Long-term effects of selexipag in systemic sclerosis-associated digital ulcers: a case control multicentre observational study

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ABSTRACT

Objectives: Digital ulcers (DUs) affect approximately 50% of systemic sclerosis (SSc) patients, causing significant pain and functional impairment. Current management involves both systemic and local therapies. However, the burden in terms of pain and quality of life due to refractory DUs still remains heavy. While selexipag is approved for SSc-associated pulmonary arterial hypertension, its potential in treating DUs is unexplored. We aimed to evaluate the long-term efficacy of selexipag compared to iloprost in treating DUs.

Methods: In this multicentre case-control study, we retrospectively evaluated 96 SSc patients with refractory DUs (32 treated with selexipag, 64 with iloprost), matched for gender, disease subset, and age. DU number, ischemic pain and Raynaud phenomenon (RP) severity were assessed at baseline, 6, 12, and 24 months. Pain and RP were evaluated using the Likert Pain Scale (LPS) and Raynaud Condition Score (RCS), respectively. Additionally, DUs recurrence and new onset were recorded. Healing rates were estimated using Kaplan-Meier analysis.

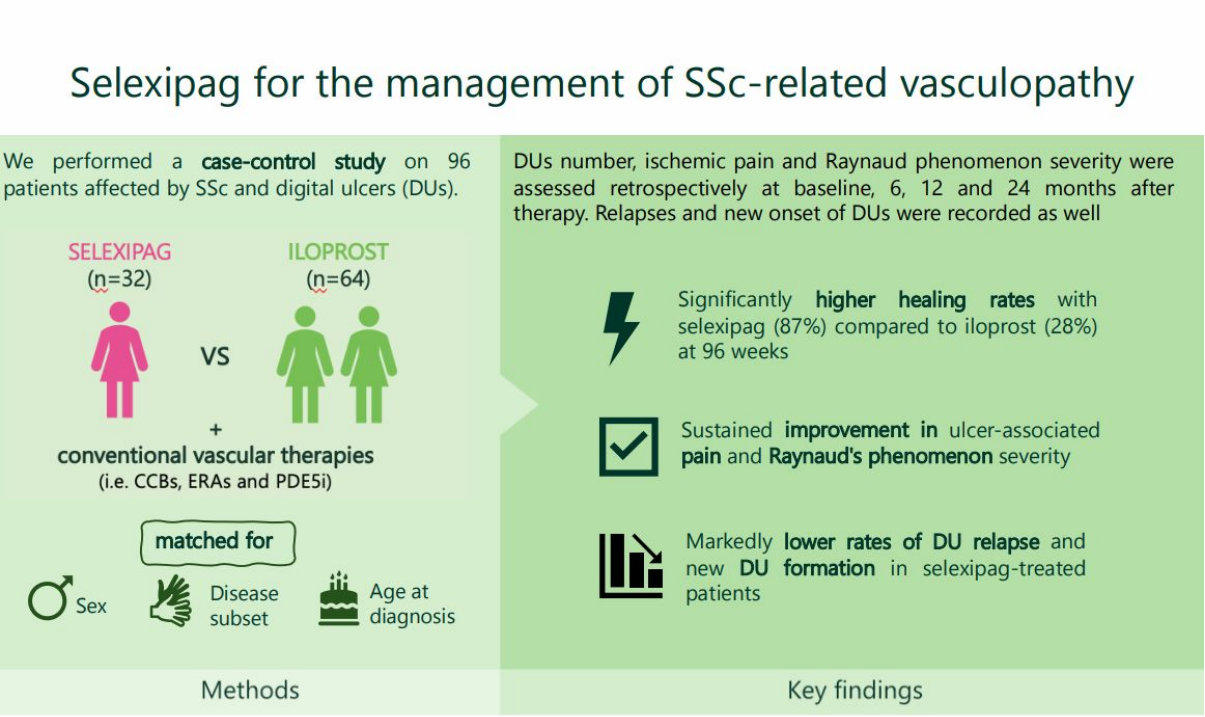
Results: Selexipag showed higher efficacy with 87% of DUs healing rate versus 28% for iloprost at 96 weeks ($p<0.001$). DUs number, RCS, and LPS showed significant improvement in selexipag-treated patients compared to iloprost ($p<0.001$ for all) throughout 24 months. Selexipag-treated patients achieved faster healing (75% by week 40) and maintained significantly lower relapse rates (5% vs 45% at 24 months, $p<0.001$). New DUs formation remained consistently lower in the selexipag group compared to the iloprost group (5% vs 40% at 24 months, $p<0.001$).

