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Candesartan Attenuates Vasculitis in a Mouse Model of Kawasaki Disease Induced by *Candida albicans* Water-Soluble Fraction

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Background: The standard treatment for Kawasaki disease is immunoglobulin therapy, but the high frequency of coronary sequelae in immunoglobulin-refractory cases indicates a need for further improvement in treatment.

Methods: Kawasaki disease-like vasculitis was induced in 5-week-old DBA/2 mice by intraperitoneal administration of 0.5 mg *Candida albicans* water-soluble fraction (CAWS) daily for 5 days followed by daily administration of candesartan, an angiotensin receptor blocker. The vasculitis suppression effect was confirmed histologically and serologically in mice sacrificed at 28 days after the start of candesartan.

Results: The area of inflammatory cell infiltration at the aortic root was 2.4±1.4% in the Control group, 18.1±1.9% in the CAWS group, and 7.1±2.3%, 5.8±1.4%, 7.6±2.4%, and 7.9±5.0% in the CAWS+candesartan 0.125-mg/kg, 0.25-mg/kg, 0.5-mg/kg, and 1.0-mg/kg groups, respectively ($p=0.0200$, $p=0.0122$, $p=0.0122$, and $p=0.0200$ vs. CAWS, respectively). The low-dose candesartan group also showed significantly reduced inflammatory cell infiltration. A similar trend was confirmed by immunostaining of macrophages and TGFβ receptors. Measurement of the inflammatory cytokines IL-1β, IL-6, and TNF-α confirmed the anti-vasculitis effect of candesartan.

Conclusions: Candesartan inhibited vasculitis even at clinical doses used in children, making it a strong future candidate as an additional treatment for immunoglobulin-refractory Kawasaki disease.

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Key words: Kawasaki disease, *Candida albicans* water-soluble fraction (CAWS), angiotensin receptor blocker, candesartan, Kawasaki disease model mouse

Introduction

Kawasaki disease in infants and young children with severe vasculitis leads to dilated lesions in coronary arteries, coronary aneurysms, and subsequent vascular remodeling, thereby producing a variety of coronary artery lesions (CAL), including stenotic lesions and occlusions. Although the disease occurs predominantly in infants and young children, vascular remodeling can continue throughout life once CAL occur in the acute phase, putting them at risk of coronary artery disease in adulthood[1–3]. When Kawasaki disease was first described, CAL developed in about one-quarter of cases. After the efficacy of high-dose immunoglobulin therapy was reported[4], various efforts[5–8] have reduced CAL as coronary sequelae after the acute phase to about 3%[9]. However, the risk of CAL is high in patients resistant to immunoglobulin treatment[10–12]. Coronary artery aneurysms begin to develop at approximately day 10 of disease onset. Control of coronary arteritis by day 10 of disease onset is the goal of initial treatment[13] and is critical for improving

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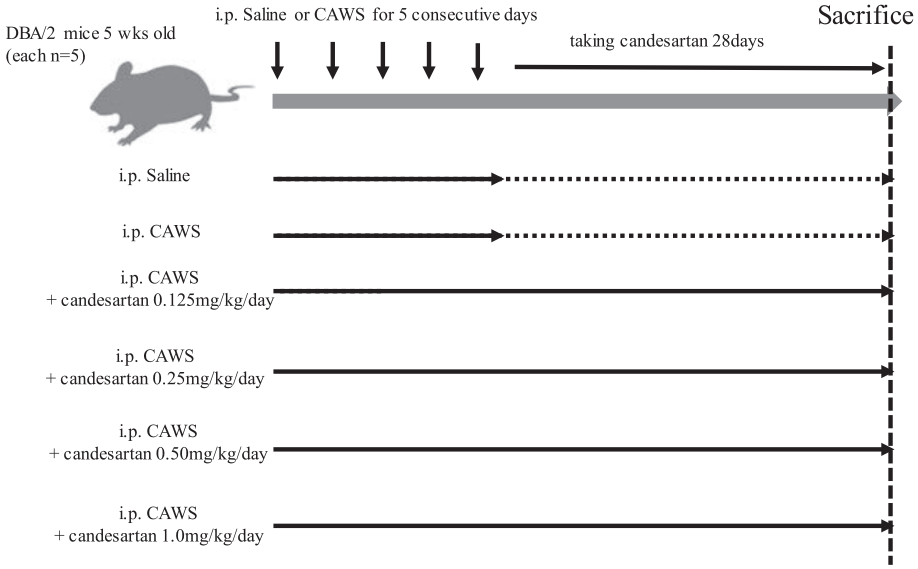

Fig. 1 Experimental methods

To create a mouse model of Kawasaki disease, *Candida albicans* water-soluble fraction (CAWS) was injected intraperitoneally into week-5 male DBA/2 mice for 5 consecutive days. The control group was injected with saline instead of CAWS. The animals were divided into six groups (n=5 each)—control, CAWS, CAWS+candesartan (candesartan 0.125-mg/kg, 0.25-mg/kg, 0.5-mg/kg, and 1.0-mg/kg)—and killed at 28 days after completion of CAWS administration, after which serum and heart tissue were collected.

treatment of acute Kawasaki disease; once a CAL develops, it requires lifelong observation and treatment.

Suppressing angiotensin II is effective in treating and preventing heart failure and atherosclerotic disease in adults[14,15]. Angiotensin receptor blockers (ARBs) may also effectively suppress vascular remodeling in the remote phase of Kawasaki disease[16]. Combined immunoglobulin and ARB therapy suppressed vasculitis in a Kawasaki disease vasculitis model using *Lactobacillus casei*[17]. The present study investigated whether clinical doses of the ARB candesartan inhibit acute-phase vasculitis in a *Candida albicans* water-soluble fraction (CAWS) model of Kawasaki disease vasculitis.

