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A New Promising Role for Selexipag in the Treatment of Scleroderma Vasculopathy: Preliminary Results From a Third Level Italian Scleroderma Center

D. Giuggioli[1] | M. Orlandi[1] | A. Spinella[1] | M. de Pinto[1] | F. Lumetti[1] | G. Amati[1] | O. Secchi[1] | A. Ariani[2]

[1]Department of Maternal, Child and Adult Medical and Surgical Sciences, Rheumatology Unit, Scleroderma Unit, University of Modena and Reggio Emilia, Modena, Italy | [2]Internal Medicine and Rheumatology Unit, University Hospital of Parma, Parma, Italy

Correspondence: M. Orlandi (martina.orlandi@unimore.it)

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ABSTRACT

Aim: Raynaud phenomenon (RP) and digital ulcers (DUs) represent the most frequent manifestations in systemic sclerosis (SSc), being signs of severe vasculopathy. Selexipag has been proposed as a useful tool for treating peripheral vasculopathy. The aim of this study was to evaluate the clinical effectiveness of Selexipag for treating complex cases of DUs as compared to the standard of care.

Methods: This is a case–control study in which SSc patients with active and long-lasting DUs were compared with a control group treated with a standard-of-care topical therapy that was stable in the previous 6 months. Clinical outcomes of RP and DUs were evaluated at T0 and after 6 months of follow-up.

Results: 23 SSc patients were enrolled. Selexipag was administered to 9 SSc patients, and its effects were compared with those in 14 SSc patients treated with standard-of- care therapy. Complete healing of DUs in Selexipag patients was higher (56% vs. 7%, $p = 0.018$). DUs diameter and pain VAS were slightly better—although not statistically significant—at the end of follow-up in the Selexipag group (respectively 0 vs. 5 $p = 0.15$ and 5 vs. 6, $p = 0.066$). All Raynaud Condition Scores outcomes improved in the Selexipag group: number of attacks (4 vs. 6, $p < 0.001$), duration (20 min vs. 25 mm, $p = 0.083$), and VAS (5 vs. 6, $p = 0.066$). Moreover, baseline DU diameter ($\beta = 0.70$, $p < 0.001$) and Selexipag treatment ($\beta = -7.1$, $p = 0.006$) were statistically significant predictors of the diameter of DUs after 6 months (F-test = 0.038). No new DUs were observed during the 6-month therapy.

Conclusions: Our preliminary results suggest a potentially new therapeutic indication of Selexipag in SSc for the treatment of SSc vasculopathy, in particular DUs and RP.

1 | Introduction

Digital ulcers (DUs) represent one of the most frequent and early manifestations in systemic sclerosis (SSc) [1, 2]. They affect almost 50% of patients, with a minority of themdeveloping severe complications such as infections, osteomyelitis, critical ischemia, and gangrene, potentially leading to amputation [3]. DUs are a major source of pain and disability (including work disability) [4, 5] and have a substantial impact on the quality of life in patients with SSc [4–7]. Moreover, these seem to be a sentinel sign of internal organ involvement [8] and are related to a poor prognosis of the disease [9]. Notwithstanding the availability of a wide range of systemic (pharmacological) therapies for the prevention and/or treatment of active DUs [10, 11], treatment of scleroderma skin ulcers remains challenging, and in clinical practice, around one-third of patients with SSc may experience refractory DU disease [4, 5]. To date, the main points of systemic therapy include oral and intravenous vasoactive therapies such

Summary

- Selexipag is safe and effective in the treatment of scleroderma digital ulcers (DUs), which are refractory to conventional therapies, and for the improvement of Raynaud phenomenon in patients with systemic sclerosis (SSc).
- This study suggests a new potential therapeutic indication of Selexipag for the treatment of SSc vasculopathy.
- Large prospective studies on Selexipag are recommended as it could significantly modify the management of DUs and vasculopathy related to SSc.

as calcium channel blockers, phosphodiesterase-5 inhibitors (PDE5-i), endothelin receptor antagonists (ERAs), and intravenous (i.v.) Iloprost, which are approved for the treatment of DU in SSc [10, 12]. However, the aforementioned therapies are not effective in cases of refractory DUs, especially if complicated by infection and gangrene, drug resistance, intolerance, or if they are contraindicated [5]. In these cases, other therapies with different mechanisms of action should be considered. Recently, some reports described rapid healing of long-lasting DUs in patients undergoing treatment with Selexipag (an oral selective prostacyclin receptor agonist) for concomitant pulmonary arterial hypertension (PAH) [13–16].