Conclusions: This observational study suggests that selexipag may be strongly effective in treating DUs refractory to conventional drugs.

Key words: Systemic sclerosis; digital ulcers; selexipag; iloprost; Raynaud condition score, vasoactive therapy; relapse;

Key messages:

- Higher healing rates with selexipag versus iloprost (87% vs 28% at 96 weeks)
- Lower rates of ulcer relapse and new formation with selexipag treatment
- Significant reduction in ulcer numbers, pain scores, and Raynaud severity observed



GRAPHICAL ABSTRACT

INTRODUCTION

Digital ulcers (DUs) are a frequent and debilitating complication affecting approximately 50% of patients with systemic sclerosis (SSc)(1,2). DUs can cause significant pain and functional impairment, severely impacting patients' quality of life and their ability to perform daily activities (2–5). The current management of DUs involves a complex approach combining systemic and local therapies (6–8). Several treatments are available, including endothelin receptor antagonists (ERAs) for prevention and vasodilatory agents for active ulcers. Among vasodilators, only phosphodiesterase-5 inhibitors (PDE5i) and intravenous iloprost have sufficient evidence to support their use (8). However, a significant proportion of patients still suffer from refractory DUs, which represent a challenging unmet need in SSc (9). Moreover, iloprost intravenous administration creates additional difficulties, including difficult venous access, high hospitalization costs, and loss of work productivity (2).

Selexipag, an oral selective prostacyclin receptor agonist (IP), is currently approved for the treatment of SSc-associated pulmonary arterial hypertension (PAH), and it acts by promoting peripheral vasodilation, decreasing cell proliferation and platelet aggregation (10). Since other drugs targeting the prostacyclin pathway (e.g., intravenous iloprost) have shown efficacy in SSc-related vasculopathy and inducing DUs healing (11–14), evaluating selexipag potential in this context was a strong rationale. However, in a randomized, placebo-controlled study, selexipag treatment did not improve the severity of Raynaud's Phenomenon (RP) (15). Few emerging evidences, derived from small cohort studies with brief follow-up periods, suggest that selexipag may be effective in promoting DUs healing in SSc patients who have

failed standard therapies (16–19). Based on these observations, we designed the present retrospective case-control study, aimed to evaluate the long-term efficacy of selexipag in treating DUs in comparison with the standard of care, namely iloprost.

METHODS

Study design.

In this case-control study, we retrospectively evaluated SSc patients with multidrug-refractory DUs who received treatment with selexipag. Each selexipag-treated patient (cases) was matched with two control patients who received iloprost. Matching was based on sex, disease subset according to LeRoy classification (20), age at diagnosis, and duration of active treatment. All enrolled patients met the 2013 classification criteria for SSc as defined by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR)(21).

This observational study was conducted on adult patients with SSc presenting with DUs that deeply impaired their daily activities and quality of life, who were refractory to all other vasoactive therapies or had contraindications to their use. The decision to initiate selexipag therapy was motivated by the failure of standard therapy to achieve DU healing, and in some cases, by difficulties in finding adequate venous access for iloprost infusion. The off-label compassionate use of selexipag was approved by hospital officials in accordance with the local regional rules for rare diseases (law 648/96). All patients were enrolled between 2018 and 2023. The total number of DUs, DUs relapse, and the development of new DUs were recorded at baseline and 6-, 12-, and 24-months therapy. DUs were defined according to the Suliman et al. characterisation (22) with evaluation and categorization following recent EUSTAR guidelines (23). Remarkably, DU relapse was defined as recurrence at a previously healed location, distinct from new DUs that developed in previously unaffected digit areas.

