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Methods: An open-label, non-controlled, single-center, prospective study, which was designed to exclude the seasonal bias. Bosentan was commenced from 62.5mg twice daily for four to six weeks, followed by 125mg twice daily for 10 to 12 weeks (total period was 16 weeks). Bosentan was reduced or discontinued if adverse events were appearing. Patients without adverse events for 16 weeks continued the trial for 52 weeks.

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Abstract- Objective: To assess the effects of bosentan on Raynaud's phenomenon and the skin temperature of hands and feet in patients with connective tissue diseases (CTDs) complicated with digital ulcers or pulmonary arterial hypertension (PAH).

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Results: In 13 enrolled patients, six were patients with suspected PAH and eight had digital ulcers. Ten patients were diagnosed with systemic sclerosis (eight with limited cutaneous and two with diffuse cutaneous form), two with mixed connective tissue disease and one with systemic sclerosis (diffuse cutaneous form)-polymyositis overlap syndrome.

After 16-week bosentan therapy, the frequency and the duration of Raynaud's phenomenon was significantly decreased ($P=0.009$, $P = 0.008$, respectively). Not the numbness, but the cold sensation of hands and feet was also improved ($P = 0.021$). Skin temperature measured by thermography was not increased after 16-week treatment, but the significant increases were seen after 52 weeks, respectively ($P = 0.038$ & $P = 0.025$). Nasal bleeding in one patient and liver dysfunction in four patients was investigated.

Conclusions: It was suggested that the long-term treatment of bosentan could improve the decreased skin temperature in CTD patients with secondary Raynaud's phenomenon.

Keywords: digital ulcers, endothelin receptor antagonist, pulmonary arterial hypertension, secondary Raynaud's phenomenon, systemic sclerosis, thermography.

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I. INTRODUCTION

Endothelins are consisted with 21-amino acid and induce potent vasoconstriction (1). There are three isoforms in endothelins (ET1-3) and their receptors are divided into ETA, ETB1, ETB2 and ETC. Bosentan is an antagonist of ETA and ETB and is clinically indicated for pulmonary arterial hypertension (PAH) and ongoing digital ulcers (2). PAH is one of serious complications in some connective tissue diseases (CTDs), such as mixed connective tissue disease (MCTD), systemic sclerosis (SSc) and systemic lupus erythematosus, and influences to their prognosis (3).

On the other hand, Raynaud's phenomenon is another symptom in CTDs that is not commonly critical, but often impairs quality of life and may lead occasionally digital ulcers. Raynaud's phenomenon is induced by cold temperature or emotional stress. It gets worse in winter, and is diminished since the end of winter and usually disappears during the summer. To judge the effectiveness of medicines for Raynaud's phenomenon, the timing to evaluate is very important. For example, it is not fair to estimate the efficacy in spring or summer for the therapy starting from midwinter. However the point to evaluate Raynaud's phenomenon has not been clear in most of the reports (4-11). Herein, to exclude the seasonal bias, we set observation time strictly and investigated the efficacy of bosentan on Raynaud's phenomenon and the skin temperature in patients with CTDs.

II. MATERIALS AND METHODS

a) Study design

The probe was planned as an open-label, non-controlled, single-center, prospective study. Patients were recruited from the outpatient clinic of the Department of Rheumatology and Applied Immunology, the Saitama Medical University Hospital. Bosentan was

commenced since the end of November, from 62.5mg twice daily for four to six weeks, followed by 125mg twice daily for 10 to 12 weeks (total period was 16 weeks). Bosentan was reduced or discontinued if

adverse events were appearing. Patients without adverse events for 16 weeks continued the trial for 52 weeks. Prior medications administered for more than 12 weeks were permitted to continue (Table 1).

Table 1 : Patient background

No.	Disease	Gender	Age (years)	Disease Duration (years)	PAH (WHO FC)	No. of DU or DUS	Prior Medication
1	lcSSc	F	77	21	0	2U, 1S	Beraprost Sarpogrelate
2	lcSSc	F	76	17	III	0	Sarpogrelate
3	lcSSc	F	71	25	II	0	Beraprost
4	lcSSc	F	71	15	0	1U	Beraprost
5	lcSSc	F	65	16	II	0	Beraprost Sarpogrelate
6	lcSSc	F	62	1	0	6S	Beraprost
7	lcSSc	F	53	18	0	2U, 1S	Beraprost Sarpogrelate
8	lcSSc	M	53	1	II	0	NA
9	dcSSc	M	71	16	III	1S	Beraprost Sarpogrelate
10	dcSSc	F	45	11	0	2U	Sarpogrelate
11	lcSSc PM	F	59	24	0	1U, 1S	Beraprost Sarpogrelate
12	MCTD	F	58	11	II	0	NA
13	MCTD	F	45	7	0	1U	Beraprost Sarpogrelate