The aim of this study was to evaluate the clinical effectiveness of Selexipag for the treatment of complex DUs.

2 | Methods

This is a pilot observational case–control study conducted at the referral center for SSc-DUs in Modena from December 2023 to June 2024. The research project was approved by the local Institutional Ethics Committee (protocol no. 275/16). The use of the drug was off-label and compassionate, approved in accordance with National Laws. All patients gave their informed consent.

All consecutive patients with SSc classified according to the ACR/EULAR criteria with active and long-lasting DUs (from 6 to 12 months), as previously reported [17] and with stable vasoactive immunosuppressant therapies in the previous 6 months, were enrolled and divided into two subgroups: the Selexipag group (SG) and the Control group (CG). Treatment with Selexipag was administered in cases of DUs (as previously described) refractory to standard local debridement, dressing, and systemic vasoactive therapies. Exclusion criteria were the presence of vascular disease, diabetes mellitus, arterial hypertension, dyslipidemia, use of corticosteroids, and overlapping diseases.

2.1 | Data Collection

Baseline information included demographic data, clinical signs and symptoms, organ involvement, current therapies classified as vasoactive/vasodilating drugs, and immunosuppressant therapy. Data regarding DUs included quantity, location, and diameter, together with patient self-evaluation of pain using a Visual Analogue Scale for pain (VAS). In case of multiple DUs, the cardinal ulcer was taken into consideration for data collection [18]. In addition, the severity of Raynaud Phenomenon (RP) was also evaluated using the Raynaud Condition Score (RCS), a Likert scale ranging from 0 to 10 for patient's self-evaluation of the mean difficulty caused by their Raynaud's condition in the last 2 weeks [19], in terms of number of attacks, frequency, and pain. All patients were evaluated at baseline (T0) and after 6 months of follow-up (T1).

The SG received a 200-μg dose twice a day, which was then titrated with a weekly increase of 200 μg up to the maximum tolerated dose. Other ongoing vasoactive and immunosuppressant therapies were stable for the previous 6 months and were not modified during the study period. In addition to systemic therapy, each ulcer was treated with advanced topical medications, in accordance with TIME protocols [20, 21]. CG was treated with standard therapy. In the SG, side effects were also considered.

The effectiveness of Selexipag was evaluated by comparing the number (%) of healed patients (defined as a T6 ulcer with a diameter equal to zero) in the treated group with that of the untreated group. Furthermore, the presence of any other factors influencing the reduction in the diameter of the ulcers was evaluated (diameter of DUs at T0, sex, age, number of DUs, autoimmune profile, and duration of DUs).

2.2 | Statistical Analysis

Continuous parameters are reported as the median with interquartile range (IQR); categorical variables are expressed as absolute numbers or percentages. The parameters of the two subgroups were compared using the Mann–Whitney test or the chi-squared (Fisher's) test, as appropriate.

The changes between baseline and follow-up measures were assessed with the Wilcoxon test. A linear regression model was performed to assess factors that could influence the diameter of DUs after 6 months of follow-up. The statistical significance level was set at a p value < 0.05. Statistical analysis was performed with theJamovi (version 2.3.21.0) statistical software.