Additionally, we assessed the time needed to heal DUs. Pain burden and RP were evaluated using a Likert Pain Scale (LPS, 0–10) and the Raynaud Condition Score (RCS, 0–10), respectively (24,25). Concomitant therapies for DUs, including ERAs, calcium channel blockers (CCBs), and PDE5i, were recorded in both groups.

Ethics.

This study was conducted in accordance with the Declaration of Helsinki and received approval from the local ethics committee (Comitato Etico Lombardia 2, ID 3339, Study number 6549). Written informed consent was obtained from all participants. The off-label compassionate use of selexipag was approved by hospital officials in accordance with the local regional rules for rare diseases (law 648/96).

Statistical analysis.

Statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS Statistics 28.0). For continuous variables, descriptive statistics were reported as median and interquartile range (IQR) or average and standard deviation according to the Gauss distribution, while categorical variables were presented as frequency and percentage. The chi-square and Fisher's exact tests were employed to compare frequencies between groups. To assess changes in continuous variables across different time points, we used ANOVA with repeated measures, followed by a post-hoc Bonferroni test for pairwise comparisons. Both linear and quadratic trends were evaluated to capture potential non-linear patterns of change, while treatment group × time interactions were examined to assess differential treatment effects. Between-group comparisons of non-parametric variables were performed using Mann-Whitney U tests at specific time points (baseline, 6, 12, and 24 months). To compare cumulative healing rates between treatment groups, we performed a Kaplan-Meier survival

analysis, where time to healing was defined as the duration from treatment initiation to complete ulcer resolution without any relapse or new onset of digital ulcer. The Log-rank test assessed the statistical significance of differences in healing rates between groups. Right censoring was applied for patients who did not achieve complete healing by the end of follow-up.

RESULTS

Cohort description

Ninety-six patients were enrolled in the study, comprising 32 patients treated with selexipag and 64 with iloprost. The groups were comparable in gender, disease subset, age at diagnosis (median 59.7 vs 56.9 years), and autoantibody profiles. At baseline, both groups exhibited similar digital ulcer burden (median 2 ulcers) and therapy initiation timing. Concomitant PAH was documented in 15 (46.9%) patients in the selexipag group and 10 (15.6%) patients in the iloprost group. The study population's detailed demographic and clinical characteristics are presented in Table 1.

Regarding concomitant medications, PDE5i, ERAs, and CCBs were comparable between the iloprost and selexipag groups, with no statistically significant differences. Further analysis of combination therapy patterns (mono-, double-, and triple-therapy) also revealed no significant differences between the groups. Further details about concomitant vasoactive and immunosuppressive therapy are detailed in Table 2.

Selexipag was administered orally following the standard regimen with a median dosage of 1600 μg/day (IQR 1100μg), while iloprost was intravenously administered at the better-tolerated dosage of 0.5-2 ng/kg/min for at least 6 hours. The treating rheumatologist established the frequency of iloprost infusion as the known lack of a standard protocol, with a

median of 2 days/month (IQR 1 day/month), after induction. Only two patients had to discontinue selexipag due to intolerance after 12 months.

Clinical Outcomes

Repeated measures analysis demonstrated that selexipag-treated patients showed more significant and sustained improvement than the iloprost group throughout the follow-up period for all three outcomes: the number of DUs, RCS, and LPS scores. The level of significance (linear and quadratic trends) was $p<0.001$ for the reduction of all three analyzed parameters (Figure 1). The difference in the treatment effect at the specific time points was analyzed using the Mann-Whitney U test. While groups were comparable at baseline for all measures (DUs $p=0.901$; RCS: $p=0.561$; LPS: $p=0.708$), significant differences emerged by 6 months and were maintained through 12 and 24 months for DUs number, RCS and LPS scores (Figure 2).

Healing of Baseline Ulcers

We then compared the cumulative healing rate between treatment groups through Kaplan-Meier analysis. Patients treated with selexipag achieved significantly faster healing, with approximately 75% healing rate by week 40, compared to only about 18% in the iloprost group. This significant difference in healing rates (log-rank $p<0.001$) was maintained throughout the 96-week follow-up period, with final healing rates reaching 87% for selexipag versus 28% for iloprost (Figure 3).

