical analyses

Data analysis was performed using Excel Statistics, 2012 (Social Survey Information). Statistically significant differences between groups were calculated using the chi-square test for categorical variables and the Mann–Whitney *U*-test for nonparametric, continuous variables. Pearson's correlation was used to examine the correlation between two continuous variables. $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Clinical findings and clinical course

Patients with anti-MDA5 antibodies had ILD more frequently, and fever and muscular symptoms less frequently. With regard to cutaneous manifestations, palmar papules/erythema (Figure 1) was

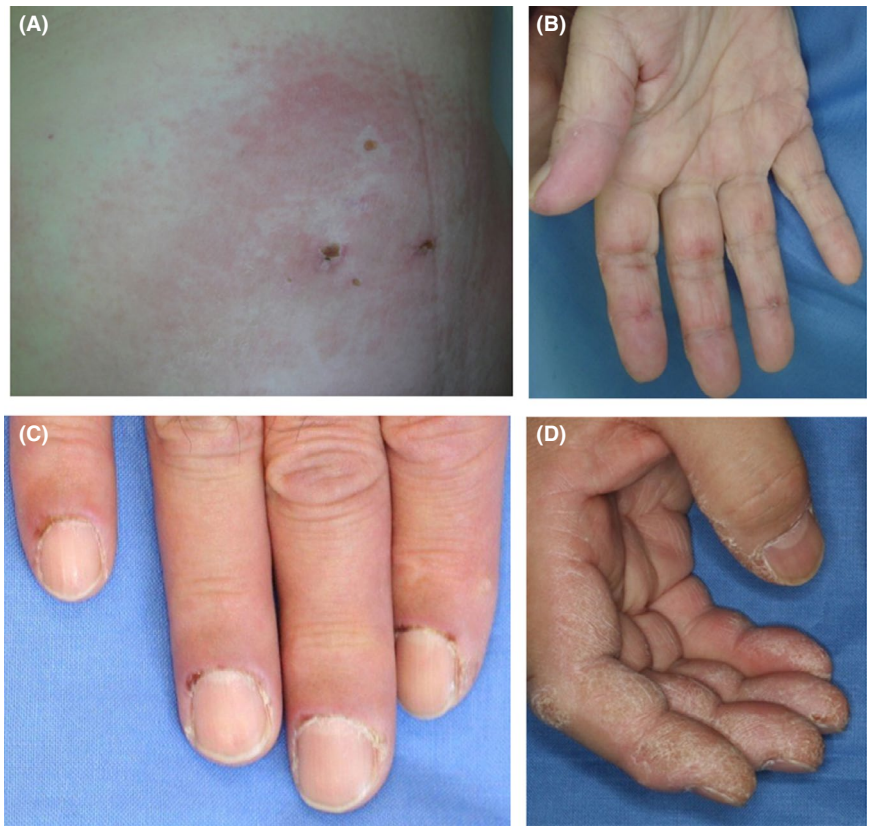

FIGURE 1 Representative cutaneous manifestations; skin ulcer (A), palmar papules (B), periungual hemorrhage (C), and mechanics' hands (D)

observed more often, but heliotrope rash less in these patients. However, Gottron's papules/sign, mechanics' hands, ulcer, calcinosis, and periungual hemorrhage were not different between two groups (Figure 1 and Table 1).

Of the 24 patients with anti-MDA5 antibody-positive DM/CADM, there were four patients in the RP-ILD group, 15 of in the pure dermato-rheumatologic symptom group, and five in the severe skin vasculopathy group with myositis.[15]

Steroid pulse therapy was administered more often in patients with anti-MDA5 antibodies (Table 1). Of the 24 DM/CADM patients with anti-MDA5 antibodies, three died in the following 6 months. Four patients experienced recurrence with re-elevation of PGRN levels associated with increased antibody titers, while re-elevation of KL-6 and ferritin levels was seen, in three patients and in one patient, respectively.

