Review Article

Effectiveness of bosentan in the treatment of systemic sclerosis-related digital ulcers: Systematic review and meta-analysis

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Background: The aim of the present systematic review and meta-analysis was to evaluate the therapeutic efficacy of bosentan, a dual endothelin receptor antagonist, for systemic sclerosis (SSc) patients with digital ulcers (DUs). **Materials and Methods:** A systematic search of MEDLINE, Embase, Web of Science, and Scopus was done using appropriate keywords till September 2021. Weighted mean difference (WMD) as the effect of therapeutic efficacy of bosentan on continuous outcomes was an estimate. Furthermore, the pooled prevalence of diffuse SSc and limited SSc was computed. Fixed or random effects models when appropriate were used for data synthesis. **Results:** Totally, 469 patients, with a mean age ranging from 48.1 to 63.7 years, from 8 studies were included in the systematic review and meta-analysis. The pooled frequency of diffuse SSc and limited SSc was 56% (95% confidence interval [CI]: 39%, 73%) and 44% (95% CI: 27%, 61%). The pooled prevalence of new DUs following bosentan treatment was 21% (95% CI: 10%, 33%). The results of the meta-analysis showed a pooled mean decrease of WMD: −0.09 (95% CI: −0.020, 0.02, $P = 0.10$), WMD: −2.82 (95% CI: −5.91, 0.27, $P = 0.07$), and WMD: −6.65 (95% CI: −9.49, −3.82, $P < 0.001$) in mean SSc-Health Assessment Questionnaire, pain, and Rodnan score, respectively. Our meta-analysis also indicated a significant pooled decrease in the number of new DUs in SSc patients compared to placebo subjects (WMD: −0.89 [95% CI: −1.40, −0.37; $P = 0.001$]) and baseline values (WMD: −1.34 (95% CI: −1.95, −0.73; $P < 0.001$). **Conclusion:** Bosentan possibly is an efficacious treatment option for SSc-related DUs. Although further large-scale randomized clinical trials are required to confirm the preliminary finding and underlying mechanisms of action.

Key words: Bosentan, digital ulcer, meta-analysis, systemic sclerosis, treatment

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INTRODUCTION

Systemic sclerosis (SSc) is a disease of connective tissue manifested by cutaneous and visceral fibrosis and vascular abnormalities.[1] There are two major subtypes of SSc according to the skin involvement comprising diffuse cutaneous SSc (DcSSc) and limited cutaneous SSc (LcSSc). The diffuse form progresses rapidly and involves skin and internal organs extensively. While LcSSc is dominated by vascular diseases and its cutaneous involvement is limited to hands and face.[2] Digital ulcers (DUs) have been known as the most common presentations of vasculopathy with a prevalence of 40%–50%.[3] It is believed that the presence of DUs in SSc patients is a predictor of severe disease course and decreased survival.[4,5] In addition, DUs are associated with great pain, decreased quality of life, and functional disability.[6,7] Thus, its effective clinical management is of great importance.

It is very challenging to find and evaluate efficacious treatment options for SSc because the pathophysiology

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of the disease is complex and not fully understood. An increased serum level of endothelin-1 (ET-1), which is a naturally occurring vasoconstrictor, has been reported in patients with SSc, suggesting its role in the vascular pathogenesis of the disease.[8] Recently, bosentan, a dual endothelin receptor (ER) antagonist which prevents the binding of ET-1 to its receptors, has been introduced for the treatment of pulmonary hypertension in patients with SSc.[9,10] Furthermore, it has been known that bosentan prevents the onset of DUs in several studies comprising two double-blind randomized controlled trial (RCT). Korn *et al*. in a multicenter RCT evaluated the effect of bosentan on the prevention of DUs in patients with SSc. The results of the study indicated that the mean number of new ulcers decreased significantly in patients treated with bosentan after 16 weeks.[9] An improvement in hand function was also observed in bosentan-treated patients. Matucci-Cerinic *et al*. also reported a significant reduction in the number of new DUs compared to placebo; however, their results failed to show any improvement in pain and disability.[11] Given the low prevalence of SSc and the small sample size of related studies, the present systematic review and meta-analysis aimed to estimate pooled data regarding bosentan efficacy in the treatment of DUs in patients with SSc.

