Longterm Treatment with Endothelin Receptor Antagonist Bosentan and Iloprost Improves Fingertip Blood Perfusion in Systemic Sclerosis

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ABSTRACT. ***Objective.*** To evaluate the longterm effects of endothelin-1 (ET-1) antagonism on peripheral blood perfusion (PBP) in patients with systemic sclerosis (SSc).

Methods. Twenty-six patients with SSc already receiving cyclic intravenous iloprost (ILO) for severe Raynaud phenomenon were enrolled. Thirteen patients continued the treatment for a further 3 years (ILO group) and 13 patients, because of the appearance of digital ulcers, received in addition bosentan (BOS; 125 mg twice/day) for 3 years (ILO + BOS group). Both PBP at fingertips and nailfold microangiopathy were evaluated yearly by laser Doppler flowmetry and nailfold videocapillaroscopy, respectively.

Results. A progressive significant increase of PBP was observed in the ILO + BOS group during the 3 followup years ($p = 0.0007$, $p = 0.0002$, $p = 0.01$, respectively). In contrast, an insignificant progressive decrease of PBP was observed in the ILO group. Difference of perfusion between the PBP evaluations at basal temperature and at 36°C (to test capillary dilation capacity), was found progressively decreased during the 3-year followup only in the ILO group ($p = 0.05$, $p = 0.26$, $p = 0.09$, respectively). A progressive increase of nailfold capillary number was observed only in the ILO + BOS group after 2 and 3 years of followup ($p = 0.05$).

Conclusion. Longterm treatment of SSc patients with ET-1 antagonism, in combination with ILO, seems to increase fingertip blood perfusion, as well as both capillary dilation capacity and number. (First Release April 1 2014; J Rheumatol 2014;41:881–6; doi:10.3899/jrheum.131284)

Key Indexing Terms:
SYSTEMIC SCLEROSIS RAYNAUD PHENOMENON LASER DOPPLER FLOWMETRY
NAILFOLD VIDEOCAPILLAROSCOPY ENDOTHELIN-1 ANTAGONIST ILOPROST

Microvascular damage with progressive loss of capillaries, reduction of peripheral blood perfusion (PBP), and increased incidence of digital ulcers (DU) are common clinical features of systemic sclerosis (SSc)[1,2,3,4]. A correlation among these disease markers was recently reported, including finger dermal thickness[2,5,6].

Different treatments are available to manage Raynaud phenomenon (RP) and digital ischemia[4]. Among drugs, iloprost (ILO) is a prostacyclin analog that blocks platelet aggregation and adhesion, dilates arterioles and venules, activates fibrinolysis, and reduces the release of oxygen-reactive species[7]. Bosentan (BOS) is a dual endothelin-1 (ET-1) receptor antagonist licensed in Europe to treat pulmonary hypertension and to prevent the onset of new DU in SSc patients with DU history[4,8].

Laser Doppler flowmetry (LDF) evaluates blood perfusion in patients with SSc at the level of the fingertips, and nailfold videocapillaroscopy (NVC) qualifies and quantifies morphological microvascular SSc impairment[1,2].

Longterm treatment with BOS in combination with ILO was recently found to interfere with progression of nailfold microvascular damage, by progressively increasing the nailfold capillary number, as assessed by NVC over a 3-year followup in patients with SSc[9]. Therefore, the primary aim of our prospective open-label study was to evaluate the functional longterm effects of BOS added to ILO cyclic

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Supported by a grant for laboratory research from Actelion to the University of Genoa.

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Accepted for publication January 9, 2014.

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intravenous (IV) infusion on fingertip blood perfusion in patients with SSc.

MATERIALS AND METHODS

We performed a prospective open-label study of patients receiving longterm cyclical ILO infusions who have been given BOS because of active DU, in comparison to patients without active DU in whom ongoing cyclical ILO has continued.

Twenty-six consecutive patients with SSc (mean age 62 ± 12 yrs, mean SSc duration 8 ± 4 yrs) were enrolled after giving informed consent. All patients had been receiving cyclic IV infusion of ILO for severe secondary RP (average 80 µg/day, for 5 continuous days, every 3 mos) for 2 years before enrollment. Thirteen patients entered the survey (T0) and continued the treatment for a further 3 years (ILO group; T1, T2, T3). The remaining 13 patients, although they continued the same cyclic IV ILO treatment as the previous group, in addition received BOS (125 mg twice/day for 3 years) owing to ischemic DU appearance (ILO + BOS group).