Methods

Five-week-old male DBA/2 mice were purchased from Sankyo Service Co., Ltd. (Tokyo, Japan). The study protocol was approved by the Animal Care and Use Committee of Nippon Medical School (approval number: 2020-029).

CAWS and Candesartan Preparation

CAWS was prepared from *C. albicans* strain NBRC1385, as reported[18]. Briefly, 5 L of C-limiting medium was maintained at 27°C in a glass incubator for 2 days; air was supplied at a rate of 5 L/min, and the mixture was swirled at 400 rpm. After culturing, an equal volume of ethanol was added. After incubating the mixture overnight, the precipitate was collected. The precipitate was dissolved in 250 mL of distilled water, and ethanol was added. The mixture was allowed to incubate again overnight. The precipitate obtained was collected and dried with acetone to obtain the CAWS. An angiotensin II receptor blocker, candesartan cilexetil (candesartan), was purchased from ASKA Pharmaceutical Holdings Co., Ltd. (Tokyo, Japan). Candesartan was crushed and dissolved in drinking water. Daily candesartan was administered directly using an oral sonde to eliminate errors due to individual differences in taking candesartan.

Experimental Procedures

Histological Evaluation of Inflammatory Area (**Fig. 1**)

DBA/2 mice aged 5 weeks, equivalent to age 1 year in humans[19], were divided into five groups (n=5 each) for comparison: 1. Control, 2. only CAWS, 3. CAWS+candesartan 0.125-mg/kg, 4. CAWS+candesartan 0.25-mg/kg, 5. CAWS+candesartan 0.50-mg/kg, and 6. CAWS+candesartan 1.0-mg/kg. CAWS (0.5 mg/mouse) was injected intraperitoneally into mice on five consecutive days. In the control group, saline was administered instead of CAWS. Subsequently, candesartan was administered orally with a sonde in the four CAWS+candesartan groups for 28 consecutive days. Mice were sacrificed with an overdose of pentobarbital at 4 weeks after CAWS

or saline injections, and the heart tissues were collected.

The heart tissues were fixed in formalin and embedded in paraffin. Serial sections were made at a thickness of 5 μm and stained with hematoxylin and eosin (H&E). Sections showing the aortic root and the most severe inflammatory cell infiltration were used. The area (mm^2) of inflammatory cell infiltration was measured with a hybrid cell count system (KEYENCE) and KEYENCE BZ-X analyzer (Osaka, Japan), as previously reported[20]. The ratio of the inflammatory area was calculated based on the total aortic root tissue area.

Immunostaining for Macrophages and Transforming Growth Factor Beta

Macrophage fraction and transforming growth factor beta (TGFβ) expression were evaluated by immunostaining conducted following a previously described procedure[21]. Briefly, the heart tissues were fixed in formalin and embedded in paraffin. Serial sections were made at a thickness of 5 μm and stained using sheep anti-rabbit antibodies. Antigens were activated in a water bath for 20 minutes using Tris-EDTA buffer (pH 9.0); 3% H_2O_2 was used to inactivate endogenous enzymes. The study used sheep anti-rabbit antibodies for immunostaining: Anti-galectin 3 (MAC-2) antibody, a non-specific marker for macrophages (1/250, 60 min room temperature [RT], Abcam, ab76245; UK), anti-CD80 (1/200, 90 min RT, Abcam, ab215166; UK), a marker specific for M1 macrophages; anti-mannose receptor (CD206) antibody (1/200, 90 min RT, Abcam, ab64693; UK), a marker specific for M2 macrophages; and anti-TGFβ receptor II antibody (1/200, 60 min RT, Abcam, ab186838; UK). The sections were further treated with the secondary antibodies and developed using HRP-conjugated DAB substrate (Abcam; ab 236466; UK). The macrophage infiltration area (mm^2) was measured using the hybrid cell count system described above.

Serum Cytokine Profiling

Serum samples were stored at −20°C until analysis. Inflammatory cytokines, including IL-1β, IL-6, and TNF-α, were measured using the Bio-plex multiplex system with Bio-PLEX Pro™ Mouse Cytokine Th17 Panel A 6-Plex (BIO-RAD; Hercules, CA, USA) according to the manufacturer's protocol.

Statistical Analysis

Statistical data are expressed as medians (interquartile range) or means (SD). Statistical analyses were performed using JMP statistical software version 17 (SAS Institute Inc., Cary, NC, USA). The Kruskal-Wallis test was used to identify significant differences among groups. When significance was detected, the Wilcoxon test was used as a post-hoc test to compare group values. A *P* value of <0.05 was considered to indicate statistical significance.

Results

Evaluation of Inflammatory Cell Infiltration Area

H&E staining showed severe inflammatory cell infiltration at the aortic root and pericoronary arteries in all CAWS-administered mice (**Fig. 2A**). The inflammatory cell infiltration area ratio was significantly greater in the CAWS group than in the control group (18.1±1.9% vs. 2.4 ±1.4%, p=0.0122). Candesartan significantly attenuated inflammatory cell infiltration in all candesartan groups (candesartan 0.125-mg/kg group, 7.1±2.3%; candesartan 0.25-mg/kg group, 5.8±1.4%; candesartan 0.5-mg/kg group, 7.6±2.4%; candesartan 1.0-mg/kg group, 7.9±5.0%; p=0.0200, p=0.0122, p=0.0122, and p=0.0200 vs. the CAWS group, respectively) (**Fig. 2B**). However, there were no significant differences between candesartan groups.