Relapse and new onset DUs

Relapse rates showed significant differences between treatment groups at all time points. In the iloprost group, relapses were observed in approximately 60% of patients at 6 months, with rates

maintaining at around 45% at both 12 and 24 months. In comparison with the iloprost group, the selexipag group demonstrated significantly lower relapse rates, i.e., 15% at 6 months ($p<0.001$), maintaining similar levels at 12 months ($p=0.001$), and further decreasing to about 5% by 24 months ($p<0.001$) (Figure 4A).

The development of new ulcers followed a similar pattern in the differently treated groups. The iloprost group showed a progressive increase in new DU formation, from approximately 15% at 6 months to 30% at 12 months, ultimately reaching about 40% at 24 months. Selexipag-treated patients maintained consistently lower rates of new ulcer formation (around 5%) throughout the follow-up period. These differences were statistically significant at all time points (Figure 4B).

DISCUSSION

In this study, we retrospectively evaluated the efficacy of selexipag in refractory DUs through a case-control design. Both study arms included patients with severe refractory RP and multiple DUs, ensuring comparable baseline disease severity between groups. Selexipag appears to be more efficacious than iloprost in achieving healing (87% vs 28%) and reducing ulcer-associated pain and RP severity.

DUs management remains a significant challenge in SSc patients since, in many cases, DUs persist for a long time despite the use of different available treatments. This has a significant impact on the quality of life of these patients (1, 3). Recent data show that over 67% of SSc patients experienced more than 5 DUs during their disease course, with a significant impact on daily activities and social relationships (9). Indeed, only one-quarter of patients reported satisfaction with their DU treatments, the significance of this unmet clinical need. In addition to this, the standard intravenous therapy with iloprost poses challenges

including difficult venous access, high hospitalization costs, and loss of work productivity (2,3). In 2017 Denton et al, evaluated selexipag in a randomized controlled trial for RP in SSc patients (15). While the study found no reduction in RP attacks compared to placebo, failing the primary endpoint, an important observation emerged: all DUs in selexipag-treated patients healed, versus only 5 out of 8 ulcers in the placebo group. This trial was not powered to evaluate its impact on DUs, and because of its short duration of only 8 weeks, it had a limited full assessment of selexipag's therapeutic potential, which is known to need more than 4 weeks for drug titration (15). These findings appear to differ from our study, as we demonstrated that selexipag significantly reduced the severity of RP measured by RCS compared to iloprost. This discrepancy may be explained by differences in patient characteristics. The Denton's cohort likely had milder RP, with no patients receiving ERA or PDE5i co-therapy (only 53% on CCBs) and few having DUs. In contrast, our study included SSc patients with refractory, multidrug-resistant DUs, with both treatment groups having similar disease phenotypes and clinical features. This difference in disease severity may also explain the relatively low healing rate observed in our iloprost group (28%) compared to rates reported in previous studies, which typically included patients without refractory DUs, not on multiple vasoactive therapies, and often without reporting baseline DU numbers (26–28). Nevertheless, our findings are consistent with recent few open studies on small groups of patients suggesting that selexipag may be effective in promoting DUs healing in SSc patients where standard therapies had failed (16–19, 29). In one of these studies, our group has already reported successful DUs healing in 6 SSc patients treated with selexipag for 3-6 months (16). Di Battista *et al.* also demonstrated early and sustained efficacy in 8 patients during 12 months of follow-up (18,19), and Langleben et al. described significant improvement in 2 patients with severe digital ischemia (17).