After enrollment, patients continued all ongoing treatments (acetylsalicylic acid, proton pump inhibitors, antihypertensive drugs, immunosuppressants), with minimal changes during the 3 years (Table 1).

PBP at fingertips and nailfold microangiopathy were evaluated yearly. Patients with SSc also were strictly followed to monitor either possible drug-related side effects or recovery/appearance of DU.

LDF was performed annually in all patients with SSc by the Periflux System 5000, equipped with a thermostatic probe (Perimed), before the beginning of scheduled ILO infusion. PBP was evaluated at both basal skin temperature and after heating of the LDF probe to 36°C to test microvascular dilation capacity[2]. The same operator (BR) performed the examinations. The patients stayed in a waiting room at 22–23°C for at least 30 min before the assessment. PBP was detected at the level of second, third, fourth, and fifth fingertip bilaterally, and measurement was started 30 s after probe positioning on the central area of each fingertip, waiting for the minimal variation of the perfusion wave, and the recording was continued for 1 min in each finger[5]. During recording, the patient was relaxed and in a noise-free environment. The average blood perfusion from the 8 fingers was then calculated by adding the average perfusion values from the fingers together and then dividing the final value by finger number. The results were expressed as perfusion units (PU)[2].

NVC was performed in each patient using a videocapillaroscopy optical probe, equipped with a 200× contact lens, connected to image analysis software (Videocap, DS Medica). The same operator performed the NVC examination in all patients with SSc the same day as the LDF, according to published methods[1,10,11]. Each capillary abnormality was scored by a validated semiquantitative rating scale by considering the average of 8 fingers, in accordance with previous studies (0–3 score for each variable, where 0 = no changes, 1 = < 33% capillary alterations/reduction per linear mm, 2 = 33–66% capillary alterations/reduction per linear mm, and 3 = > 66% capillary alterations/reduction per linear mm)[10,11].

Statistical analysis was carried out by parametric procedures (Student's t test), and confirmed by nonparametric tests. Mann-Whitney U test was performed to compare unpaired groups of variables, and the Wilcoxon signed-rank test to compare paired groups of variables. Any p value < 0.05 was considered statistically significant. Results are given as mean ± SD, along with mean differences and 95% lower and 95% upper CI to report effect sizes.

RESULTS

Baseline clinical characteristics of the patients are reported in Table 1.

A progressive statistically significant increase of PBP was observed in the ILO + BOS group at basal skin temperature during the 3-year followup (mean ± SD T0 53 ± 29, T1 74 ± 35, T2 92 ± 34, T3 93 ± 31 PU, respectively; Figure 1A). Table 2 gives statistical significance, mean differences, and 95% lower and 95% upper CI. In the same group, PBP was assessed by heating the LDF probe at 36°C to test capillary dilation capacity and was found significantly increased during the 3-year followup (mean ± SD T0 89 ± 50, T1 112 ± 54, T2 128 ± 57, T3 125 ± 47 PU, respectively; Figure 1B and Table 2).

In contrast, a progressive decrease of PBP (not statistically significant) was observed during 3 years in the ILO group at basal skin temperature (mean ± SD T0 85 ± 49, T1 81 ± 45, T2 71 ± 45, T3 66 ± 47 PU, respectively), while a statistically significant progressive reduction of PBP was observed at

Table 1. Baseline clinical characteristics of the study patients.

Characteristics	Total SSc Patients	ILO Group	ILO + BOS Group
No. patients	26	13	13
Age, yrs ± SD	62 ± 12	65 ± 4	59 ± 18
Sex, male/female	4/22	1/12	3/10
SSc duration, yrs ± SD	8 ± 4	7 ± 3	9 ± 3
Raynaud duration, yrs ± SD	16 ± 4	20 ± 15	14 ± 4
NVC pattern (early/active/late)	0/7/19	0/5/8	0/2/11
ANA indirect immunofluorescence pattern (centromeric/speckled/homogeneous/nucleolar)	16/7/0/3	12/1/0/0	4/6/0/3
Specific autoantibody positivity (ACA or Scl-70)	16/6	12/1	4/6
Skin involvement, limited/diffuse	13/13	7/6	6/7
Gastrointestinal involvement, yes/no	2/24	1/12	1/12
Lung involvement, yes/no	2/24	1/12	1/12
Pulmonary arterial hypertension, yes/no	1/25	0/13	1/12
Heart involvement, yes/no	0/26	0/13	0/13
Renal involvement, yes/no	0/26	0/13	0/13
Digital ulcers, yes/no	13/26	0/13	13/13
Treatments (cardioaspirin/PPI/antihypertensive drugs/cyclosporine/MTX)	22/23/9/8/4	11/11/3/4/1	11/12/6/4/3