Evaluation of Macrophage Infiltration by Immunostaining

Macrophage infiltration was observed in all groups injected with CAWS.

a) Anti-Galectin 3 (MAC2) Staining

The non-specific macrophage infiltration area ratio was significantly greater in the CAWS group than in the control group (7.9±2.7% vs. 0.2±0.1%, p=0.0119) (**Fig. 3A**). Candesartan significantly attenuated macrophage infiltration (candesartan 0.125-mg/kg group: 1.8±1.3%, candesartan 0.25-mg/kg group: 1.4±1.0%; p=0.0200 and p= 0.0200 vs. the CAWS group, respectively) (**Fig. 3B**). There were no significant differences between candesartan groups.

b) CD80 Staining

CD80-positive macrophages (M1 macrophages) were detected along the area of non-specific macrophages detected by MAC2 staining; M1 macrophages had a higher infiltration area ratio in the CAWS group and less infiltration with candesartan. The scale in **Figure 4A** bar represents 200 μm.

The M1 macrophage infiltration area ratio was significantly higher in the CAWS group than in the control group (7.40±3.0% vs. 0.1±0.2%, p=0.0122). Candesartan significantly attenuated M1 cell infiltration (candesartan 0.125-mg/kg group: 3.6±1.5%, candesartan 0.25-mg/kg group: 1.8±0.7%; p=0.0373 and p=0.0200 vs. the CAWS group, respectively) (**Fig. 4B**). There were no significant differences between candesartan groups.

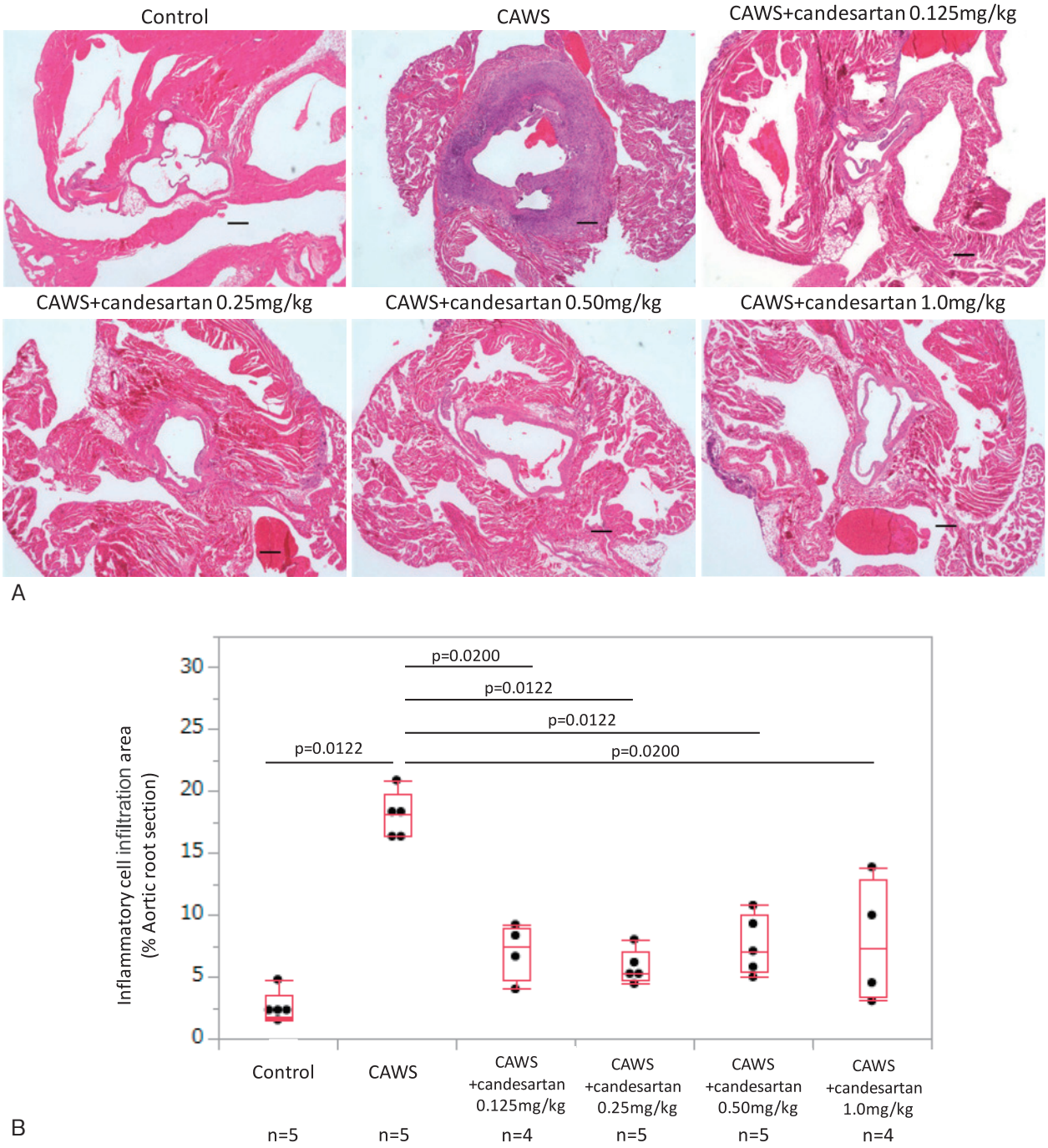

Fig. 2 Vasculitis of the aortic root caused by *Candida albicans* water-soluble fraction (CAWS)

A: Severe vasculitis is observed in the aortic root region in the CAWS group. Inflammation is reduced in all the candesartan groups (0.125-mg/kg, 0.25-mg/kg, 0.5-mg/kg, and 1.0-mg/kg). The scale bar represents 200 μm.

B: The inflammation area is assessed using the Keyence hybrid cell counting system and a BZ-X analyzer. The area infiltrated by inflammatory cells is calculated as a ratio of the total aortic root area. CAWS significantly increased the inflammatory area compared to the control group (p=0.0122). Compared to the CAWS group, the inflammatory area is significantly smaller in all candesartan groups (0.125-mg/kg: p=0.0200, 0.25-mg/kg: p=0.0122, 0.50-mg/kg: p=0.0122, 1.0-mg/kg: p=0.0200).

c) Anti-Mannose Receptor (CD206) Staining

CD206-positive macrophages (M2 macrophages) were detected along the area of non-specific macrophages detected by MAC2 staining; M2 macrophages had a higher infiltration area ratio in the CAWS group and less infiltration with candesartan. The scale bar in **Figure 5A** represents 200 μm.