3.2 | Serum PGRN levels in DM/CADM patients vs healthy volunteers

The mean serum PGRN level in DM/CADM patients before initiating treatment was 128 ± 77 ng/ml (range 27-430), which was significantly elevated compared to that in healthy volunteers, 49 ± 6 ng/ml (range; 39-56) ($p < 0.001$). The mean serum PGRN level in DM/CADM patients after the initiation of treatment was 75 ± 53 ng/ml (range; 25-262), which was also significantly higher than that in healthy adults ($p < 0.001$) (Figure 2).

3.3 | Serum PGRN levels in MDA5 antibody-positive vs MDA5 antibody-negative DM/CADM patients

Among the DM/CADM patients, serum PGRN levels were compared between anti-MDA5 antibody-positive and anti-MDA5 antibody-negative patients. Serum PGRN levels were significantly higher in the former group, both before and after the start of treatment ($p < 0.01$), and were also found to have reduced after the start of treatment in both patient groups (Figure 3).

3.4 | Clinical course and serum PRGN levels

Serum PGRN levels gradually decreased with treatment in eight DM/CADM patients with anti-MDA5 antibodies (Figure 4A), who were followed-up periodically for at least 6 months. The mean PGRN levels decreased after treatment initiation (Figure 4B).

3.5 | Correlation between laboratory data and serum PRGN levels

Serum PGRN levels were positively correlated with anti-MDA-5 antibody titers, and ferritin and KL-6 levels. However, CRP, ESR, and LD levels did not correlate with PGRN levels (Figure 5).

TABLE 1 Clinical findings and clinical course of DM/CADM[a] with and without anti-MDA5 antibodies

	DM/CADM with anti-MDA5 antibody *n* = 24 (%)	DM/CADM without anti-MDA5 antibody *n* = 12 (%)	*p* value
A) Background			
Gender (females)	18 (75)	6 (50)	0.134
Age	51.8 ± 23.4	54.6 ± 20.8	0.102
B) General symptoms			
Fever	4 (16.7)	7 (58.3)	<0.05*
Muscular symptoms	2 (8.3)	12 (100)	<0.001***
ILD[b]	23 (95.8)	6 (50)	<0.01**
Arthropathy	6 (25)	5 (41.7)	0.306
C) Cutaneous manifestations			
Gottron's papules/sign	24 (100)	11 (91.7)	0.151
Heliotrope rash	11 (45.8)	11 (91.7)	<0.05*
Mechanics' hands	18 (75)	6 (50)	0.134
Palmar erythema/papule	16 (66.7)	2 (16.7)	<0.01**
Ulcer	4 (16.7)	1 (8.3)	0.496
Calcinosis	1 (4.2)	2 (16.7)	0.201
Periungual hemorrhage	10 (41.7)	4 (33.3)	0.629
Raynaud's phenomenon	3 (12.5)	1 (8.3)	0.708
D) Treatment			
Systemic steroids	24 (100)	10 (83.3)	<0.05*
Steroid pulse therapy	16 (66.7)	2 (16.7)	<0.01**
Immunosuppressants	20 (83.3)	8 (66.7)	0.257
IVCY[c]	10 (41.7)	4 (33.3)	0.629
E) Clinical courses			
Death within 6 months	3 (12.5)	2 (16.7)	0.733

[a]Dermatomyositis or clinically amyopathic dermatomyositis.
[b]Interstitial lung disease.
[c]Intravenous cyclophosphamide.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

4 | DISCUSSION

Progranulin is an extracellular glycoprotein containing seven and one-half repeats of cysteine-rich motifs. PGRN is synthesized by macrophages and is cleaved by extracellular proteases, such as proteinase 3 (PR3) and elastase, into granulin (GRN),[20] which ranges in molecular weight from 6 to 25 kDa. Moreover, PGRN and/or GRN act as soluble cofactors for toll-like receptor 9 (TLR9) signaling and enhance it.[28] Serum PGRN levels are significantly elevated in SLE patients in parallel with the disease activity.[21] PGRN may play a role in the pathogenesis of SLE, partly by enhancing the TLR9 signaling and interleukin (IL)-6 production.[19]