The present multicenter case-control study is the first study carried out on a larger number of patients. Moreover, it compares 32 selexipag-treated patients with 64 iloprost

controls matched for key clinical features. The long observation period of 24 months allowed us to demonstrate not only the early efficacy of selexipag in inducing DU healing but also sustained benefits over time, with significantly lower DUs relapse rates in the selexipag group. Additionally, the long period of follow-up suggests that improvements may be not strongly conditioned by seasonal variations, addressing a key limitation of shorter-term studies. Our study has some limitations that should be acknowledged. The retrospective design may introduce potential bias and there may be unknown confounding variables that could have influenced the results. Furthermore, a detailed analysis of local therapy with regards to healing outcomes was not feasible in this study, representing an additional limitation. Local treatments were not administered uniformly to all patients, and when applied, they varied considerably due to the absence of standardized protocols. However, this study represents the first and largest comparative analysis of selexipag effects on the complications of SSc-related digital vasculopathy. Finally, our matching strategy for controls and the multicenter approach may be effective in mitigating some of these limitations.

CONCLUSIONS

This multicenter case-control study suggests that selexipag is more effective than iloprost in promoting DU healing in SSc patients, with sustained benefits over a 24-month period. The consistent improvement across multiple outcome measures, including healing rates, pain and RP severity reduction, suggests that selexipag could be a valuable therapeutic option for SSc patients with refractory DUs. Our promising results should be confirmed and may encourage the design of a prospective randomized controlled trial to evaluate the effect of selexipag on DUs in SSc.

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Competing interests: The authors have declared no conflicts of interest.

Data availability statement: The data underlying this article will be shared on reasonable request to the corresponding author.

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LEGEND TO THE FIGURES

Figure 1. Clinical outcomes over 24 months of follow-up in SSc patients treated with selexipag versus iloprost using repeated measures ANOVA. (A) Mean number of digital ulcers (DUs) over time. (B) Mean Likert Pain Scale (LPS) scores, ranging from 0 (no pain) to 10 (worst pain). (C) Mean Raynaud Condition Score (RCS), ranging from 0 to 10. Data points represent means with error bars indicating standard error. Statistical significance is indicated by asterisks: **p=0.001, ***p<0.001.

Alt Text Figure 1: Line graphs with error bars showing mean digital ulcer count (A), pain scores (B), and Raynaud Condition Score (C) for iloprost versus selexipag over 24 months

Figure 2. Clinical outcomes in SSc patients treated with selexipag or iloprost during 24 months of follow-up. Mann-Whitney U test analysis. (A) Number of active digital ulcers (DUs). (B) Raynaud Condition Score (RCS; range 0-10). (C) Likert Pain Scale scores (LPS; range 0-10). Data are presented as box plots showing median, interquartile range, and whiskers representing minimum and maximum values. Differences between groups at each timepoint

were analyzed using Mann-Whitney U test. Statistical significance is indicated by asterisks: **p=0.001, ***p<0.001.

Alt Text Figure 2: Box plots comparing digital ulcer count (A), Raynaud Condition Score (B), and Likert Pain Scale (C) between iloprost and selexipag groups at baseline, 6, 12 and 24 months

Figure 3. Kaplan-Meier analysis showing cumulative healing rates of DUs in SSc patients treated with selexipag versus iloprost over 96 weeks of follow-up. The vertical dashed line indicates week 40. Censored events are indicated by vertical marks on the curves.

Alt Text Figure 3: Kaplan-Meier survival curve comparing cumulative digital ulcer healing rates between iloprost and selexipag treatments over 96 weeks with significance indicator.

Figure 4. Digital ulcer relapse and new ulcer formation in SSc patients treated with selexipag versus iloprost over 24 months. (A) Percentage of patients experiencing DU relapse at previous ulcer sites. (B) Percentage of patients developing new DUs at previously unaffected sites. Statistical significance is indicated by asterisks: **p=0.001, ***p<0.001.

Alt Text Figure 4: Bar charts comparing digital ulcer outcomes between treatments. Chart A shows relapse percentages for iloprost versus selexipag over time. Chart B shows new ulcer formation rates.

Alt Text for Graphical Abstract: Graphical abstract comparing selexipag and iloprost treatments for systemic sclerosis-related digital ulcers. It shows study design with 32 selexipag

versus 64 iloprost patients, all receiving conventional vascular therapies. Key findings highlight selexipag's 87% healing rate compared to iloprost's 28%, markedly lower rates of digital ulcer relapse and formation, and sustained improvement in both ulcer pain and Raynaud's phenomenon severity.