3 | Results

Twenty-three consecutive SSc patients with chronic long-lasting DUs as previously described were enrolled in this study. Selexipag was administered to 9 patients with SSc (SG) (8 females, mean age 46 [IQR 45–53] years) in addition to the standard topical and systemic medications, and its effects were compared against 14 patients with SSc (11 females, mean age 59 [IQR 52–65]) treated with standard therapy (CG). All DUs were located on the upper limbs, and most patients had at least 1 DU. Most of patient were female (M:F, 4:19), with a limited form of the disease (14/23), a mean age of 54 [IQR 44–63], and a mean disease duration of 10 [IQR 8–19]. ACA positivity was found in 14 of 23 patients (61%), PAH in eight of 23, and interstitial lung disease in six of 23 (26.1). Almost all patients enrolled (21 of 23 patients) were on double vasodilating therapy

with Iloprost and an endothelin receptor antagonist (Bosentan or Macitentan), while 6 patients were on triple therapy with a combination of i.v. Iloprost, ERAs, and PDE5-i (Sildenafil). Twelve patients were not on immunosuppressive therapy. All patients underwent the same advanced medication during the 6 months of follow-up. Considering the baseline demographic and main clinical characteristics, the two cohorts were comparable with the exception of a longer duration of the disease in SG (20 vs. 10 years; $p = 0.01$). Patients in SG had larger and more painful DUs (diameter 18 mm vs. 10 mm; $p = 0.009$ and VAS 10 cm vs. 7 cm; $p = 0.003$). Importantly, vasodilating, vasoactive, and immunosuppressive therapies were similar in the two groups. Main demographic and clinical data of the enrolled patients at baseline and of the 2 cohorts are detailed in Table 1. A paired t-test carried out on the entire cohort highlighted significant differences in all the following items: DU diameter ($p = 0.009$), pain ($p = 0.008$), RCS number of attacks ($p = 0.013$), RCS VAS pain ($p = 0.014$), and RCS attacks duration ($p = 0.014$). After 6 months, there was a significant improvement in DUs in both subgroups, reported as reduction in ulcer diameter and pain VAS ($p = 0.009$ and $p = 0.008$, respectively) (Figure 1). At the end of follow-up, DU diameter and VAS pain were slightly better—although not statistically significant—in SG than in CG (0 [IQR 0–9] vs. 5 [IQR 3–8],

TABLE 1 | Descriptive statistics of the sample at baseline.

		Total cohort	SG	CG	*p*-value
N		23	9	14	—
M:F		4:19	1:8	3:11	nss
Age, years [IQR]		54 [44–63]	46 [43–53]	59 [52–65]	nss
Disease duration, years [IQR]		10 [8–19]	20 [13–27]	10 [5–11]	**0.01**
SSc subset, *n*	Limited Diffused	14 9	6 3	8 6	nss
Autoimmunity, *n*	Anti-Scl70 ACA Anti-RNA pol III None	7 14 1 1	3 6 0 0	4 8 1 1	nss
PAH, *n*		8	4	4	nss
ILD, *n*		6	4	2	nss
Smoke habits ever, *n*		3	1	2	nss
Immunosoppressive therapy, *n*	MMF Rituximab	10 5	5 2	5 3	nss
Vasoactive/vasodilative therapy, *n*	Calcium blockers ERA PDE4i Iloprost i.v.	8 22 5 21	3 9 3 9	5 13 2 12	nss
Number of DUs, *n* [IQR]		1 [1–3]	2 [1–2]	1 [1–3]	nss
DU diameter, mm [IQR]		12 [8–18]	18 [16–20]	10 [6–12]	**0.009**
DU pain VAS, cm [IQR]		8 [6–10]	10 [9–10]	7 [5–8]	**0.003**
RCS, number of attacks, *n* [IQR]		7 [6–8]	6 [5–8]	7 [6–8]	nss
RCS, duration of attacks, min [IQR]		30 [25–38]	30 [25–40]	28 [25–34]	nss
RCS, VAS pain of attacks, cm		7	8	7	nss
[IQR]		[6–8]	[7, 8]	[6–8]	

Note: Significant *p*-values are bolded.
Abbreviations: ACA, anti-centromere antibodies; CG, control group; DUs, digital ulcers; ERA, endothelin receptor antagonists; i.v., intravenous; ILD, interstitial lung disease; IQR, interquartile range; MMF, mycophenolate mofetil; PAH, pulmonary arterial hypertension; PDEi, phosphodiesterase inhibitors; pts., patients; RCS, Raynaud Condition Score; Scl70, anti-topoisomerase antibodies; SD, standard deviation; SG, Selexipag group; SSc, systemic sclerosis; VAS, Visual Analogue Scale.