The M2 macrophage infiltration area ratio was significantly larger in the CAWS group than in the control group (4.4±1.4% vs. 0.8±0.3%, p=0.0122). Candesartan

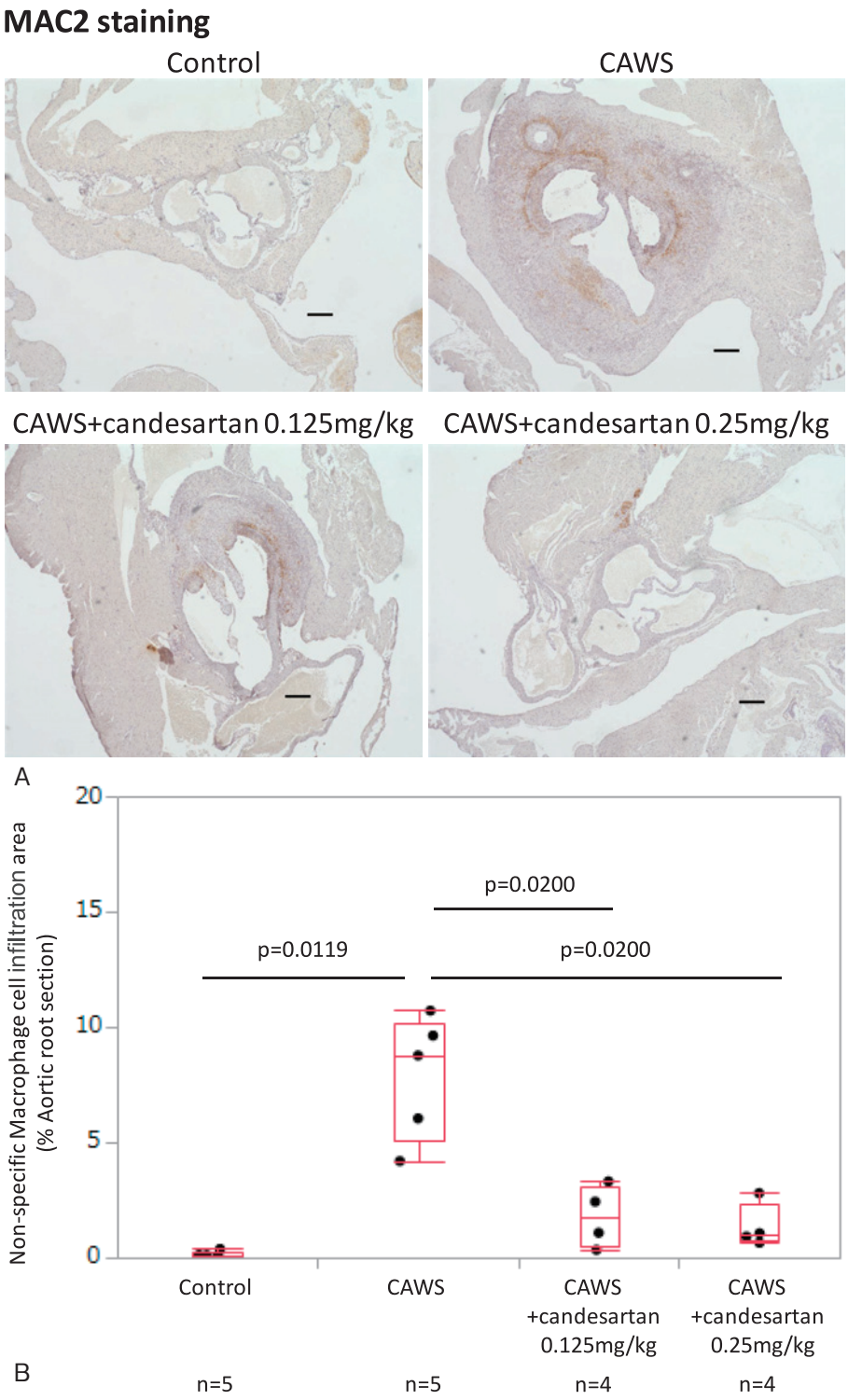

Fig. 3 Assessment of MAC2-positive macrophages

A: MAC2-positive macrophages (nonspecific macrophages) were detected along the area of inflammatory cell infiltration by hematoxylin and eosin (H&E) staining; MAC2-positive macrophages have an increased infiltration area ratio in the *Candida albicans* water-soluble fraction (CAWS) group and reduced infiltration with candesartan. The scale bar represents 200 μm.

B: The infiltration area of MAC2-positive macrophages in the aortic root is expressed as a percentage of the total aortic root area. The CAWS group had a significantly larger area of MAC2-positive macrophage infiltration than the control group (p=0.0119). All candesartan groups also had a significantly smaller MAC2-positive macrophage infiltration area than the CAWS group (0.125-mg/kg oral group, p=0.0200; 0.25-mg/kg oral group, p=0.0200).