METHODS

Search strategy

A systematic search of MEDLINE, Embase, Web of Sciences, and Scopus databases was done to identify the studies investigating the therapeutic effect of bosentan in patients with digital ulcers from inception to September 2021. The following terms were used: "Bosentan" OR "Farantan" OR "Sentobiox" OR "Tracleer" OR "'Endothelin receptor antagonist" OR "ET-1antagonist" OR "stayveer" AND "Finger ulcer" OR "'Digital ulcer" OR "Gangrene" OR "Calcinosis" OR "Raynaud" AND "Scleroderma" OR "'Systemic sclerosis" OR "Dermatosclerosis" OR "Sclerema" OR "scleroderma adultorum" OR "scleroderma" OR "skin sclerosis." After removing duplicates, an independent screen of the titles and abstracts was done by two independent reviewers (M.H and R.N) and relevant articles were short-listed. To determine the eligibility of short-listed articles, their full texts were screened by the same reviewers and any disagreement was resolved by consensus with a third review author (P.M). The reference list of included studies was manually searched to find relevant studies.

Eligibility criteria and data extraction

All observational and interventional studies concerning the therapeutic efficacy of bosentan for SSc patients with DUs published in English were included in the present systematic review and meta-analysis. The exclusion criteria were (1) editorials, case reports, conference reports, and review articles; (2) unavailable data or full texts; (3) studies on subjects younger than 18 years old or those diagnosed with other connective tissue disorders than SSc; and (4) studies investigating the treatment of SSc-related DUs with bosentan in combination with other medications. Two independent researchers (M.H and R.N) extracted data from the included studies. The following variables were extracted: the first author, the publication year, the study design, region, sample size, population demographics (age and sex), condition information, and outcomes comprising the prevalence of new DUs as well as the mean of pain, Rodnan score, and SSc-Health Assessment Questionnaire score (SSc-HAQ).

Data synthesis and statistical analysis

Mean changes were calculated as follows: Measure at end of the treatment period minus measure at baseline. The weighted mean difference (WMD) along with a 95% confidence interval (CI) for WMD was calculated to assess the effects of treatment on continuous outcomes. For those studies that did not report standard error of the means (SEMs) values, the computation was done based on the available data using the following standard formula: (SEM = Standard deviation (SD)/square root of the number of subjects. SDs of the mean difference were calculated as: SD = square root ([SD pretreatment] ^{2}+ [SD posttreatment] ^{2}− [2 R × SD pretreatment × SD posttreatment]), considering a correlation coefficient $R = 0.6$.

To estimate the pooled prevalence and corresponding 95% CI, weighted prevalence rates were calculated using the "MetaProp program" in STATA software.[12] Heterogeneity of the included studies was assessed using Higgins' I^2 statistic and Cochran Q test and expressed as percentage. Values of 25%, 50%, and 75% for I^2 were considered low, medium, and high levels of heterogeneity, respectively.[13] Data were pooled using fixed effects when heterogeneity was low and random effects model in case of high levels of heterogeneity among included studies. Possible sources of heterogeneity were explored by sensitivity analyses and meta-regression. Publication bias was tested using Egger's and Begg's test and visual inspection of the funnel plot.[14] In the existence of a bias, trim-and-fill analysis was conducted to detect the contribution of the bias to the overall effect. All data synthesis was performed using STATA version 14 (STATA, College Station, TX, USA).

RESULTS

The systematic search found a total of 1257 results [Figure 1]. After removing 243 duplicates, 1104 titles and abstracts remained to screen. Ultimately, 16 full texts were retrieved for further examination. A total of eight articles met our inclusion criteria, comprising three RCTs,[11,12,16] four

prospective,[17-20] and one retrospective[21] study conducted between 2004 and 2021. Details of the included studies in the systematic review and meta-analysis are summarized in Table 1. Four studies were from Europe and North America,[11,12,20,21] two from Asia,[15,18] one from Eurasia,[16] and one from South America.[17] Eligible studies included a total of 469 SSc patients with a mean age ranging from 48.1 to 63.7 years. Investigated subjects were mainly women with a frequency ranging from 61.5% to 100%.

The frequency of DcSSc and LcSSc ranged from 33.3% and 25.8% to 74.2%, and 66.6%, respectively. The results of meta-analysis indicated that overall frequency of DcSSc and LcSSc were 56% (95% CI: 39%, 73%) [Figure 2a] and 44% (95% CI: 27%, 61%) (I^2 = 73.03%, P < 0.001) [Figure 2c]. There was no publication bias according to Egger's test (P > 0.05) and visual inspection of the funnel plot [Figure 2b and d]. As shown in Table 2, meta-regression analysis found no statistically significant association between mean age, disease duration, and sample size, as confounding, variables with the frequency of DcSSc and LcSSc (P > 0.05).