SSc: systemic sclerosis; ILO: iloprost; BOS: bosentan; NVC: nailfold videocapillaroscopy; ANA: antinuclear antibodies; ACA: anticentromere antibodies; Scl-70: topoisomerase; PPI: proton pump inhibitors; MTX: methotrexate.

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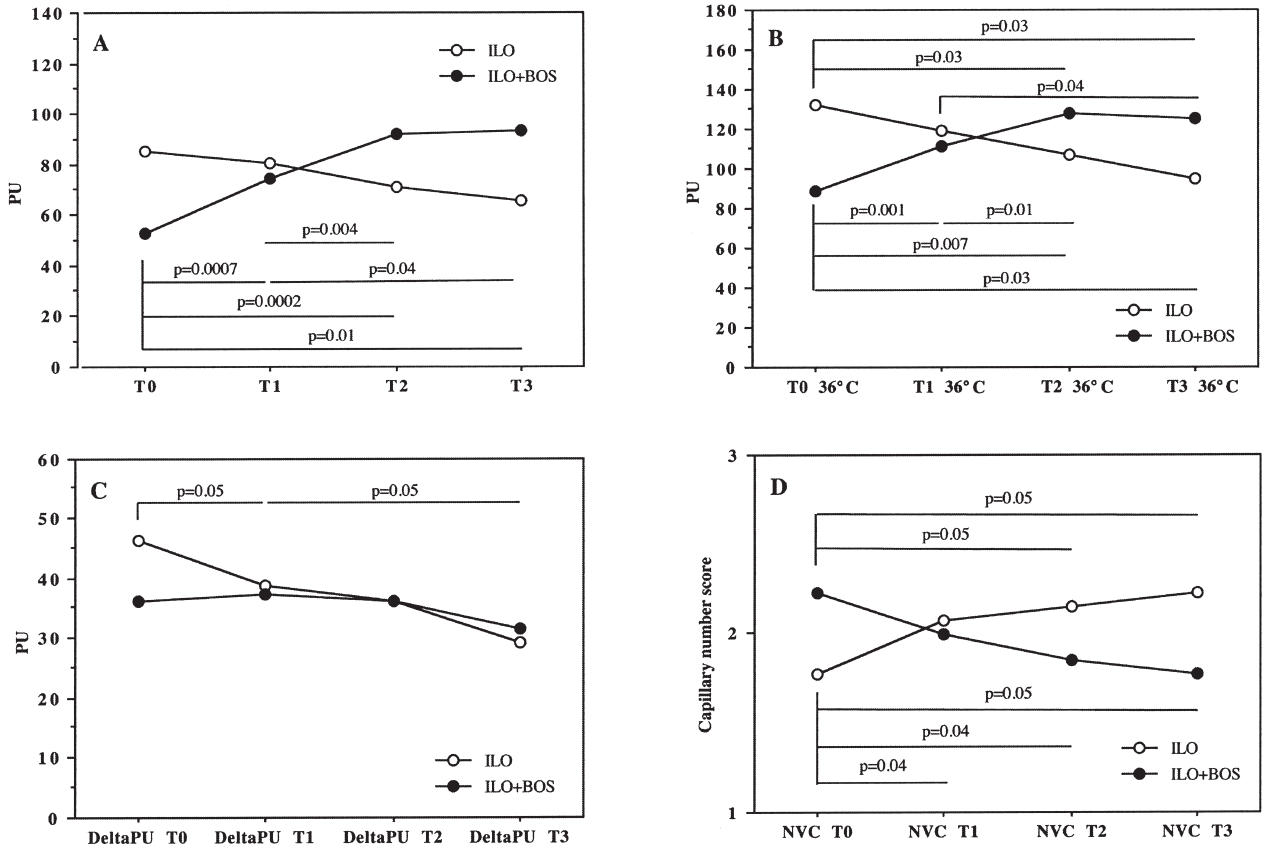