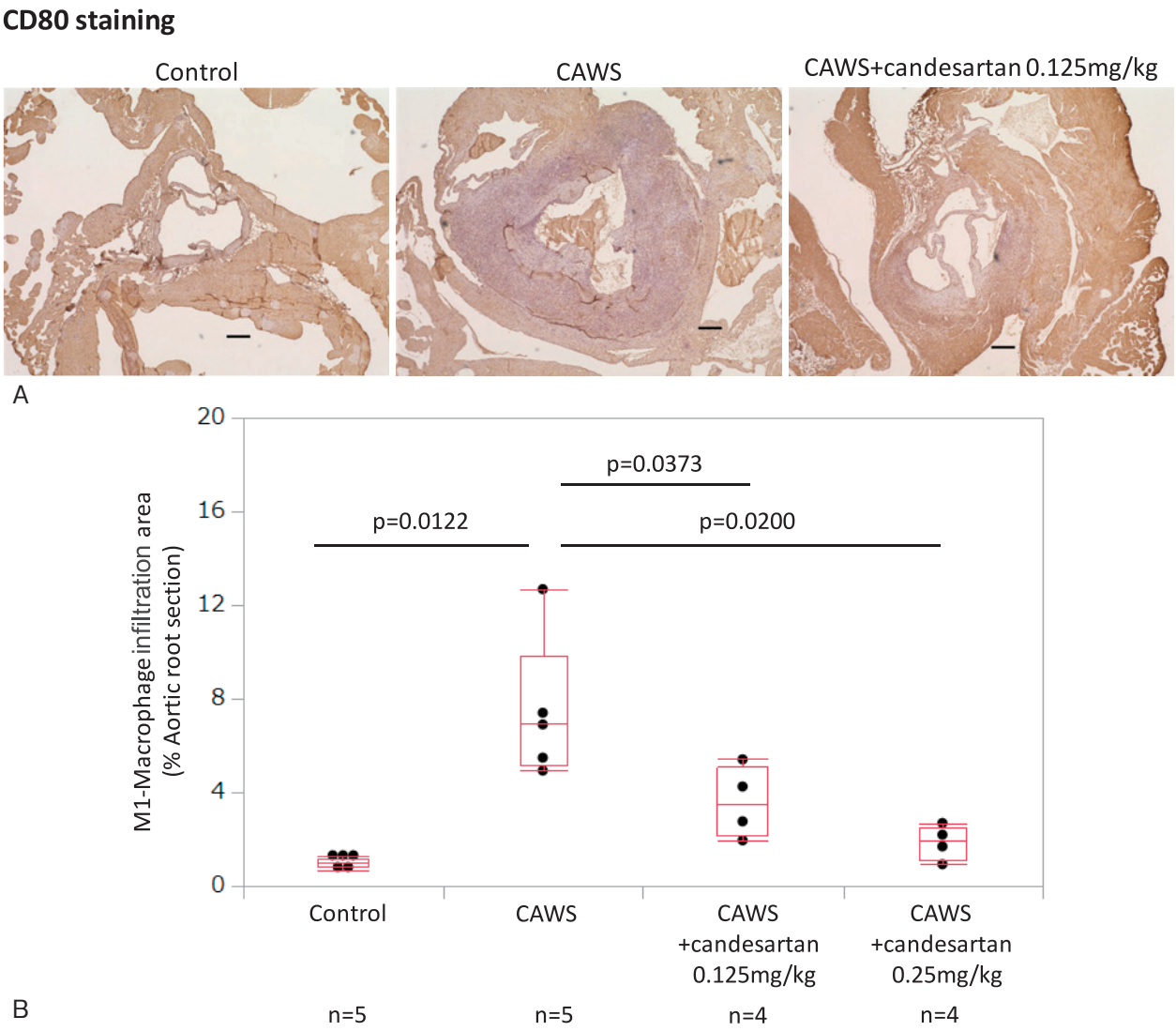

Fig. 4 Assessment of CD80-positive macrophages

A: CD80-positive macrophages (M1 macrophage) are detected along the area of nonspecific macrophage detected by MAC2 staining; M1 macrophages have an increased infiltration area ratio in the *Candida albicans* water-soluble fraction (CAWS) group and reduced infiltration with candesartan. The scale bar represents 200 μm.

B: The infiltration area ratio of CD80-positive macrophages was significantly greater in the *Candida albican*s water-soluble fraction (CAWS) group than in the control group (p=0.0122); infiltration was reduced in the candesartan group (0.125-mg/kg group, p=0.0373; 0.25-mg/kg group, p=0.0200).

significantly attenuated M2 macrophage infiltration in the candesartan 0.25-mg/kg group (1.1±0.7%, p=0.0200), but not in the candesartan 0.125 mg/kg group (2.8±1.8%, p=0.1779), as compared with the CAWS group (**Fig. 5B**). There were no significant differences between candesartan groups.

d) M2/M1 Macrophage Cell Ratio

The M2/M1 macrophage cell ratio in the same sample was calculated. No significant differences were found between the CAWS group and other groups (p=0.3940). M2 macrophages did not increase during candesartan treatment.

e) Transforming Growth Factor Beta (TGFβ) Staining

TGFβ receptor-positive cells were detected in the areas of M1 and M2 macrophage staining; TGFβ receptor-positive cells had a larger infiltration area ratio in the CAWS group and less infiltration with candesartan. The scale bar in **Figure 6A** represents 200 μm.

The TGFβ receptor expression area ratio was significantly larger in the CAWS group than in the control group (8.8±2.1% vs. 0.9±0.8%, p=0.0122). Candesartan significantly decreased TGFβ receptor expression (candesartan 0.125-mg/kg group: 4.6±1.4%, candesartan 0.25-mg/kg group: 1.9±0.9%; p=0.0200 and p=0.0200 vs. the CAWS group, respectively; **Fig. 6B**). There were no sig-