The study protocol conformed to the principles of the Declaration of Helsinki and was approved by the institutional review board of the Saitama Medical University Hospital (09-028-1).

b) Patients

Patients with SSc (12) and systemic lupus erythematosus (SLE) (13) were diagnosed according to the American College of Rheumatology criteria, MCTD according to the criteria proposed by the Special Research Committee for MCTD of the Japanese Ministry of Health and Welfare (Kasukawa criteria) (14) and polymyositis (PM) according to the Bohan and Peter's criteria(15). PAH was suspected from more than four out of six clinical and laboratory findings, including exertional dyspnea, systolic pulsation on the left sternum, increase of the pulmonary segment of the second cardiac sound, enlargement of the base of the pulmonary artery or protrusion of the left second aortic arch in the chest X-ray, right ventricular hypertrophy or load as diagnosed by the electrocardiogram, right ventricular enlargement, right ventricular load or right ventricular pressure greater than 35 mmHg by the Doppler echocardiogram. Patients with ischemic heart diseases, valvular diseases unrelated with PAH and congenital heart diseases were excluded.

c) Clinical evaluation

Raynaud's phenomenon was evaluated by the diaries as follows; the number of the attacks daily, the duration of the attacks daily and an assessment of

severity of cold sensation and numbness of hands and feet by a visual analogue scale (VAS) of 100 mm. The number of digital ulcers and scars were recorded at the baseline, at Week 16 and at Week 52, or at the time of dropped-out. Thermography was carried out just before starting bosentan, after 16 weeks and after 52 weeks receiving bosentan. After sitting on the chair for 20 min in the room at 26°C, 50 ± 10% humidified, the skin temperature of hands and feet was measured by the thermography (Nihon Kohden, Tokyo, Japan). We compared the mean temperature of twelve points on the regions between the back side of interphalangeal joints and the base of thumbnails, between the back side of distal interphalangeal joints and the base of the other fingernails, between the back side of interphalangeal joints and the base of first toenails, between the back side of distal interphalangeal joints and the base of the other toenails and on the center of the back of hands and feet before and after the administration of bosentan (Fig 3a, b).

d) Statistical analysis

Wilcoxon's signed rank test was used for comparisons between paired data. P values of less than 0.05 were considered significant. Statistical analyses were performed using IBM SPSS statistics software version 18.0 (IBM SPSS Japan, Tokyo, Japan).

III. RESULTS

a) Patients

Three patients were recruited in 2009, five in 2010, two in 2011 and three in 2012. Enrolled in this study were 13 patients, of which half a dozen patients had suspected PAH (four; NYHA functional class II and two; class III) and eight had digital ulcers. No one underwent right heart catheterization. Ten patients were diagnosed with SSc (eight with limited cutaneous and two with diffuse cutaneous form), two with MCTD and one with SSc (diffuse cutaneous form)-PM overlap syndrome. The patient background was summarized in Table 1. Raynaud's phenomenon was present in all patients and ten patients were accompanied with nail fold bleeding. Bosentan was discontinued in one patient due to nasal bleeding at Week 6. Since liver dysfunction appeared at the dosage of 250mg bosentan in four patients, the dosage was decreased to 125mg. Of those patients, two discontinued at Week 16 and two continued for 52 weeks. Eight patients could be increased to 250mg of bosentan, of which, one patient transferred to the nearby clinic after week 16 and seven continued for 52 weeks.

b) Raynaud's phenomenon

After 16-week treatment with bosentan, the frequency and the duration of Raynaud's phenomenon were significantly decreased ($P=0.009$ and $P = 0.008$, respectively, Fig. 1a, b); both frequency and duration of Raynaud's phenomenon improved in nine patients and only the duration improved in one patient. Two patients did not experience any changes. Not the numbness, but the cold sensation with VAS was also significantly improved (Fig. 1c,d). After the treatment of 52-week administration of bosentan, the frequency and the duration of Raynaud's phenomenon were significantly decreased as well (data not shown).