The accumulation of ferritin-producing macrophages has been shown in a CADM-related acute interstitial pneumonia autopsy case.[29] Since macrophage activation is also considered to underlie the pathogenesis of DM/CADM, serum IL-6[30,31] and ferritin[13] can be biomarkers of DM/CADM. However, elevated levels of these markers are not limited to myositis-specific antibodies (Figure 5).

Because PGRN is highly expressed in macrophages,[32] elevation of serum PGRN levels in DM with acute IP also reflects macrophage activation as that of ferritin. PGRN is reported to be important in the initiation of inflammation by recruiting fibroblasts, macrophages, and neutrophils to the site of inflammation.[33] PGRN is also converted to GRN by the elastase that is produced by leukocytes and other cells[33]; however, recent mouse studies have shown that GRN possesses inflammatory functions.[34,35] Thus, PGRN may be converted to GRN in the lungs and be associated with the early phase of pathogenesis of DM with acute ILD. However, it is difficult to investigate the function of GRN in human studies since the measurement of GRNs is not currently available. In our study, serum PGRN levels showed a significant positive correlation with serum anti-MDA5 antibody titers, and serum levels of ferritin and

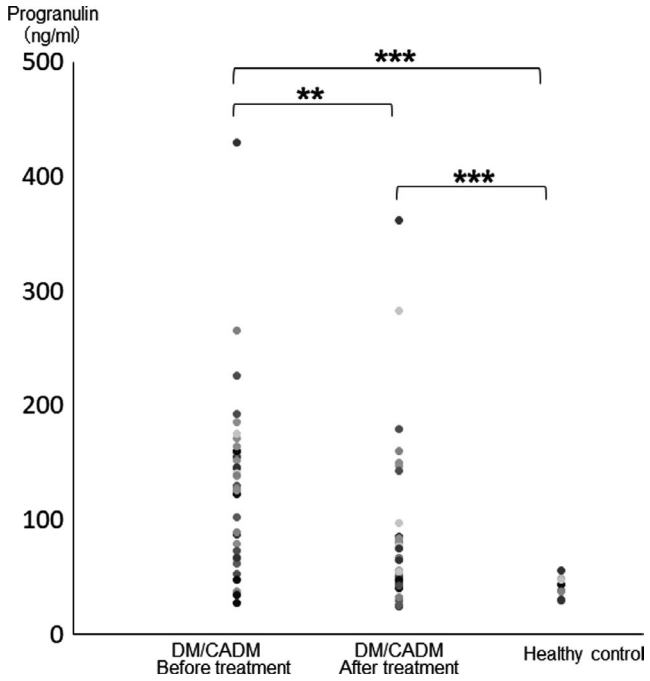

FIGURE 2 Serum progranulin levels in dermatomyositis (DM) or clinically amyopathic dermatomyositis (CADM) patients before and after treatment (approximately 1 month after the start of treatment) compared with healthy controls. $^{**}p < 0.01$, $^{***}p < 0.001$