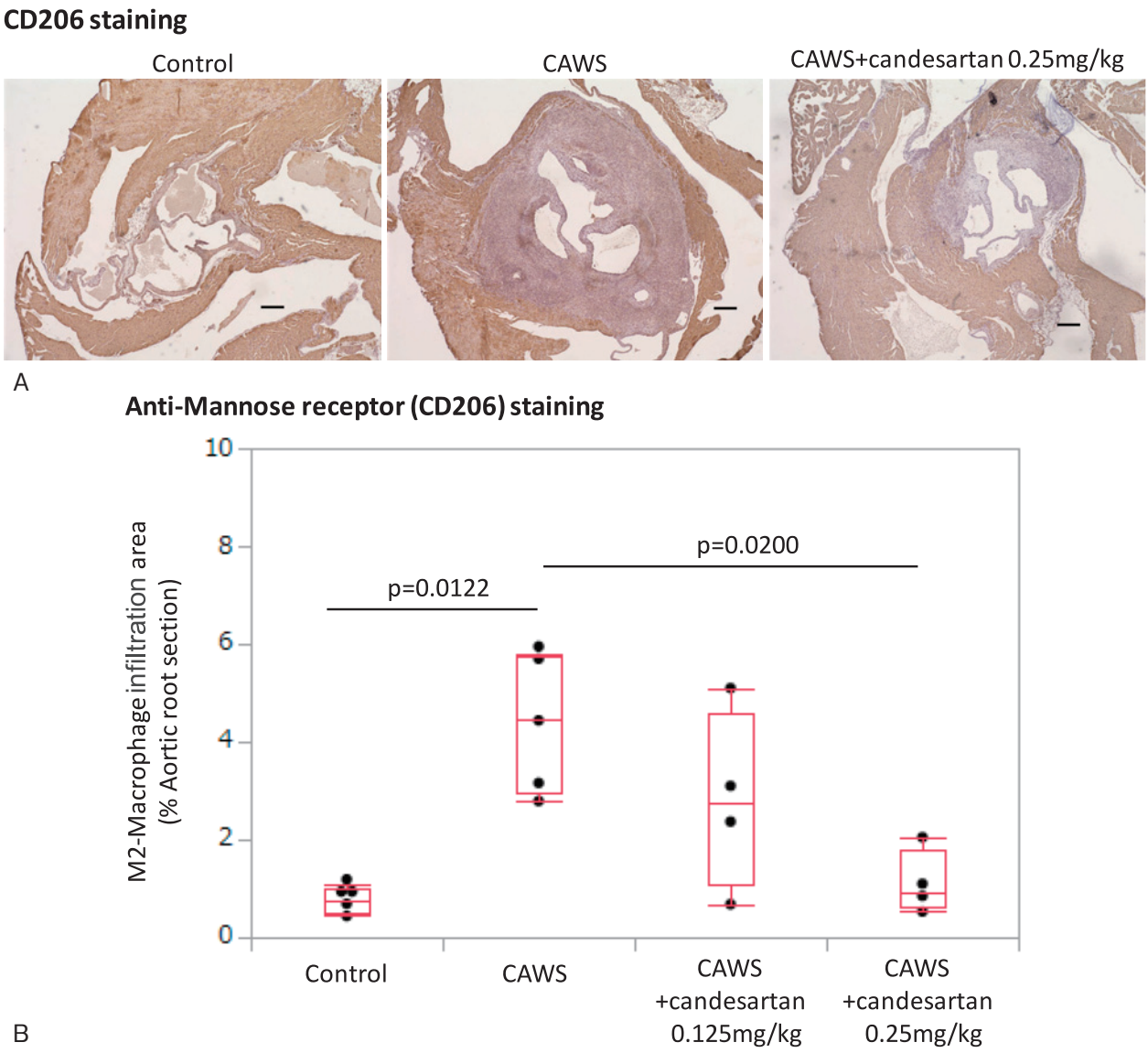

Fig. 5 Assessment of CD206-positive macrophage

A: CD206-positive macrophages (M2 macrophage) are detected along the area of nonspecific macrophages detected by MAC2 staining; M2 macrophages have an increased infiltration area ratio in the *Candida albicans* water-soluble fraction (CAWS) group and reduced infiltration with candesartan. The scale bar represents 200 μm.

B: The infiltration area ratio of CD206-positive macrophage was significantly greater in the CAWS than in the control group (4.4±1.4% vs. 0.8±0.3%, p=0.0122); infiltration was significantly reduced in the candesartan 0.25-mg/kg group (1.1±0.7%, p=0.0200) but not in the candesartan 0.125 mg/kg group (2.8±1.8%, p=0.1779).

nificant differences between candesartan groups.

Serum Cytokine Profiling

Cytokine profiles were determined by using serum extracted from the mice.

a) IL-1β

Serum IL-1β levels in the Control, CAWS, CAWS+candesartan 0.125-mg/kg, and CAWS+candesartan 0.25-mg/kg groups were 1.07±0.54 pg/mL, 2.11±0.71 pg/mL, 1.67 ±0.18 pg/mL, and 1.72±0.42 pg/mL, respectively (**Fig. 7 A**). Candesartan attenuated the increase in IL-1β by CAWS; however, the difference was not significant.

b) IL-6

Serum IL-6 levels in the Control, CAWS, CAWS+candesartan 0.125-mg/kg, and CAWS+candesartan 0.25-mg/kg groups were 7.33±4.58 pg/mL, 35.1±6.67 pg/mL, 9.97± 10.0 pg/mL, and 27.8±26.8 pg/mL, respectively. As compared with the CAWS group, serum IL-6 levels were significantly lower in the control (p=0.0122) and 0.25-mg/kg (p=0.0200) groups (**Fig. 7B**).

c) TNF-α

Serum TNF-α levels in the Control, CAWS, CAWS+candesartan 0.125-mg/kg, and CAWS+candesartan 0.25-