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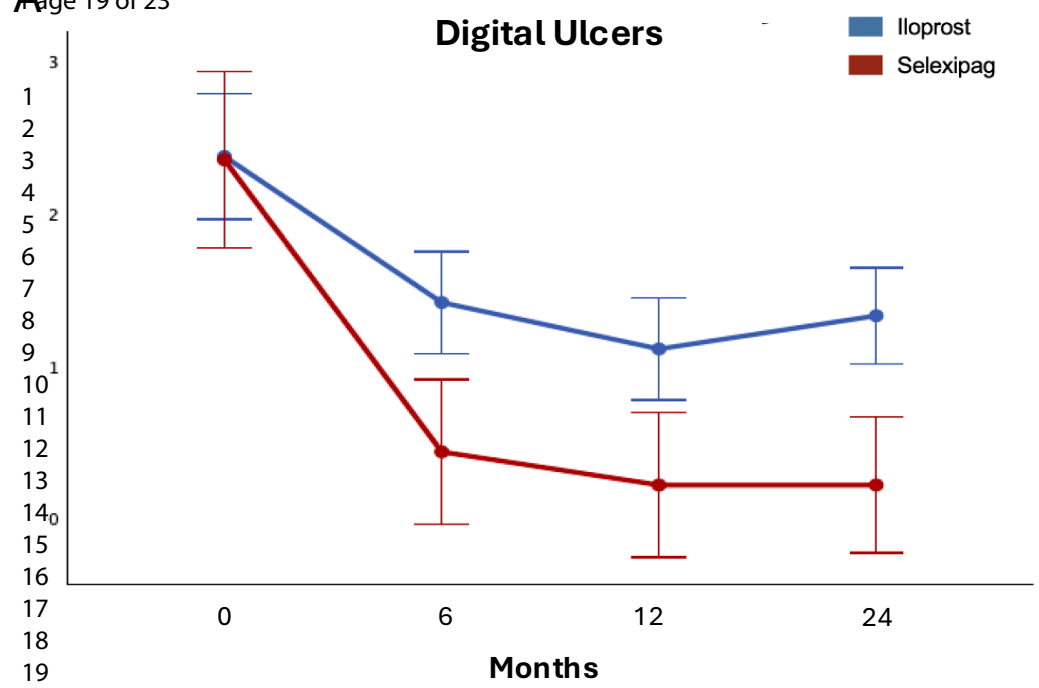

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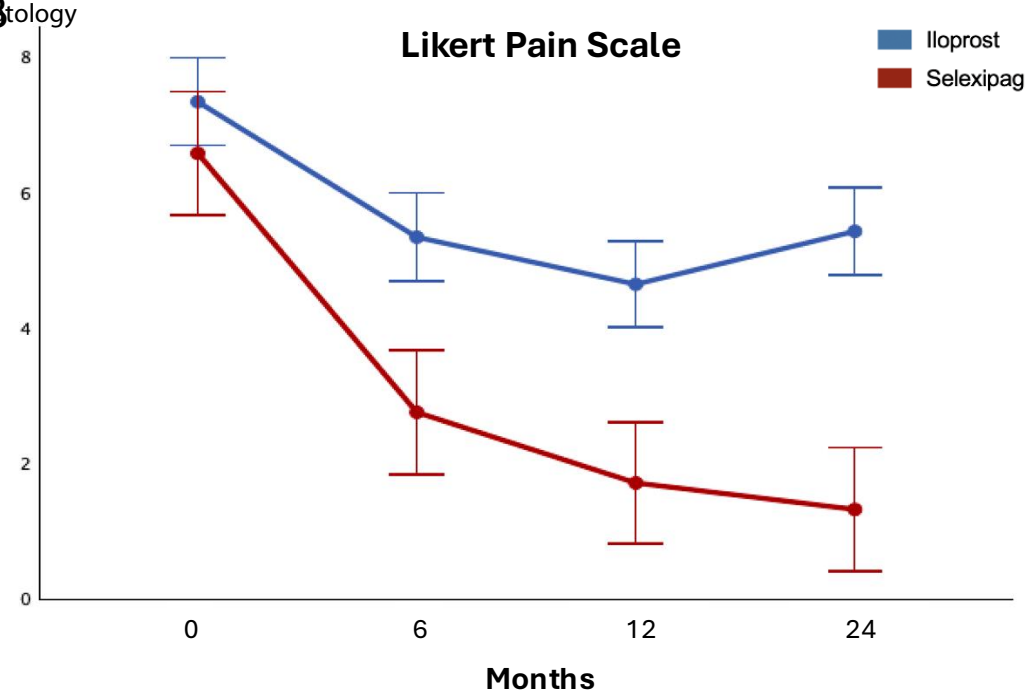