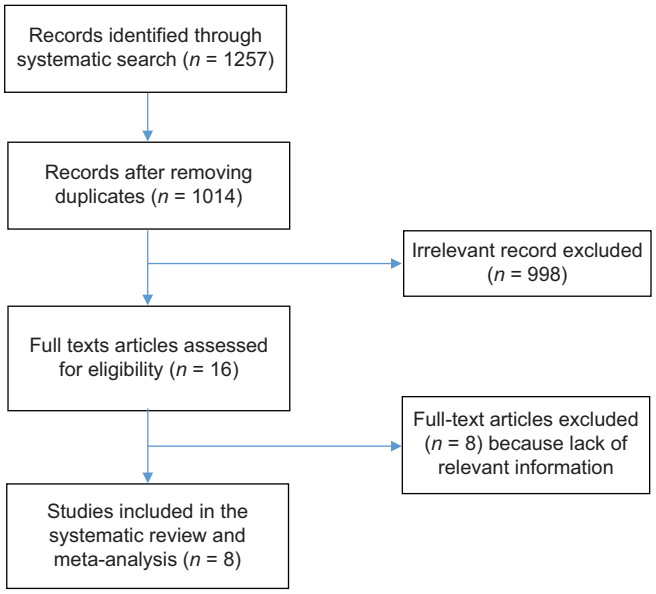

Figure 1: Flow diagram of study selection

Prevalence of new DUs after bosentan treatment was assessed in seven studies ranging from 0% to 66.3%.[11,12,16-19,21] Fixed random effect meta-analysis across eligible studies showed a pooled prevalence of new DUs of 21% (95% CI: 10%, 33%; I^2 = 75.93%, P < 0.001) [Figure 3a]. The results of Egger's test (P = 0.03) and funnel plot showed a significant publication bias [Figure 3b] and after trim-and-fill analysis for correction of publication bias, results did not change. The meta-regression test failed to show any significant association between mean age, disease duration, DcSSc, and LcSSc frequency with the prevalence of new DUs after bosentan treatment (P > 0.05) [Table 2].

The weighted mean difference (WMD) of SSc-HAQ score following bosentan treatment was reported in four studies.[11,12,18,20] Our results indicated a nonsignificant pooled WMD decrease of −0.09 (95%CI: −0.020,0.02, P = 0.1; I^2 = 0%, P = 0.96) in SSc-HAQ score [Figure 4a]. In addition, a nonsignificant publication bias was suggested according to Egger's test (P > 0.05) and funnel plot [Figure 4b]. Meta-regression did not show a statistically significant association between mean age, disease duration, DcSSc,