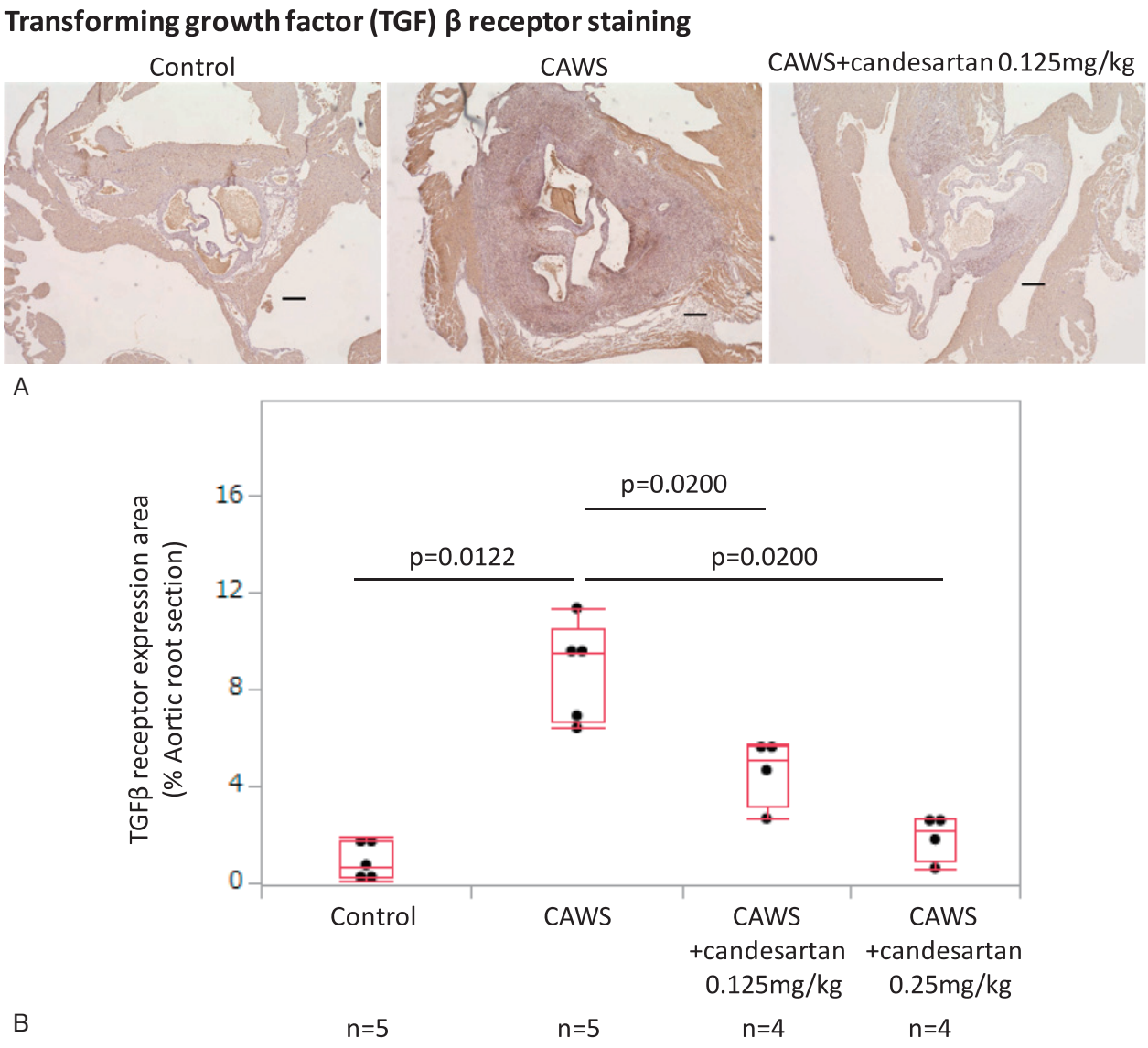

Fig. 6 Assessment of TGFβ receptor–positive cells

A: TGFβ receptor–positive cells are detected along the area of the M1 and M2 macrophage staining; TGFβ receptor–positive cells have an increased infiltration area ratio in the *Candida albicans* water-soluble fraction (CAWS) group and reduced infiltration with candesartan. The scale bar represents 200 μm.

B: The area of infiltration of TGFβ receptor–positive cells was significantly greater in the *Candida albicans* water-soluble fraction (CAWS) group than in the control group (p=0.0122) and significantly lower in the candesartan groups (0.125-mg/kg group, p=0.0200; 0.25-mg/kg group, p=0.0200) than in the CAWS group.

mg/kg groups were 22.04±9.71 pg/mL, 163±85.2 pg/mL, 20.0±6.04 pg/mL, and 20.4±11.1 pg/mL, respectively. As compared with the CAWS group, serum TNF-α levels were significantly lower in the control (p=0.0122), 0.125-mg/kg (p=0.0200), and 0.25-mg/kg (p=0.0200) groups (**Fig. 7C**).

Discussion

This study confirmed histologically and serologically that the ARB candesartan suppresses CAWS vasculitis at low doses equivalent to those used clinically. Even at the usual clinical dosage of candesartan used for children (0.05-0.4 mg/kg/day)[22], ARBs suppressed vasculitis, suggesting possible future clinical applications. The infiltrating inflammatory cells in CAWS vasculitis were predominantly macrophages, particularly M1 macrophages. ARBs significantly inhibited M1 macrophage infiltration, confirming that they suppressed inflammation. Macrophages can be divided into two types: M1, which induce inflammatory cytokines and cause tissue damage, and M2, which induce anti-inflammatory cytokines and act in tissue repair[23]. Motoji et al.[21] observed a decrease in M1 macrophages with calming of CAWS vasculitis in evaluations at 6 and 10 weeks after CAWS administration and