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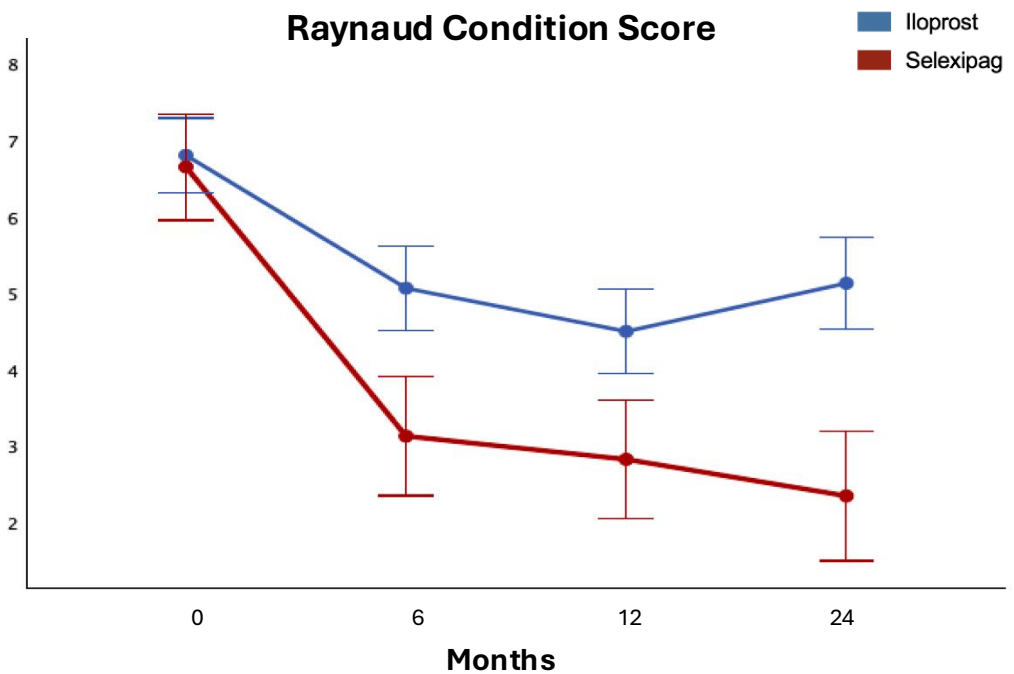