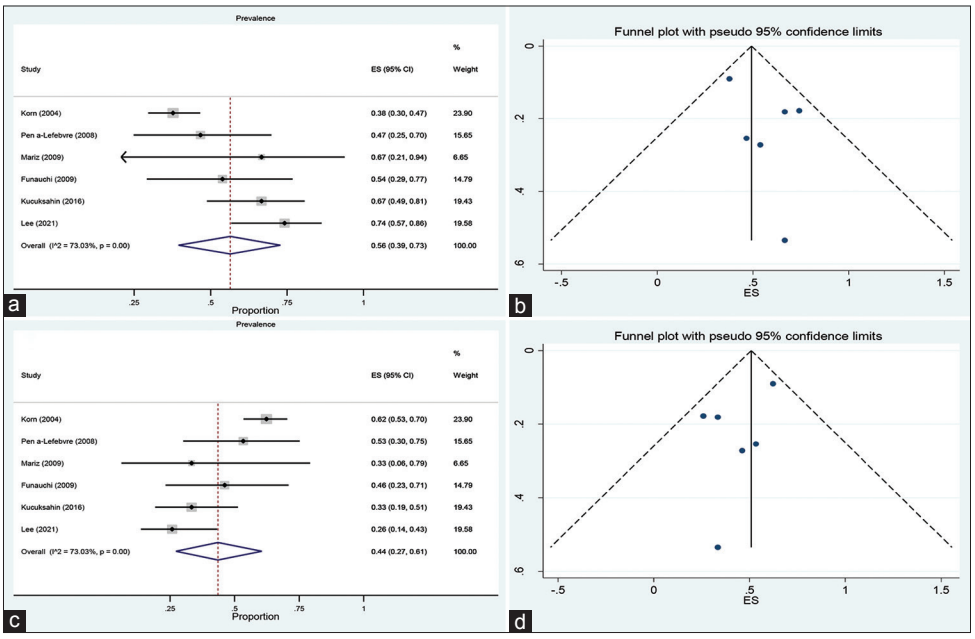

Figure 2: Forest plot for the frequency of diffuse cutaneous systemic sclerosis (a), Eager's funnel plot asymmetry test for publication bias (b), Forest plot for the frequency of limited cutaneous systemic sclerosis (c), Eager's funnel plot asymmetry test for publication bias (d)

Table 1: Detailed characteristics of included studies in the systematic review and meta-analysis

First author (year)	Region	Study design	Sample size (*n*)	Female (%)	Age (years), mean±SD	Disease duration (years), mean±SD	DSSc (%)	LSSc (%)	Prevalence of new DUs after treatment (%)	Mean difference of SSc-HAQ score	Mean difference of pain	Mean difference of Rodnan score
Korn[9] (2004)	Europe and North America	RCT	122	78.7	51.8±12.9	9.13±7	37.7	62.3	58	−0.1	NR	NR
García de la Peña-Lefebvre[19] (2008)	Europe	Prospective	15	80	48.1±9.8	14.5±6.3	33.3	66.6	NR	−0.1	NR	−0.9
Mariz[17] (2009)	South America	Prospective	3	100	50±5	9±1	66.6	33.3	0	NR	−3.00	NR
Funauchi[18] (2009)	Asia	Prospective	13	61.5	63.7±4.3	7.2±4.3	53.85	46.15	0	NR	NR	LSSc=−9.5 DSSc=−7.5
Roman Ivorra[20] (2011)	Europe	Retrospective	67	NR	NR	NR	NR	NR	32.1	NR	NR	NR
Matucci-Cerinic[11] (2011)	Europe and North America	RCT	188	79	49.55±12.45	8.7±8.05	41	59	66.3	−0.04	−1.7	NR
Kucuksahin[16] (2016)	Eurasia	Prospective	30	86.7	49.6±15.4	8.8±8	66.67	33.33	26.7	−0.23	NR	NR
Lee[15] (2021)	Asia	RCT	31	83.9	55±9.83	4±4.44	74.2	25.8	11.4	NR	NR	NR

DUs=Digital ulcers; SSc=Systemic sclerosis; DSSc=Diffuse cutaneous SSc; LSSc=Limited cutaneous SSc; NR=Not reported; SD=Standard deviation; RCT=Randomized controlled trials; HAQ=Health Assessment Questionnaire

and LcSSc frequency with the mean difference of SSc-HAQ score after bosentan treatment ($P > 0.05$) [Table 2].

According to our meta-analysis results, a pooled WMD decrease of − 2.82 (95% CI: −5.91, 0.27; $P = 0.07$, $I^2 = 0\%$, $P = 0.77$) and − 6.65 (95% CI: −9.49, −3.82; $P < 0.001$, $I^2 = 89.9\%$, $P < 0.001$) was also observed in mean pain and Rodnan score, respectively [Figure 5a and b]. The mean age and disease duration were not statistically contributed to the mean difference of Rodnan score after bosentan treatment ($P > 0.05$) [Table 2].

Two studies reported changes in the mean number of DUs compared to the placebo group[11,12] or baseline values.[12,17] Our meta-analysis indicated a significant pooled WMD of − 0.89 (95% CI: −1.40, −0.37; $P = 0.001$, $I^2 = 5.8\%$, $P = 0.36$) in the number of new DUs in the SSc group compared to the placebo group. In addition, a significant pooled WMD of new DUs compared to baseline values was observed (WMD: −1.34 (95% CI: −1.95, −0.73; $P < 0.001$, $I^2 = 54.0\%$, $P = 0.04$)).

DISCUSSION

Bosentan has been approved for the treatment of DUs in Europe recently; however, its efficacy in the healing of DUs is a matter of debate. Thus, the present systematic review and meta-analysis were performed to investigate the effect of bosentan treatment on various outcomes of SSC patients with DUs.