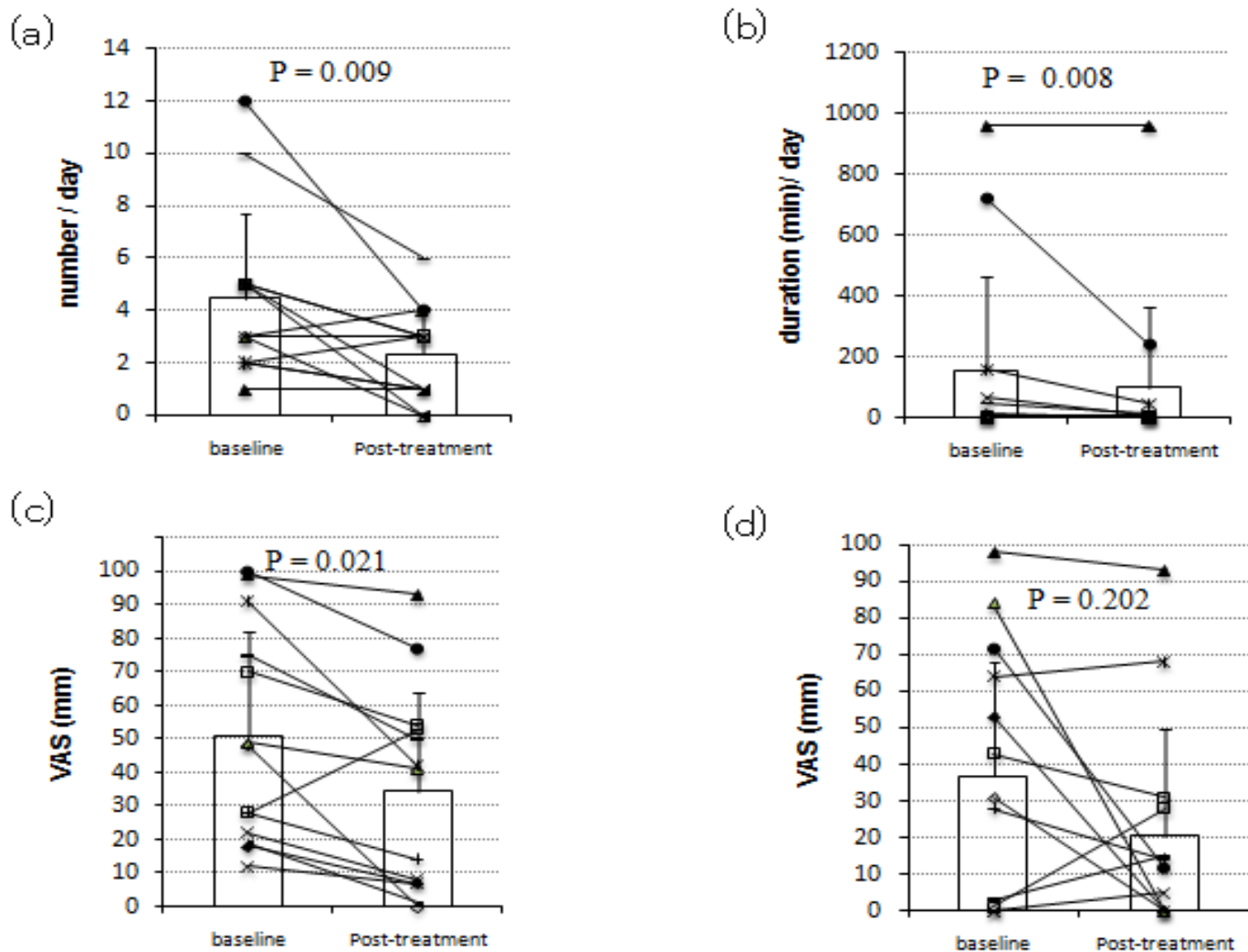


Figure 1 : Effect of bosentan treatment on Raynaud' s phenomenon after 16-week treatment

One patient was dropped out at week six. Open columns and error bars mean average and standard deviation (n=12)

(a) the daily frequency of Raynaud's phenomenon, (b) the daily duration of Raynaud's phenomenon, (c) severity of the cold sensation of hands and feet by visual analogue scale (VAS), (d) severity of numbness of hands and feet by VAS.

c) Digital ulcers

Digital ulcers of all patients became scarred or disappeared after bosentan administration. Namely, nine digital ulcers improved to six scars in seven patients and ten digital ulcer scars decreased to six in five patients after the treatment for 16 weeks. New digital ulcers were not recognised throughout the treatment.

d) Thermography

The skin temperature of ten patients were monitored by thermography at Week 16 and nine patients at Week 52. No significant increase of the skin temperature was detected at Week 16, but the significant increase was seen at Week 52, respectively (Fig. 2, P = 0.038 & P = 0.025). Representative results were shown in Fig. 3c and d.