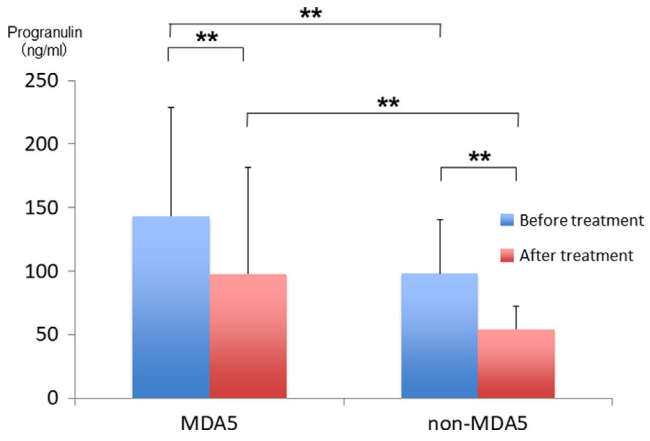

FIGURE 3 Serum progranulin levels in dermatomyositis (DM) or clinically amyopathic dermatomyositis (CADM) patients with or without antimelanoma differentiation-associated protein 5 (anti-MDA5) antibodies. Before treatment (blue column) and approximately 1 month after the start of treatment (red column). $^{**}p < 0.01$

KL-6. Recent studies have suggested serum ferritin level is a marker for severity of acute progressive ILD in DM and CADM patients.[5] Serum ferritin levels in CADM patients with acute ILD are already elevated in the early stages of the disease, before the progression of ILD.[5] KL-6 reflects the regeneration and proliferation of pneumocytes after damage to the pulmonary tissue.[36] Thus, PGRN could also be an acute marker for ILD like ferritin as well as a regeneration marker like KL-6.

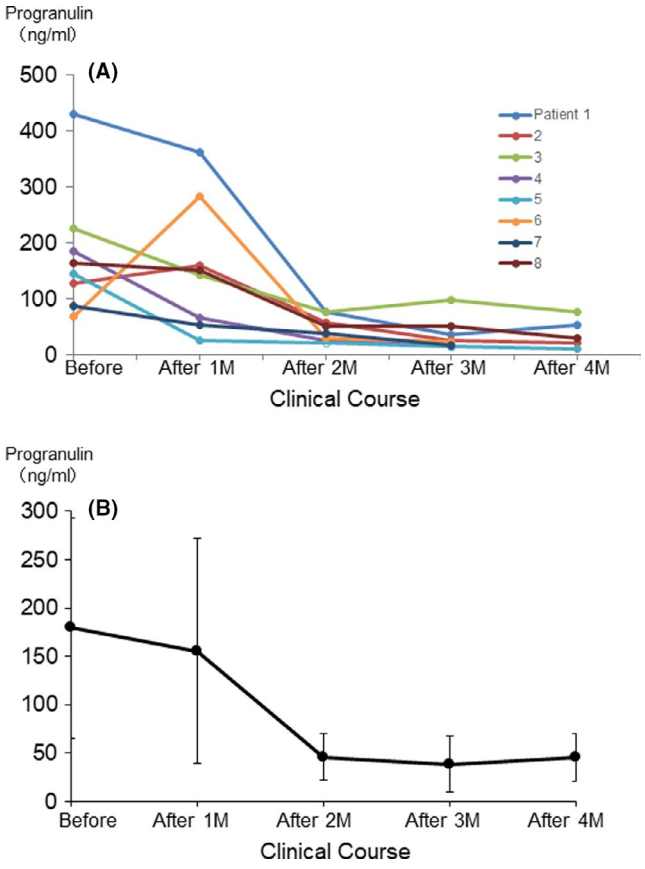

FIGURE 4 Time course of serum progranulin levels after treatment in eight dermatomyositis or clinically amyopathic dermatomyositis (DM/CADM) patients with antimelanoma differentiation-associated protein 5 (anti-MDA5) antibodies; time course of eight patients (A) and the average of progranulin levels in eight patients (B)

Macrophage-derived PGRN is a key regulatory factor in inflammation and wound healing. Several reports in recent years have concluded that serum PGRN level is elevated in conditions such as breast cancer, rheumatoid arthritis,[22] and systemic lupus erythematosus[21] and that it may be a prognostic factor. Accordingly, PGRN is not a disease-specific marker, rather a probable marker of immune activation.