Figure 1. Reported trends at baseline (T0) and during further 3 years (T1, T2, T3) for peripheral blood perfusion at both basal skin temperature (A) and at 36°C (B), difference of perfusion between basal and 36°C laser Doppler flowmetry assessment (C), nailfold videocapillaroscopy score for capillary loss (D). ILO: iloprost; BOS: bosentan; PU: perfusion units; NVC: nailfold videocapillaroscopy; T0: at study entry; T1: after 1 year of study; T2: after 2 years of study; T3: after 3 years of study.

36°C (mean ± SD T0 132 ± 57, T1 120 ± 55, T2 107 ± 59, T3 95 ± 62, respectively; Figure 1A, 1B, and Table 2).

PBP difference between ILO and ILO + BOS groups was not statistically significant at baseline assessment (T0; p = 0.08) or at any time.

Differences of PU between the LDF evaluations at basal skin temperature and at 36°C were found progressively decreased during the followup in the ILO group (mean ± SD T0 46 ± 32, T1 39 ± 30, T2 36 ± 30, T3 29 ± 37), but not in the ILO + BOS group (mean ± SD T0 36 ± 32, T1 37 ± 35, T2 36 ± 33, T3 32 ± 31). However, this trend was statistically significant only in the ILO group (Figure 1C and Table 2).

On the other hand, a progressive statistically significant decrease of NVC score for capillary loss (meaning increase of nailfold capillary number) was observed in the ILO + BOS group after 2 and 3 years (mean ± SD T0 2.23 ± 0.6, T1 2.00 ± 0.4, T2 1.85 ± 0.4, T3 1.77 ± 0.4 PU, respectively). Conversely, a statistically significant increase of NVC score for capillary loss (meaning decrease of nailfold capillary number) was detected in the ILO group (mean ± SD T0 1.77 ± 0.6, T1 2.08 ± 0.3, T2 2.15 ± 0.4, T3 2.23 ± 0.4 PU, respectively). NVC score difference between ILO and ILO + BOS groups was not statistically significant at any time (Figure 1D and Table 2).

All baseline DU healed in the ILO + BOS group; however, 2 patients (15%) in the ILO + BOS group experienced new DU, as did 4 (31%) in the ILO group. Three patients asked to stop the treatment with BOS after 2 years owing to improvement of clinical condition but they did not experience new DU during the next year of followup. No serious side effects were observed. Transient increase of transaminases was managed by temporary discontinuation of BOS treatment.

DISCUSSION

In this open study, longterm treatment with ET-1 receptor antagonism in combination with ILO was found to significantly increase fingertip blood perfusion in patients with SSc, in contrast to the treatment with ILO alone. The observation is of interest because previous studies demonstrated that fingertip blood perfusion correlated with nailfold microangiopathy extent in patients with SSc (NVC SSc patterns), and that BOS in combination with ILO seems to increase both nailfold capillary number and effective neo-

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Table 2A. Mean values along with SD of clinical variables at different times in both groups of patients.

A	Group	Mean ± SD
PBP T0	ILO	85 ± 49
basal temp. (PU)	ILO+BOS	53 ± 29
PBP T1	ILO	81 ± 45
basal temp. (PU)	ILO+BOS	74 ± 35
PBP T2	ILO	71 ± 45
basal temp. (PU)	ILO+BOS	92 ± 34
PBP T3	ILO	66 ± 47
basal temp. (PU)	ILO+BOS	93 ± 31
PBP T0	ILO	132 ± 57
36°C (PU)	ILO+BOS	89 ± 50
PBP T1	ILO	120 ± 55
36°C (PU)	ILO+BOS	112 ± 54
PBP T2	ILO	107 ± 59
36°C (PU)	ILO+BOS	128 ± 57
PBP T3	ILO	95 ± 62
36°C (PU)	ILO+BOS	125 ± 47
Delta PBP T0	ILO	46 ± 32
(PU)	ILO+BOS	36 ± 32
Delta PBP T1	ILO	39 ± 30
(PU)	ILO+BOS	37 ± 35
Delta PBP T2	ILO	36 ± 30
(PU)	ILO+BOS	36 ± 33
Delta PBP T3	ILO	29 ± 37
(PU)	ILO+BOS	32 ± 31
NVC score for capillary number T0	ILO	1.77 ± 0.60
	ILO+BOS	2.23 ± 0.60
NVC score for capillary number T1	ILO	2.08 ± 0.28
	ILO+BOS	2.00 ± 0.41
NVC score for capillary number T2	ILO	2.15 ± 0.38
	ILO+BOS	1.85 ± 0.38
NVC score for capillary number T3	ILO	2.23 ± 0.44
	ILO+BOS	1.77 ± 0.44