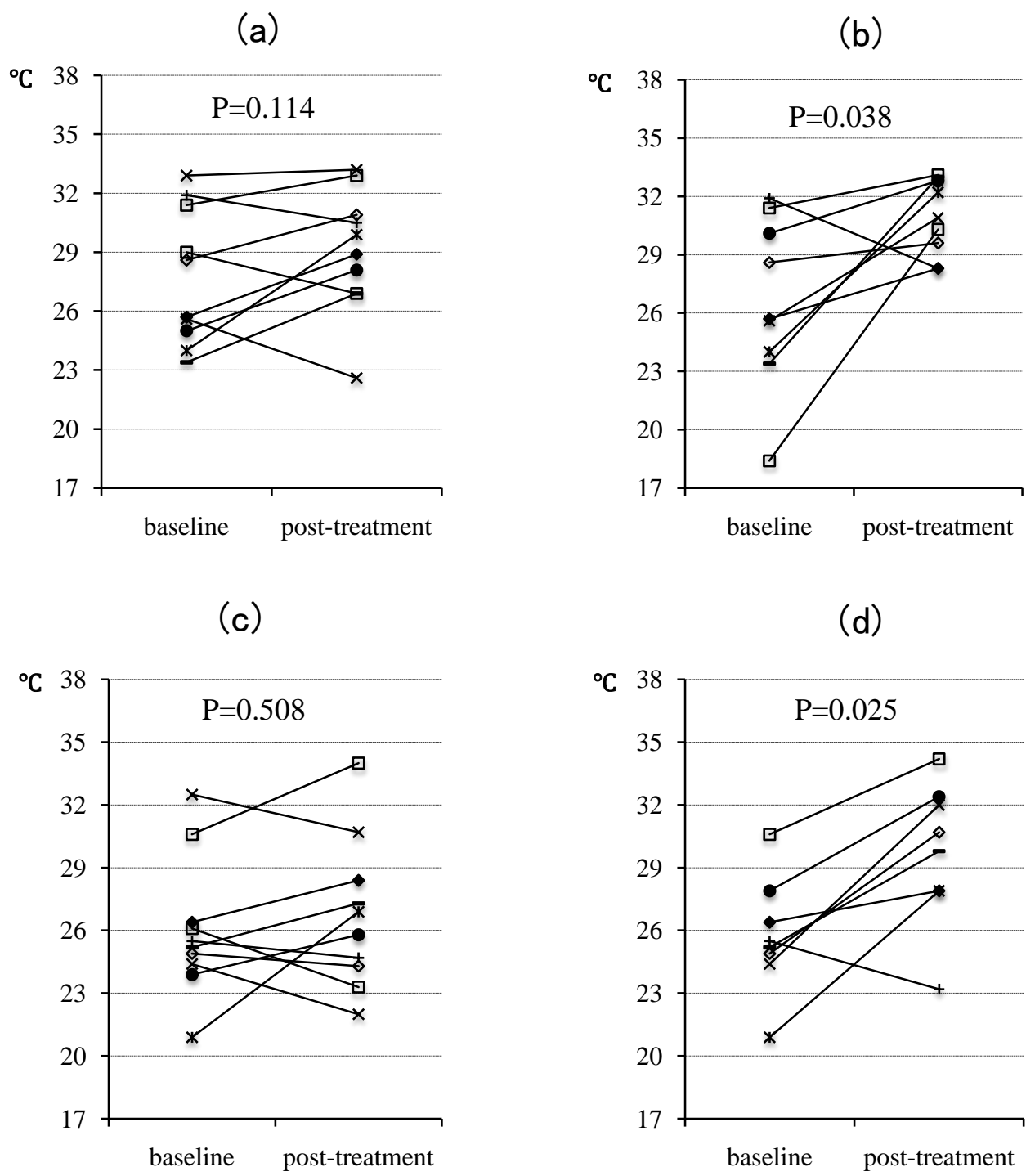
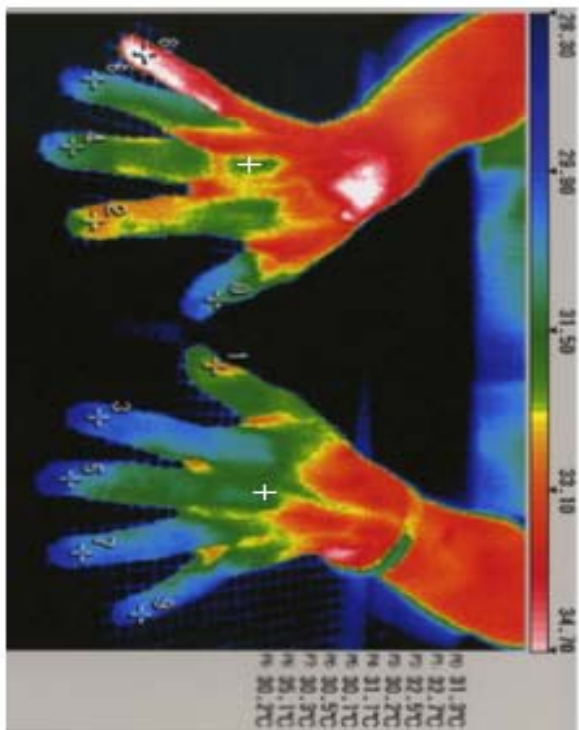
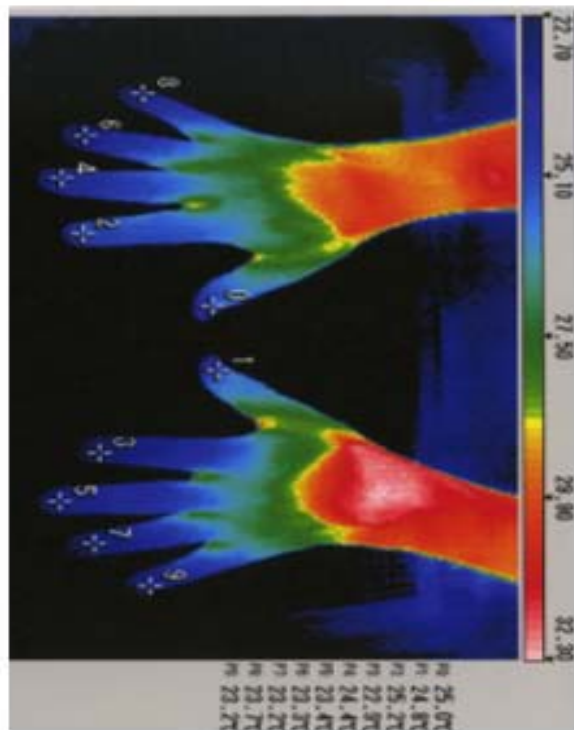