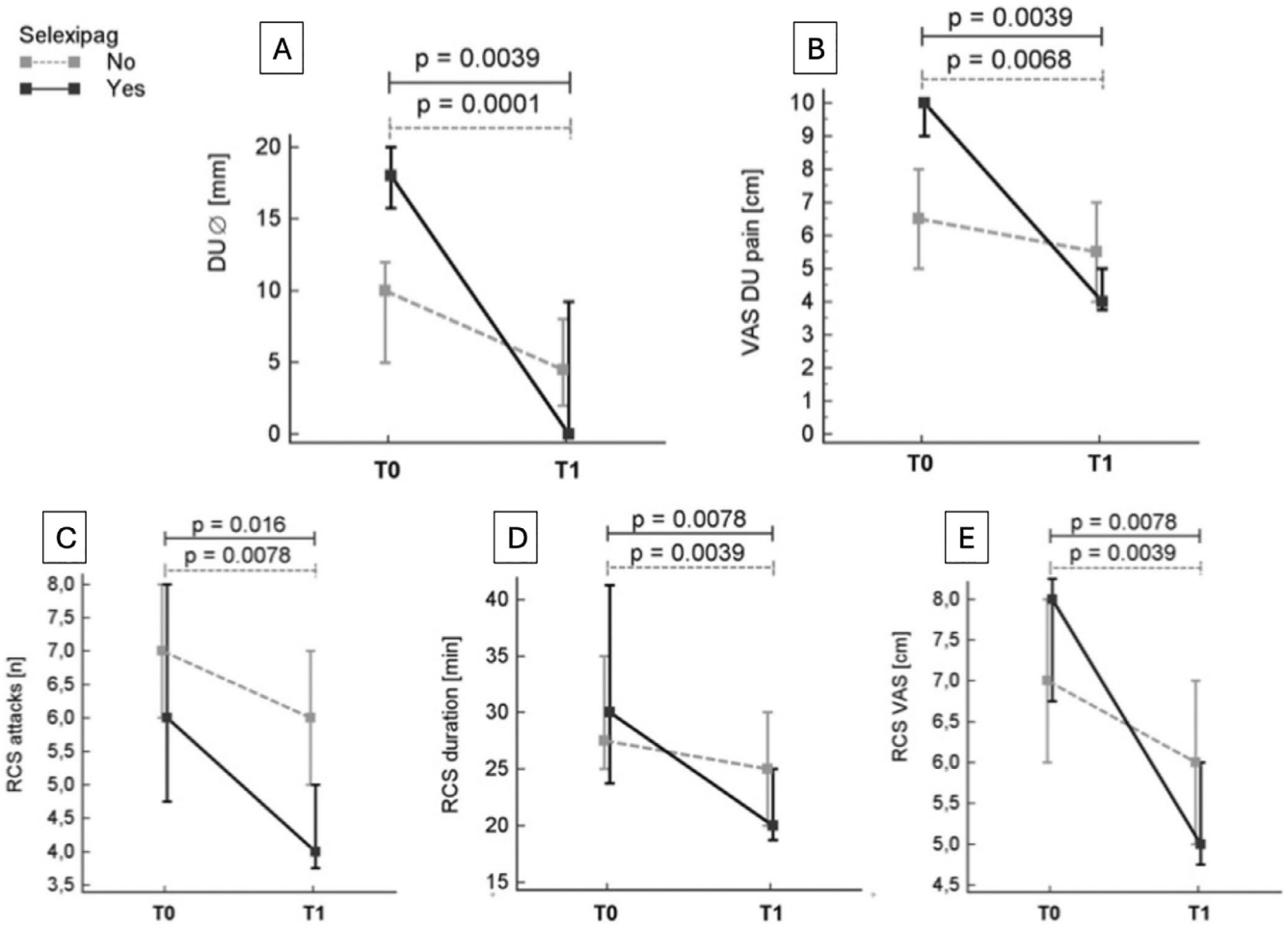

FIGURE 1 | Effect of Selexipag on digital ulcers and Raynaud's phenomenon from T0 (baseline) to T1 (after 6 months of follow-up). (A B) The effect of Selexipag on digital ulcers diameter (A) and pain VAS (B) is shown. (C–E), the effect of Selexipag on Raynaud's Phenomenon outcomes is shown, that is, RCS attack in (C), RCS duration in (D), and RCS pain VAS in (E). DUs, digital ulcers; RCS, Raynaud Condition Score; VAS, Visual Analogue Scale.

$p = 0.15$, and 5 [IQR 5–6] vs. 6 [IQR 5–7], $p = 0.066$, respectively). The outcomes related to RP significantly improved during follow-up (Figures 1 and 2). All RCS improved in the SG compared with that in the CG: number of attacks (4 [IQR 4–5] vs. 6 [IQR 5–7], $p < 0.001$, respectively), duration (20 min [IQR 20–25] vs. 25 min [IQR 21–29], $p = 0.083$, respectively), and VAS (5 [IQR 5–6] vs. 6 [IQR 5–7], $p = 0.066$, respectively) (Figure 1). The prevalence of complete healing of DUs in SG was higher than that in the CG (56% vs. 7%, $p = 0.018$). The statistically significant predictors of the diameter of DU after 6 months ($R^2 = 0.71$ F-test = 0.038) were the baseline DU diameter (beta coefficient = 0.70, $p < 0.001$) and Selexipag treatment (beta coefficient = −7.1, $p = 0.006$); other tested predictors (age, sex, number of DU, autoimmunity, disease duration, and DUs duration) were not statistically significant. Moreover, no new DUs were observed during the 6 months of therapy.

Selexipag was safe and well tolerated for all the treated patients; in fact, none of the patients had to interrupt treatment due to side effects. Only 3 of 8 patients reported hypotension, for whom the dose of Selexipag was not titrated. Most patients (seven of eight) had a low dose of Selexipag (200 and 400 μg twice daily), while only two patients with concomitant PAH reached 800 μg twice daily. During maintenance dosage, all side effects subsided in intensity.

4 | Discussion

This pilot study suggests that Selexipag may be safe and effective in the treatment of scleroderma DUs, which are refractory to conventional therapies, and for the improvement of RP in patients with SSc.

DUs complicate the course of SSc in almost half of the patients, leading to pain, disability, and reduced quality of life [4–7]. Despite the numerous and latest therapeutical options available, the management of DUs is challenging and requires a complex treatment program, including both systemic and local therapies [22, 23]. The pathophysiology of DUs is primarily observed in vasculopathy occurring in SSc. Vascular involvement affects microvasculature which, during the course of the disease, manifests in the form of RP, DUs, PAH, and SRC [24]. These vascular manifestations share some pathogenetic courses and could therefore be treated using the same drugs. Despite cross-sectional studies showed that patients with SSc–DU had a worse outcome of the