angiogenesis, as assessed by NVC over a 3-year follow-up[2,5,9]. Our study shows that for the first time, to our knowledge, longterm treatment of patients with SSc with ET-1 receptor antagonism and ILO was able to functionally improve both PBP and nailfold microvascular damage, together with reducing the incidence of new DU.

This observation seems relevant because nailfold capillary number was already found to be a prognostic index for development of digital trophic lesions in patients with SSc, and ET-1 receptor antagonism is known to reduce the DU incidence[4,12,13].

The progressive increase of PBP in the ILO + BOS group was detected by measuring blood perfusion at local basal temperature, as well as by heating the thermostatic LDF probe to 36°C to test capillary dilation capacity, which is reduced in patients with SSc in comparison to healthy subjects[2].

Patients in the ILO + BOS group did not show during the followup a decrease of the difference of perfusion between basal and 36°C temperature (meaning a preserved capillary dilation capacity). Conversely, patients with SSc in the ILO group showed a statistically significant reduction of capillary dilation capacity over time, suggesting that only the addition of ET-1 receptor antagonism treatment was able to improve this clinical functional aspect of SSc microvascular impairment. Possibly, the ILO + BOS combination, by increasing the tissue perfusion through the ILO effects, may increase the targeting of BOS on ET-1 cell receptors by exerting further inhibitory effects on ET-induced vasoconstriction.

Previously, ILO was shown to increase fingertip blood perfusion in patients with SSc after 7 days of continuous IV infusion[2]. However, the positive effect on microcirculation was transitory, because over the long term it was found unable to maintain the PBP improvement. On the other hand, previous short-term treatment studies did not find any positive effect even for BOS alone on microvascular structure and function over 4 and 6 months[14,15]. Of interest, patients in the ILO + BOS group had worse microcirculatory status at baseline than did those in the ILO group (presence of DU; lower PBP, and lower capillary number even if at the limit of statistical significance, $p = 0.08$ and $p = 0.06$, respectively), but the addition of BOS to cyclic ILO treatment significantly improved all these clinical aspects.

One limitation of the current study is the loss of 3 patients in the ILO + BOS group after 2 years of treatment. The reduction of the study cohort can interfere with both statistical evaluations and mean values of PBP and capillary number at T3. Therefore, a further evaluation with a larger cohort of patients might better demonstrate the longterm microvascular effects of the ET-1 receptor antagonism described here. However, in agreement with reported studies, BOS was recently found to improve NVC patterns and to foster microvascular de-remodeling in SSc patients with pulmonary hypertension after 1 year of administration, by increasing capillary number and favoring angiogenesis[16]. A further possible limitation of this work is that clinical characteristics of RP (Raynaud condition score, no. and duration of Raynaud attacks) were not evaluated[17]. Further, the patients were not randomized and the operators were not blind to the patient treatment status.

Concerning autoantibody frequencies, 61% and 23% of patients showed respectively anticentromere and antitopoisomerase (anti-Scl-70) positivity (Table 1); further, anti-Scl-70 as well as the nucleolar pattern of antinuclear antibodies (ANA) determined by indirect immunofluorescence (possibly including specific SSc-related autoantibodies such as anti-RNA polymerase, Th/To, antifibrillarin) were more frequently expressed in the ILO + BOS group of patients. Present results are in line with the literature, because it should be considered that the cohort of patients was selected by the presence of severe RP and DU. As recently shown, organ involvement (including DU) seems more evident in patients with both anti-Scl-70 positivity and nucleolar staining pattern of ANA[18].

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Table 2B. Statistical data.