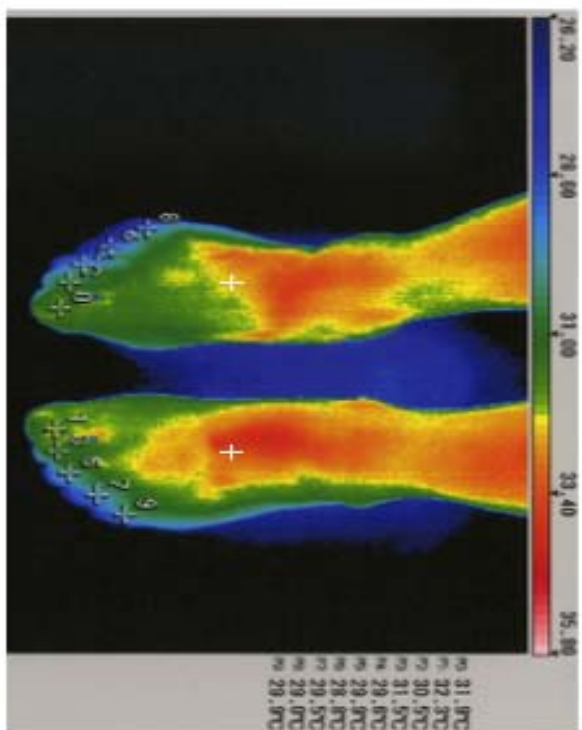
Figure 2 : The skin temperature of hands and feet measured by thermography before and after bosentan treatment. Hands (a) and feet (c) before and after the 16 week treatment (n=10), hands (b) and feet (d) before and after the 52 week treatment (n=9).



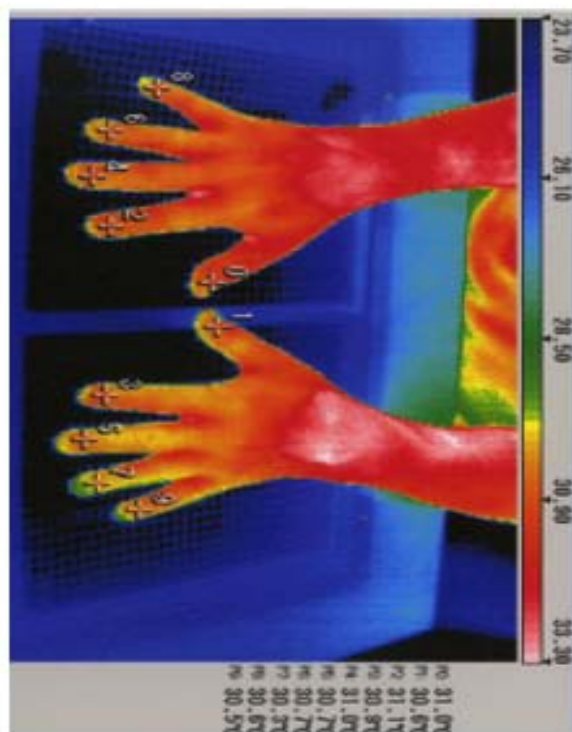
(a)