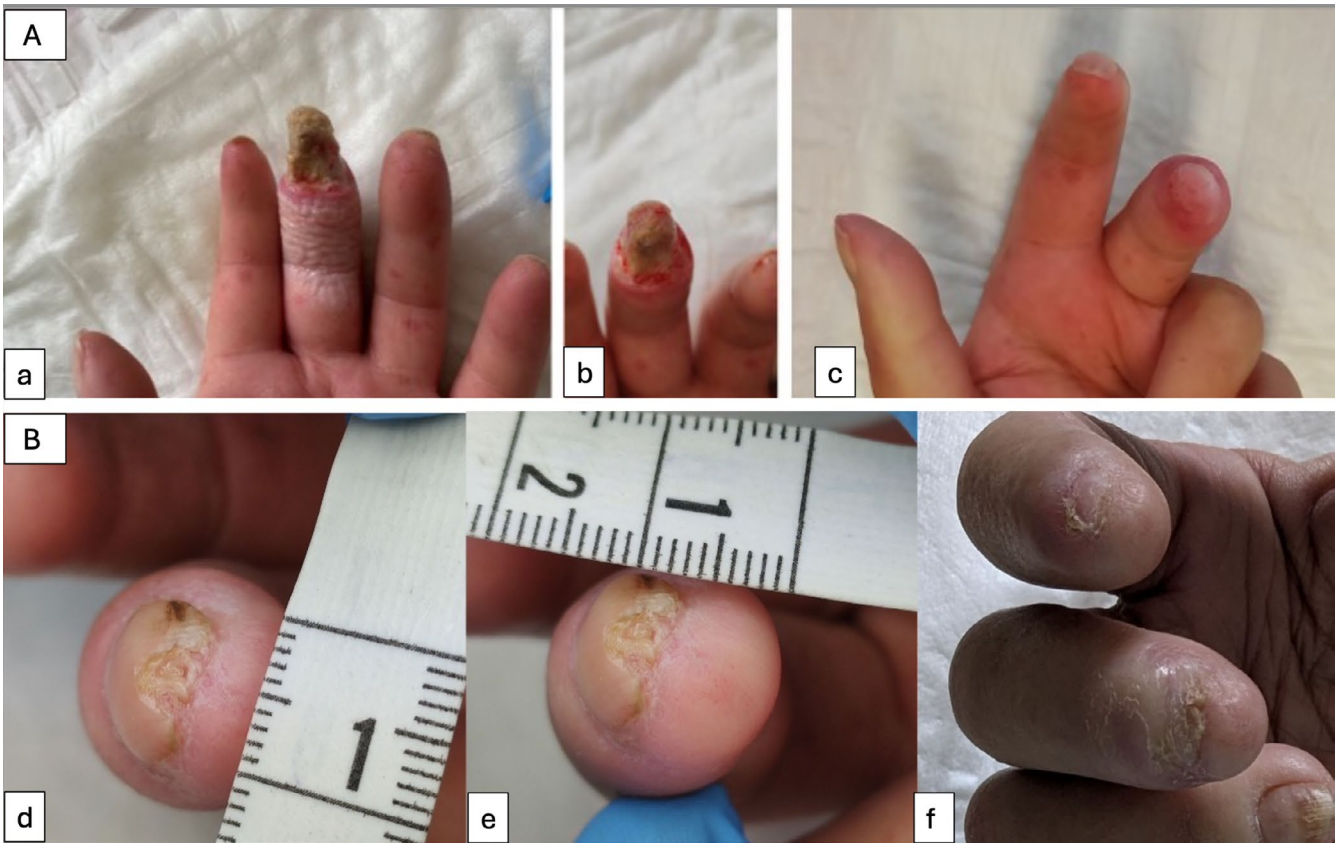

FIGURE 2 | Effect of Selexipag on DU healing. Two examples of the effect of Selexipag on DU complete healing after 6 months of follow-up. (A) A patient with SSc affected by a chronic DU of the III finger of the left hand at baseline (a), after 3 months (b), and after 6 months (c). (B) Patient with SSc affected by a chronic DU of the III finger of the right hand at baseline (d), after 3 months (e), and after 6 months (f). DU, digital ulcer; SSc, systemic sclerosis.

disease, neither a higher incidence of pulmonary arterial hypertension (PAH) nor scleroderma renal crisis (SRC) was found [25]. Selexipag is an oral, selective prostacyclin receptor agonist, approved for the treatment of PAH even when associated with systemic autoimmune diseases such as SSc both in monotherapy and in combined therapy with other vasoactive treatments (such as ERAs and PDE5-i) [26]. The rationale lying behind the use of Selexipag for the treatment of DUs in SSc consists in the activation of prostacyclin receptors, which induces vasodilatation, and possibly a peripheral vasodilatory effect. In 2017, in a randomized controlled trial (RCT), Denton et al. reported that Selexipag failed to demonstrate effectiveness on SSc-related RP; however, healing of DUs was recorded in all the three patients, including the ones in the active arm of the RCT [14]. Some issues could have influenced the RCT, in fact most patients (83%) had taken the final Selexipag dose of ≤ 800 μg bid, similar to our Selexipag dosage, however, with treatment lasting only 8 weeks—which was shorter than the treatment period for our patients—establishing the appropriate dosage is fundamental.