	Group	T1 Statistical Significance, Mean Difference, 95% Lower, 95% Upper CI	T2 Statistical Significance, Mean Difference, 95% Lower, 95% Upper CI	T3 Statistical Significance, Mean Difference, 95% Lower, 95% Upper CI
PBP T0 basal temp. (PU)	ILO	p = 0.35 –4.68 5.79, –15.14	p = 0.14 –14.40 5.55, –34.36	p = 0.09 –19.58 3.59, –42.75
	ILO+BOS	p = 0.0007 21.67 32.06, 11.27	p = 0.0002 39.19 49.82, 28.56	p = 0.01 40.95 51.17, 30.73
PBP T1 basal temp. (PU)	ILO	—	p = 0.14 –9.72 3.81, –23.26	p = 0.07 –14.90 1.41, –31.21
	ILO+BOS	—	p = 0.004 17.53 29.44, 5.61	p = 0.04 19.28 29.68, 8.89
PBP T2 basal temp. (PU)	ILO	—	—	p = 0.10 –5.18 1.07, –11.42
	ILO+BOS	—	—	p = 0.72 1.76 12.35, –8.84
PBP T0 36°C (PU)	ILO	p = 0.12 –12.29 3.92, –28.49	p = 0.03 –24.54 –0.08, –48.99	p = 0.03 –36.76 –6.01, –67.52
	ILO+BOS	p = 0.003 22.98 36.40, 9.56	p = 0.0001 39.4 54.85, 23.95	p = 0.002 36.49 57.15, 15.83
PBP T1 36°C (PU)	ILO	—	p = 0.08 –12.25 1.84, –26.34	p = 0.04 –24.48 –2.71, –46.25
	ILO+BOS	—	p = 0.01 16.42 28.76, 4.08	p = 0.11 13.51 30.57, –3.55
PBP T2 36°C (PU)	ILO	—	—	p = 0.06 –12.23 0.32, –24.77
	ILO+BOS	—	—	p = 0.70 –2.91 13.27, –19.08
Delta PBP T0 (PU)	ILO	p = 0.05 –7.61 –0.02, –15.20	p = 0.26 –10.13 8.38, –28.65	p = 0.09 –17.19 3.22, –37.59
	ILO+BOS	p = 0.69 1.32 8.33, –5.69	p = 0.97 0.21 11.77, –11.36	p = 0.58 –4.46 12.54, –21.46
Delta PBP T1 (PU)	ILO	—	p = 0.69 –2.53 11.04, –16.09	p = 0.05 –9.58 –0.05, –19.11
	ILO+BOS	—	p = 0.79 –1.11 7.70, –9.92	p = 0.40 –5.77 8.78, –20.33
Delta PBP T2 (PU)	ILO	—	—	p = 0.26 –7.05 5.92, –20.03
	ILO+BOS	—	—	p = 0.41 –4.66 7.17, –16.50
NVC score for capillary number T0	ILO	p = 0.04 0.31 0.60, 0.02	p = 0.04 0.38 0.69, 0.08	p = 0.05 0.46 0.86, 0.06
	ILO+BOS	p = 0.19 –0.23 0.13, –0.59	p = 0.05 –0.38 –0.08, –0.69	p = 0.05 –0.46 –0.15, –0.78

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Table 2B. Continued.

	Group	T1 Statistical Significance, Mean Difference, 95% Lower, 95% Upper CI	T2 Statistical Significance, Mean Difference, 95% Lower, 95% Upper CI	T3 Statistical Significance, Mean Difference, 95% Lower, 95% Upper CI
NVC score for capillary number T1	ILO	—	p = 0.34 0.08 0.24, –0.09	p = 0.16 0.15 0.38, –0.07
	ILO+BOS	—	p = 0.16 –0.15 0.07, –0.38	p = 0.08 –0.23 0.03, –0.50
NVC score for capillary number T2	ILO	—	—	p = 0.34 0.08 0.24, –0.09
	ILO+BOS	—	—	p = 0.34 –0.08 0.09, –0.24

Delta is difference expressed in PU between basal and 36°C temperature at laser Doppler flowmetry assessment. ILO: iloprost; BOS: bosentan; PBP: peripheral blood perfusion; T0: baseline; T1: first year; T2: second year; T3: third year; NVC: nailfold videocapillaroscopy; PU: perfusion units.

Longterm treatment of patients with SSc with ET-1 antagonist BOS in combination with ILO seems to increase fingertip blood perfusion as well as both capillary dilation capacity and number.

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