(c)



(b)



(d)

Figure 3: Thermography findings The skin temperature of twelve points in hands (a) and feet (b) was checked out by thermography. Representative thermographic pictures of the good responder (case 8) at week 0 (c) and week 52 (d).

IV. DISCUSSION

Concerning the remedy for Raynaud's phenomenon, calcium channel blockers (CCBs) (16), oral prostacyclin analogues (4), or serotonin receptor antagonists (17, 18) have been prescribed. As CCBs lower blood pressure strongly, patients with hypotension cannot be administered them sufficiently. The effect of latter two agents is almost insufficient as well. ET

participates in not only pulmonary circulation, but also peripheral circulation. Accordingly, the ET-receptor antagonist, bosentan has an anti-PAH effect, but also is expected to have an improving effect of peripheral circulatory disturbance. In fact, many researchers reported that bosentan was subjectively effective for Raynaud's phenomenon (5-7, 19, 20), oppositely, others did that the medicine was ineffective (8-10). These reports were shown in table 2.

Table 2 : Comparison between literatures and the present study

Study	Design	Disease: patient number	Entry time	Evaluation time	Subjective effect	Objective effect	Remarks
Ramos-Casals et al. ¹⁶	Case report	dcSSc: 1, lcSSc: 3	Unknown, 1, January; 2, December;1	Unknown: 1, May: 3	Effective	NT	None
Funauchi et al. ⁶	Single center, retrospective	dcSSc: 7, lcSSc: 6, MCTD: 2	Unknown, various	Various	Effective	NT	None
Hettema et al. ⁵	Single center, prospective	lcSSc: 15	Unknown	Week 8, 16	Effective	Not improved by photoelectric plethymography	The outdoor temperature was higher at Week16 than baseline.
Giordano et al. ⁷	Single center, retrospective	dcSSc: 4, lcSSc: 10	Unknown	Week 4, 12, 24, 48	Effective at Week 12, 24, 48, not at Week4	Effective by videocapillaroscopy at Week 48	None
Selenko-Gebauer et al. ²⁰	Single center, retrospective	lcSSc: 1, MCTD: 1, pre-SSc: 1	November	Week 16 (March)	Effective	Effective by thermography	None
The present study	Single center, prospective	dcSSc: 2, lcSSc: 8, dcSSc-PM: 1, MCTD: 2	End of November	Week 16, 52	Effective	Effective by thermography at Week52, not at Week16	None
Rosato et al. ⁸	Single center, open-label, prospective	Bosentan (PAH+): dcSSc: 14, lcSSc: 16, nifedipine (PAH-): dcSSc: 15, lcSSc: 15	Winter?	Week 4, 8, 16	Ineffective	Effective by laser doppler perfusion imaging at Week 8 and 16, not at Week4, ineffective by videocapillaroscopy	None
Moore et al. ¹⁰	Single center, prospective	dcSSc: 6, lcSSc: 12	Unknown,	Week 24	Ineffective	Ineffective by videocapillaroscopy at Week24	None
Nguyen et al. ⁹	Single center, randomized, prospective, double-blind	Bos: dcSSc: 3, lcSSc: 6, placebo: dcSSc: 1, lcSSc: 7	Winter	Week 16	Ineffective	NT	DcSSc was more in the bosentan group than placebo. Effectivity of the placebo group (57%) was fairly high.

Bos: bosentan; dc SSs: diffuse cutaneous systemic sclerosis; lc SSs: limited cutaneous systemic sclerosis; MCTD: mixed connective disease; NT: not tested; PAH: pulmonary arterial hypertension; PM: polymyositis