Del Papa et al. [15] described a case series of patients with SSc where the addition of oral Selexipag therapy proved to beeffective in thehealing ofDUs in 8 patients. Recently, Di Battista et al. [16, 27] reported a significant decrease in the number of daily episodes and mean duration of RP after 12 years of follow-up in a small series of 8 patients with SSc. In the same study, all patients achieved a complete healing of their DUs within 6 months.

To the best of our knowledge, our study is the first case–control study exploring the effectiveness of Selexipag for DUs and RP in patients with SSc. Our data show that implementing Selexipag in addition to systemic vasoactive therapy and topical dressings is effective for complete healing of DUs compared with that of the CG.

In our cohort, Selexipag dramatically reduced DU diameter and pain (Figure 2). All outcomes related to RP significantly improved during follow-up in the SG. Moreover, given that patients often present with multiple and recurrent DUs, an important finding is that no new DUs were observed in the SG during the 6 months of follow-up.

Finally, our preliminary study shows that Selexipag treatment and baseline DU diameter are predictors of the diameter of DUs after 6 months.

The overall improvement in both DUs and RP in the enrolled cohort is directly correlated with two main factors: (1) Almost all patients were on double vasoactive therapy, which confirms the importance of vasodilating and vasoactive therapy in scleroderma patients with RF and DUs; (2) all enrolled patients received advanced medications every 2–3 days at the wound care clinic of the scleroderma unit, an advanced center for the treatment of ulcers, regardless of the systemic therapy administered. Once again, this underlines the importance of a highly specialized center for the treatment of DUs.

It must be emphasized that the two cohorts are comparable in terms of demographic characteristics, clinical involvement, and therapy, with the exception of a longer duration of the disease in SG. CG was approximately 13 years older than SG; however, this difference is not statistically significant. Moreover, even if most patients were on Bosentan therapy, which could certainly influence DU healing, no significant difference in vasoactive therapy between the two groups was found.

This is an open observational case–control analysis on a limited number of patients, suggesting a potential new therapeutic indication of Selexipag in SSc, especially in the more complex DUs or in patients with contraindications to the standard vasoactive treatment. Further investigation into the use of oral Selexipag is recommended as it could significantly modify the management of DUs and vasculopathy related to SSc in general. Indeed, together with the promising effects on SSc vasculopathy, Selexipag could have other benefits: Oral intake reduces hospitalization for intravenous recovery, work-leave, and resolves the issues that characterize venous access. Daily intake guarantees a constant availability of the drug, overcoming the lack of a standardized protocol for infusion, curbing healthcare costs (fewer prostanoid infusions resulting in a shorter hospital recovery for infusion), and providing a global improvement in the patient's quality of life. This paper presents some limitations. Firstly, this is a pilot study that includes a small sample without double-blinding. Regarding this aspect, it must be highlighted that Selexipag was administered as an off label drug and patients' samples and the study protocol were in line with the previous literature. Moreover, the efficacy included both subjective and objective measurements in order to avoid a possible placebo effect. Regarding the study methods, another limitation is the lack of assessment with ultrasound and PD, information regarding mRSS value, and characteristics of DUs according to TIME protocols. In addition, we did not perform nailfold video capillaroscopy due to the limited follow-up time.

In conclusion, our preliminary data indicate a new potential therapeutic indication of Selexipag for the treatment of SSc vasculopathy, in particular DUs and RP, suggesting also its possible efficacy in other vascular complications of the disease.

Author Contributions

The author takes full responsibility for this article.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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