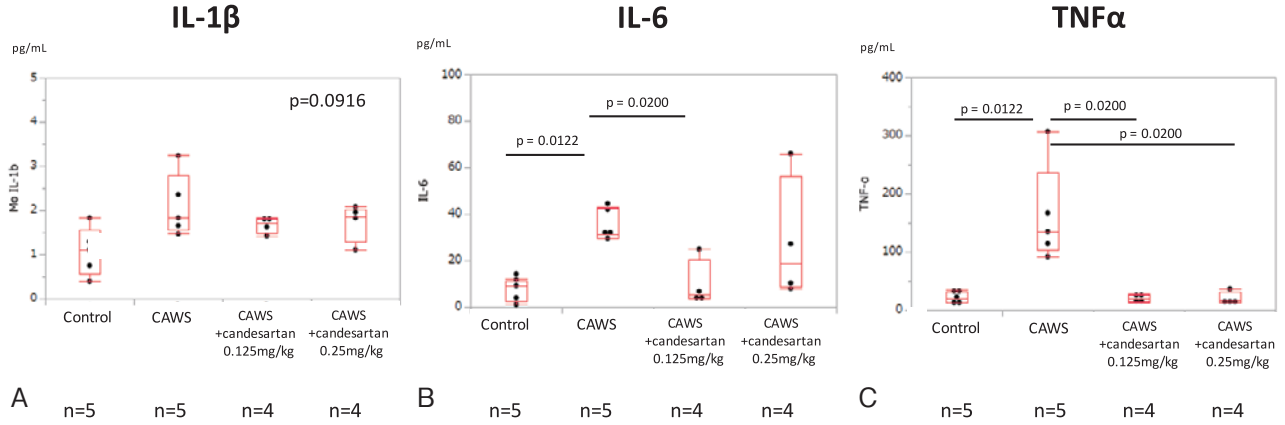

Fig. 7 Assessment of serum inflammatory cytokines

Interleukin-1β (IL-1β) was nonsignificantly increased in the *Candida albicans* water-soluble fraction (CAWS) group, but the increase was suppressed in the candesartan group (p=0.0916) (A). Interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α were significantly elevated in the CAWS group, as compared with the control group (IL-6: p=0.0122 TNF-α: p=0.0122) and significantly decreased in the candesartan group as compared with the CAWS group (IL-6 0.125-mg/kg group, p=0.0200; TNF-α 0.125-mg/kg group, p=0.0200; 0.25-mg/kg group, p=0.0200) (B, C).

a relative increase in M2 macrophages, suggesting M2 macrophages have an anti-inflammatory effect. In an evaluation at 4 weeks after CAWS administration, no significant increase was found in M2 macrophages in the candesartan group. This result suggests that M2 macrophages, which are involved in remodeling, were less involved in the acute-phase anti-inflammatory effect of candesartan.

TGFβ is a cytokine that inhibits macrophages and promotes tissue fibrosis and vascular remodeling[24,25]. The TGFβ pathway is closely related to vasculitis and aneurysm formation in Kawasaki disease[26,27]. A study of Kawasaki disease patients[26] revealed a TGFβ pathway in which TGFβ secreted by inflammatory cells acts on fibroblasts, mesangial smooth muscle cells, and fibroblasts of the peripheral circulation to generate myofibroblasts, which secrete cytokines and chemokines and further recruit inflammatory cells. TGF suppression by candesartan in the acute phase likely suppresses vasculitis and CAL formation. Immunoglobulin therapy (IVIG), the first-line treatment for Kawasaki disease, suppresses CAWS vasculitis[28]. Adding losartan to IVIG was superior to IVIG alone in suppressing vasculitis in Lactobacillus vasculitis[17]. Therefore, a synergistic effect between IVIG and candesartan can also be expected in CAWS vasculitis. The risk of CAL formation is higher in patients that do not respond to IVIG[13]. For this reason, adding an ARB to IVIG for IVIG-refractory cases is a highly promising treatment to prevent the development of CAL.

The renin-angiotensin system (RAS) is deeply involved in cardiovascular disease. Angiotensin II promotes atherosclerosis, exacerbates heart failure, and has hypertensive effects[29]. Many reports have shown that RAS-inhibiting treatment improves cardiovascular disease outcomes[14,30–33]. Elevated levels of angiotensin-converting enzyme (ACE) 2 have been observed in the acute phase of Kawasaki disease, and ACE2 is elevated in Kawasaki disease patients with CAL[34]. Regarding treatment of the remote phase of Kawasaki disease, conference reports show that candesartan effectively prevented stenotic lesions in CAL due to vascular remodeling[16]. Although the level of evidence is weak, US and Japanese guidelines for treatment of remote-phase Kawasaki disease recommend using ACE inhibitors and ARBs to prevent cardiac events[1,35].

Candesartan has been shown to have anti-inflammatory, anti-atherosclerotic, and vascular remodeling inhibitory effects in animal studies[36,37]. The finding that candesartan inhibits acute Kawasaki disease-like vasculitis at clinical doses raises hopes for its clinical application. Losartan ameliorated vasculitis in a mouse model of Kawasaki disease using Lactobacillus[17]. The researchers administered losartan dissolved in drinking water (100 mg/L)—assuming that the normal daily drinking volume of mice was 4-7 mL/day and that a mouse body weight of 20 g would result in a losartan dose of 20-35 mg/kg/day of—which is greater than the dose usually used in children (0.7-1.4 mg/kg/day)[22]. This study was conducted using near-clinical doses, which is promising for clinical application.

This study has limitations. First, CAWS vasculitis is a mouse model of Kawasaki disease, but the phenotype is not identical to actual Kawasaki disease. Therefore,

whether the results obtained in CAWS vasculitis directly apply to human Kawasaki disease is unclear. Second, candesartan is already widely used in pediatric patients. The dosage is normal, so the hurdle to clinical application is low. In Japan, candesartan is covered by insurance only when used for hypertension in children. Therefore, several hurdles need to be overcome before its use in Kawasaki disease.

This study confirmed histologically and serologically that the usual clinical dose of candesartan suppresses CAWS vasculitis in mice. Because of the limitations of immunoglobulin therapy and increased frequency of CAL in immunoglobulin-refractory cases, steroids and immunosuppressive drugs are recommended as additional treatments[13]. Our future research will continue to examine candesartan as an additional treatment option.

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Conflict of Interest: The authors declare no conflicts of interest.

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