As mentioned above, the timing of the evaluation is very important to judge restrictly the effectiveness of treatments for Raynaud's phenomenon. For example, one of patients was estimated the efficacy in May in Ramos-Casals and co-workers' report (19), and Hettema et al. (5) reported the improvement of Raynaud's phenomenon at Week 8 and Week 16, but the outdoor temperature was significantly higher at Week 16, it was thought that seasonal improvement might be appended to their final results. Funauchi et al. (6) reported that Raynaud's phenomenon improved somewhat in 13 out of 15 patients with a median of eight weeks of treatment and that Raynaud's phenomenon disappeared in eight of them after a median of 14 weeks. They did not indicate when bosentan had initiated. Giordano et al. (7) reported 14 patients decreased in daily numbers and daily duration of Raynaud's phenomenon at 12 weeks, 24 weeks and 48 weeks, but not at four weeks after the administration of bosentan. They did not indicate when bosentan had initiated either. Therefore the improvement at 24 weeks must be influenced with seasonal recovery and the result at 12 weeks was not clear either. In contrast to these, Nguyen et al. reported that bosentan did not improve the frequency, duration, pain or severity of Raynaud's phenomenon after 16-week treatment as compared with placebo (8). The trial was the only one double-blinded test of bosentan for Raynaud's phenomenon. It is superior to other reports in the point which was able to exclude the placebo-effect. But the protocol permitted participants to start from anytime in winter. Starting examination from the latter of winter, considerable participants could bring spontaneous improvement after 16 weeks. Actually, because even the placebo group showed 57% reduction of the daily frequency of Raynaud's phenomenon attacks after 16 weeks, not a few patients might be affected by not only placebo effect but also a seasonal improvement. In other double-blinded studies (16,21), the examination period was six or seven weeks and the improvement rates of placebo groups were much lower. On the other hand, Selenko-Gebauer et al. (20) were initiated bosentan in November and evaluated the outcome after 16 weeks, it seemed that the evaluation points were fairly strict. Their cases were improved, however the participants were only three. We also started bosentan from the end of November and estimated the effectiveness at the end of March, in which the temperature is same as that in November at Saitama where our hospital located, and investigated the significant improvement. Although placebo effects could not be excluded, the present study suggested that bosentan was effective to Raynaud's phenomenon.

Bosentan has been evaluated the objective effectiveness for peripheral circulation. Selenko-Gebauer et al. (20) reported that the temperature of hands by the thermography increased after 16-week treatment, but

the result was only three analyses including one patient of pre-scleroderma. Rosato et al. (9) reported that bosentan improved the blood flow of fingers by a Lisca laser Doppler perfusion imager after eight- and 16-week treatment. Hettema et al. reported that the blood flow determined by photoelectric plethysmography during cooling and rewarming did not improve after 16-week treatment (5). Giordano et al. reported that visibility and sludging of nailfold by the videocapillaroscopy improved after 48-week treatment (7). Moore et al. reported that 24-week administration showed no improvement of nail fold capillary density and dimensions by the videocapillaroscopy either (10). Our data showed no significant improvement of skin temperature by the thermography after 16-week treatment, but 52-week treatment demonstrated the significant increase. Generalizing the present findings and the other reports, it was thought that bosentan needs the long-term use to improve peripheral circulatory disturbance significantly.

Although bosentan has been indicated for the prevention of new digital ulcers, a long-term use of bosentan might not be recommended for Raynaud's phenomenon alone from a viewpoint of medical economy because the prognosis of Raynaud's phenomenon is generally much better than that of digital ulcers or PAH. When we focus on the medicines except conventional drugs or bosentan, it was reported that the efficacy of phosphodiesterase-5 (PDE-5) inhibitors is equal to or more than bosentan as for the treatment of Raynaud's phenomenon (21, 22). PDE-5 inhibitors might be more practicable because they are more inexpensive than bosentan. As for ERAs except bosentan, ambrisentan blocks selectively the binding of endothelin-1 to ETA which induces vasoconstriction. It was reported that ambrisentan decreased the number of Raynaud's phenomenon and healed digital ulcers in patients with SSc who had failed bosentan (11). Macitentan blocks both ETA and ETB as well as bosentan. The former is a non-competitive antagonist and inhibits ETA strongly compared to ETB, while the latter is a competitive antagonist. Additionally, it was reported that macitentan suppresses the proliferation of sclerodermic fibroblasts (23). These reports indicate that it is worth evaluating the efficacy of new ERAs released after bosentan on the peripheral circulatory disturbance including Raynaud's phenomenon.

In conclusion, the present study suggested that long-term use is required to pull out the full potential of bosentan on peripheral circulatory disturbance in CTDs.