There are very few epidemiological studies to investigate the incidence and prevalence of SSc, and there is considerable variability in prevalence and incidence estimates of available epidemiological reports. However, the results of previous studies indicated a higher prevalence of the disease in populations of European origin.[21,22] To the best of our knowledge, no previous study has investigated the global prevalence of two main subtypes of SSc. SSc is usually subdivided into DcSSc and LcSSc with higher skin involvement and mortality risk in diffuse subjects. According to our findings, the pooled frequency of DcSSc and LcSSc in subjects treated with bosentan was 56% and 44%, respectively. The higher frequency of DcSSc in the present systematic review and meta-analysis is probably due to the inclusion of more severe cases for bosentan treatment in research studies.

The frequency of new DUs after bosentan treatment was highly variable across included studies in the present systematic review and meta-analysis which is possibly owing to differences in studied populations and study designs. Our study estimated the pooled prevalence of new DUs to be 21% after bosentan treatment. However, the net value of new DUs frequency is not a good indicator

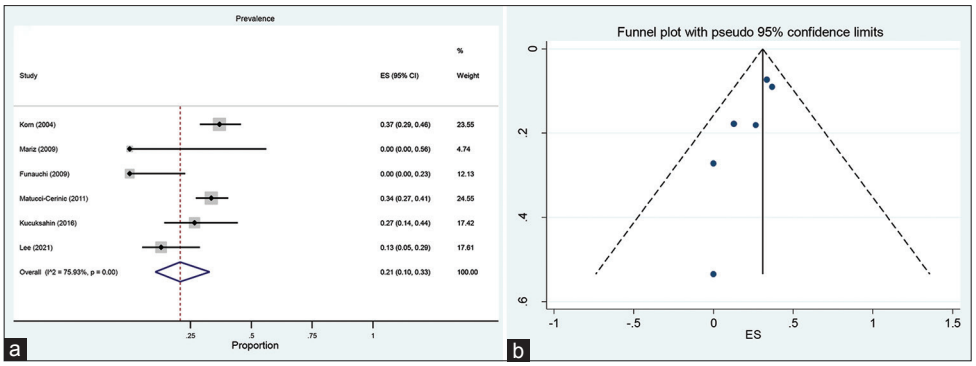

Figure 3: Forest plot of the effect of bosentan treatment on the prevalence of new digital ulcers (a), Eager's funnel plot asymmetry test for publication bias (b)

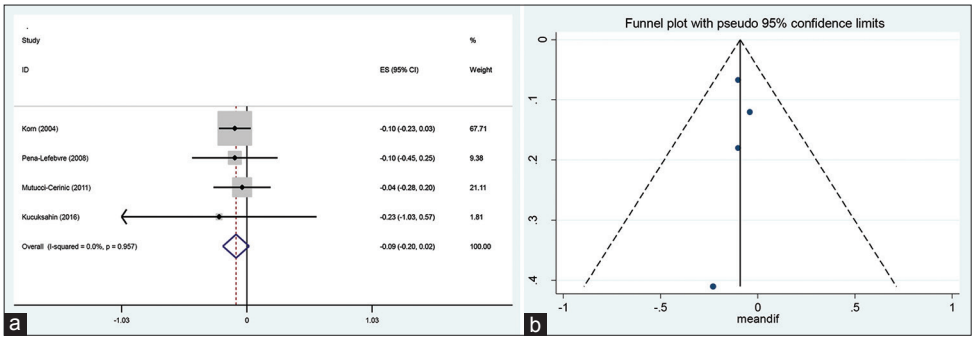

Figure 4: Forest plot of the effect of bosentan treatment on systemic sclerosis-HAQ score (a), Eager's funnel plot asymmetry test for publication bias (b). HAQ = Health Assessment Questionnaire

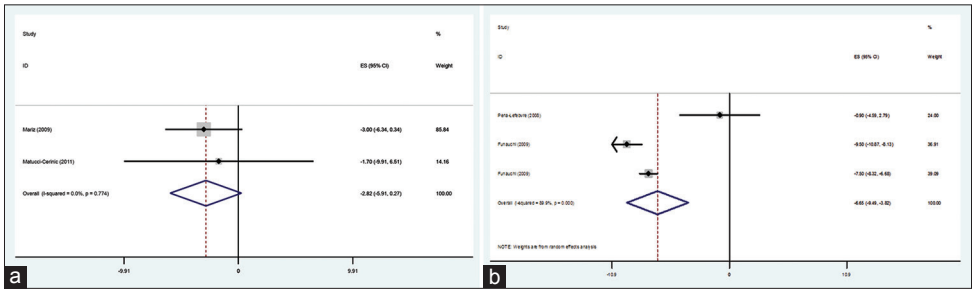

Figure 5: Forest plot of the effect of bosentan treatment on pain (a) and Rodnan score (b)