In the present study, patients with DM/CADM, especially those with anti-MDA5 antibody-positive, had significantly higher serum PGRN levels than healthy individuals. A significantly higher serum PGRN levels have been reported in DM/CADM patients complicated by acute/subacute ILD. Among the anti-MDA5 antibody-positive patients studied in this study, all except one had RP-ILD. In both DM/CADM patients with or without anti-MDA5 antibodies, serum PGRN levels decreased with the start of treatments. On recurrence, serum PGRN levels increased rapidly with an increase in antibody titers in all recurrent cases, and serum levels of ferritin and KL-6 did not in all of the cases.

To our knowledge, this is the first study to show that PGRN levels were significantly elevated in the sera of DM/CADM patients, particularly in those with MDA5 antibodies, and that its concentrations

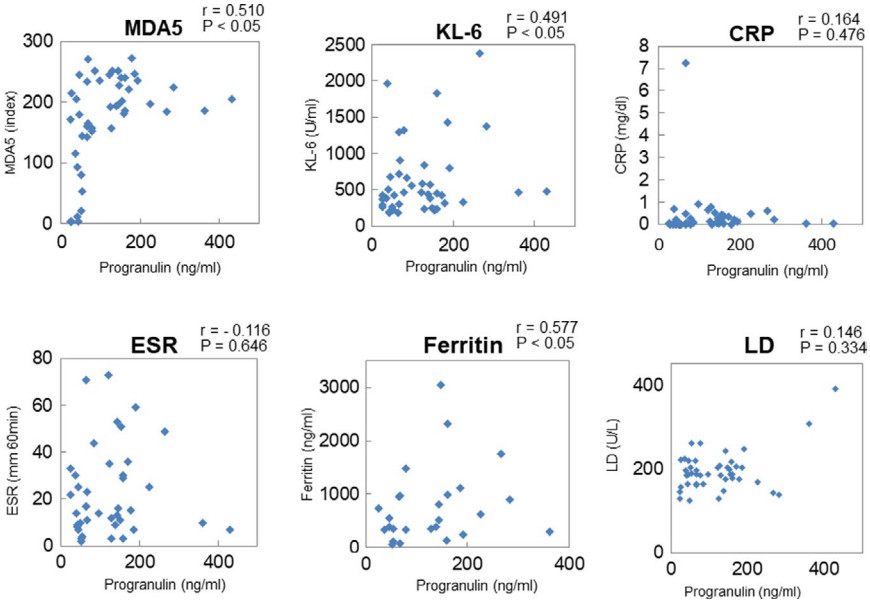

FIGURE 5 Correlation between the serum progranulin levels and antimelanoma differentiation-associated protein 5 (anti-MDA5) antibody titers, KL-6, C-reactive protein (CRP), erythrocyte sedimentation rate at 1 h (ESR), ferritin, and lactate dehydrogenase (LD) levels

were positively correlated with the anti-MDA5 antibody titers, ferritin, and KL-6 levels. Nonetheless, we must acknowledge a limitation of this study. The sample size in this study was small, thus affecting the reliability of the results. Statistical tests usually require a larger sample size to justify that the effect did not occur by chance alone.

Our study showed that PGRN could be a useful biomarker for disease activity in DM patients with ILD. These findings will provide new insights into the pathogenesis and treatment of DM. Further studies are required to reveal the mechanisms of PGRN in human autoimmune diseases more precisely.

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CONFLICT OF INTEREST

The authors declares no conflict of interest.

AUTHOR CONTRIBUTIONS

AF had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YHM, MK, KM, YM, and ES contributed to the acquisition, analysis, and interpretation of the data. MS contributed to the drafting of the manuscript and supervision of the study. All authors read and approved the final manuscript.

DECLARATION SECTION

Approval of the research protocol: The protocol for this study was approved by the Ethical Committee of the Gifu University Graduate School of Medicine (approval ID: 2017-146).

Informed consent: Informed consent was obtained from all participants and healthy volunteers enrolled in this study.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

ORCID

Mariko Seishima https://orcid.org/0000-0003-0007-3632

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