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REFERENCES RÉFÉRENCES REFERENCIAS

1. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y et al. A novel vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988;332 (6163): 411-5.
2. Dhillon S. Bosentan A review of its use in the management of digital ulcers associated with systemic sclerosis. *Drugs* 2009;69(14): 2005-14.
3. Shirai Y, Yasuoka H, Okano Y, Takeuchi T, Satoh T, Kuwana M. Clinical characteristics and survival of Japanese patients with connective tissue disease and pulmonary arterial hypertension: a single-centre cohort. *Rheumatology* 2012;51(10): 1846-54.
4. Vayssairat M and the French Microcirculation Society Multicentre Group for the Study of Vascular Acrosyndromes. Controlled multicenter double blind trial of an oral analog of prostacyclin in the treatment of primary Raynaud's phenomenon. *J Rheumatol* 1996;23: 1917-20.
5. Hetteema ME, Zhang D, Bootsma H, Kallenberg CGM. Bosentan therapy for patients with severe Raynaud's phenomenon in systemic sclerosis. *Ann Rheum Dis* 2007;66: 1398-9.
6. Funachi M, Kishimoto K, Shimizu H, Nagare Y, Hino S, Yano T et al. Effects of bosentan of the skin lesions: an observational study from a single center in Japan. *Rheumatol Int* 2009;29: 769-75.
7. Giordano N, Puccetti L, Papakostas P, Dipietra N, Bruni F, Pasqui AL et al. Bosentan treatment for Raynaud's phenomenon and skin fibrosis in patients with systemic sclerosis and pulmonary arterial hypertension: An open-label, observational, retrospective study. *Int J Immunopath Pharm* 2010;23(4): 1185-93.
8. Nguyen VA, Eisendle K, Gruber I, Hugl B, Reider D, Reider N. Effect of the dual endothelin receptor antagonist bosentan on Raynaud's phenomenon secondary to systemic sclerosis: a double-blind prospective, randomized, placebo-controlled pilot study. *Rheumatology* 2010;49(3): 583-8.
9. Rosato E, Molinaro I, Borghese F, Rossi C, ZPisari S, Salsano F. Bosentan improves skin perfusion of hands in patients with systemic sclerosis with pulmonary arterial hypertension. *J Rheumatol* 2010;37(12): 2531-9.
10. Moore TL, Vail A, Herrick AL. Assessment of digital vascular structure and function in response to bosentan in patients with systemic sclerosis-related Raynaud's phenomenon. *Rheumatology* 2007;46: 363-4.
11. Parisi S, Peroni CL, Lagana A, Scarati M, Ambrogio F, Bruzzone M et al. Efficacy of ambrisentan in the treatment of digital ulcers in patients with systemic sclerosis: a preliminary study. *Rheumatology* 2013;52: 1142 4.
12. Masi AT and Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23(5): 581-90.
13. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus (SLE). *Arthritis Rheum* 1982;25(11):1271-7.
14. Kasukawa R, Tojo T, Miyawaki S. Mixed connective tissue disease: preliminary diagnostic criteria. *Jpn J Rheumatol (Mod Rheumatol)* 1988;1:263-7.
15. Bohan A and Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975;292: 403-7.
16. Rodeheffer RJ, Rommer JA, Wigley F, Smith CR. Controlled double-blind trial of nifedipine in the treatment of Raynaud's phenomenon. *N Engl J Med* 1983;308(15): 880-3.
17. Coleiro B, Marshall SE, Denton CP, Howell K, Blann A, Welsh KI et al. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology* 2001;40: 1038-43.
18. Akiyama Y, Ohno S, Asaoka T, Katagiri T, Takeishi M, Omata H et al. The combination therapy with sarpoglerate hydrochloride and kampo medicine (Oren-gedoku-to or Toki-shakuyaku-san) for Raynaud's phenomenon. *Jpn Soc Orient Med* 2001;51(5): 1101-8 (in Japanese).
19. Ramos-Casals M, Brito-Zeron P, Nardi N, Claver G, Risco G, Parraga FD et al. Successful treatment of severe Raynaud's phenomenon with bosentan in four patients with systemic sclerosis. *Rheumatology* 2004;43: 1454-6.
20. Selenko-Gebauer N, Duschek N, Minimair G, Stingl G, Karlhofer F. Successful treatment of patients with severe secondary Raynaud's phenomenon with the endothelin receptor antagonist bosentan. *Rheumatology* 2006;45: 45-8.
21. Shenoy PD, Kumar S, Jha LK, Choudhary SK, Singh U, Misra R et al. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. *Rheumatology* Dec2010;49(12):2420-8.
22. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systemic review and meta-analysis of randomized trials. *Ann Rheum Dis* 2013;72: 1696-9.
23. Corallo C, Pecetti CC, Iglarz M, Volpi N, Franci D, Montella A et al. Macitentan slows down the dermal fibrotic process in systemic sclerosis: in vitro findings. *J BiolRegulHomeost Agents* 2013;27(2): 455-62.