for evaluating the efficacy of bosentan treatment. Rather, changes in the frequency of new DUs after bosentan treatment compared to baseline values can give us an accurate assessment of the effect of this treatment on the reduction of new DUs frequency. Therefore, using the available data, the change in the mean of new DUs compared to placebo or baseline values was examined. Our results showed a significant pooled weighted mean decrease of 0.89 and 1.34 in the number of new DUs compared to the placebo group and baseline values, respectively.

SSc-HAQ is one of the most widely used tools to assess the disability caused by SSc.[23] This 20-item questionnaire comprises HAQ and five visual analog scales of Reynold's phenomenon, DUs, gastrointestinal symptoms, lung symptoms, and disease severity. The final score of the questionnaire ranged from 0 to 3 and five 15-cm length visual analog scales.[24] Some studies have evaluated the SSc-HAQ score to assess an improvement in the disability and function of SSc patients following bosentan treatment. Our results indicated that bosentan treatment resulted in a decrease in SSc-HAQ WMD; however, the difference was not significant. Meta-regression analysis also failed to show the confounding role of age, disease duration, and the prevalence of SSc on the SSc-HAQ mean difference.

In DcSSc patients, skin thickness has been proposed as an indicator of disease activity, severity, and mortality. As skin thickening in early dcSSc is often associated with internal organ involvement and increased mortality. The modified Rodnan score is used for estimating skin thickness in SSc patients.[25] This score can also be used in research studies as a primary or secondary outcome to address the efficacy of various treatment options. According to our findings, bosentan treatment was associated with a significant reduction in Rodnan score. However, no statistically

Table 2: Meta-regression for moderator analysis

Variables	Coefficient	SE	*t*	95% CI	*P*
Prevalence of new DUs					
Mean age	−0.02	0.02	−1.31	−0.07-0.02	0.26
Disease duration	0.05	0.04	1.33	−0.05-0.15	0.25
DcSSc	0.007	0.004	1.59	−0.008-0.02	0.21
lcSSc	0.003	0.002	1.52	−0.003-0.01	0.23
HAQ score					
Mean age	−0.008	0.04	−0.20	−0.19-0.17	0.86
Disease duration	−0.003	0.03	−0.10	−0.15-0.14	0.93
DcSSc	0.0003	0.004	0.08	−0.06-0.06	0.95
lcSSc	0.0003	0.002	0.11	−0.03-0.03	0.93
Frequency of DcSSc					
Mean age	0.00 5	0.02	0.25	−0.06-0.07	0.82
Disease duration	−0.03	0.03	−1.05	−0.12-0.05	0.35
Sample size	−0.002	0.001	−1.82	−0.006-0.001	0.14
Frequency of LcSSc					
Mean age	−0.005	0.02	−0.25	−0.07-0.06	0.82
Disease duration	0.03	0.03	1.05	−0.05-0.12	0.35
Sample size	0.003	0.001	1.82	−0.001-0.006	0.14
Rodnan score					
Mean age	−0.45	0.16	−3.02	−2.51-1.55	0.20
Disease duration	1.03	0.34	3.02	−3.31-5.37	0.20

P<0.05 was considered statistically significant. DUs=Digital ulcers; HAQ=Health Assessment Questionnaire; SSc=Systemic sclerosis; DcSSc=Diffuse cutaneous SSc; LcSSc=Limited cutaneous SSc, SE=Standard error; CI=Confidence interval

significant reduction was observed in pain score, assessed by the Visual Analog Scale.

The present systematic review and meta-analysis have several limitations that should be acknowledged. First, a few eligible studies were included in the review. Second, substantial heterogeneity was observed in the investigated outcomes. The meta-regression was performed to assess the influence of several variables; however, it could not quantify the confounding role of age, disease duration, sample size, and SSc subtypes frequency. However, the preliminary results of this study can be used as a guide for future studies.

CONCLUSION

The findings of the current study showed that bosentan treatment maybe an efficacious approach for the reduction of new DUs and skin involvement of SSc, although further randomized clinical trials are required to examine the effect of the treatment on the quality of life, function, and SSc-related pain.

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Conflicts of interest

There are no conflicts of interest.

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