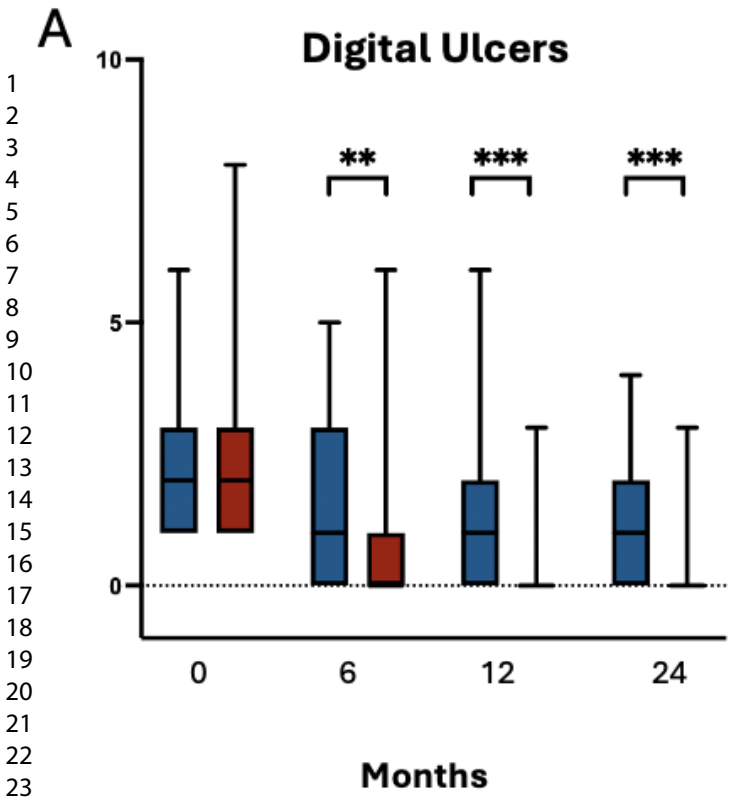

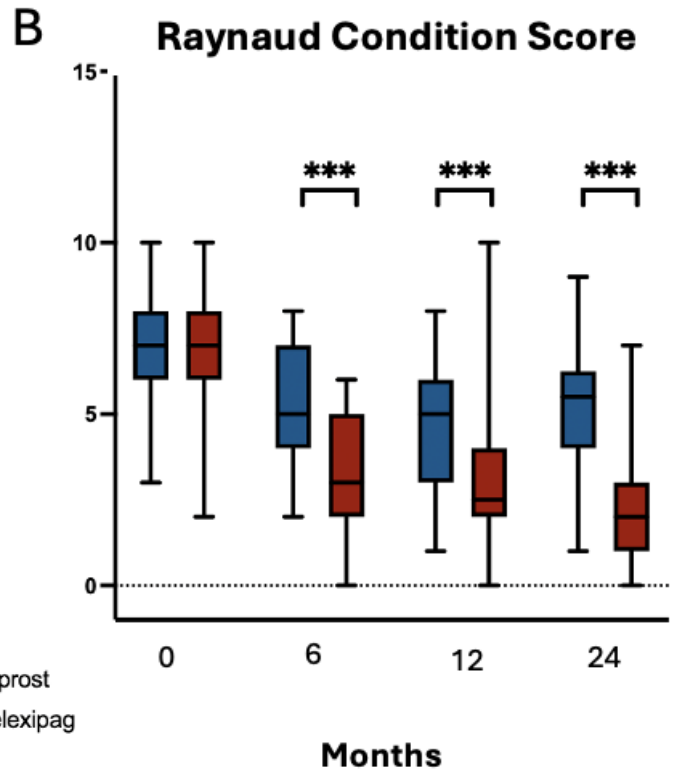

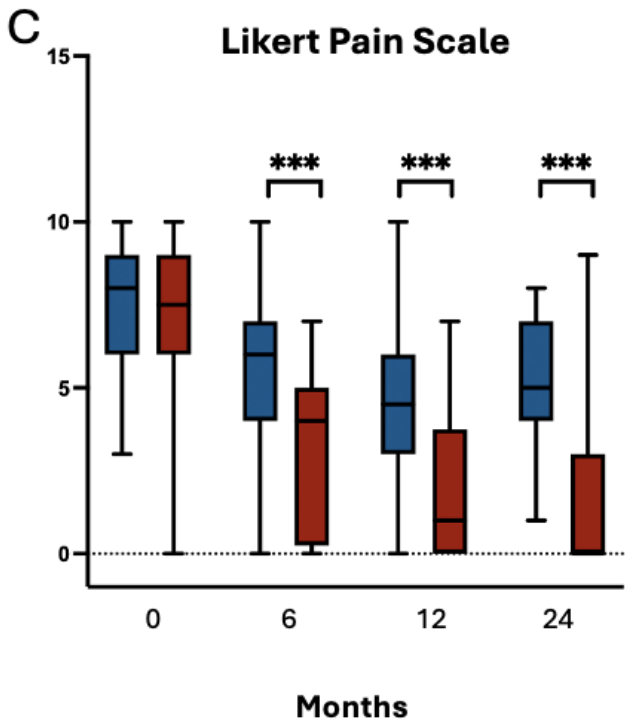

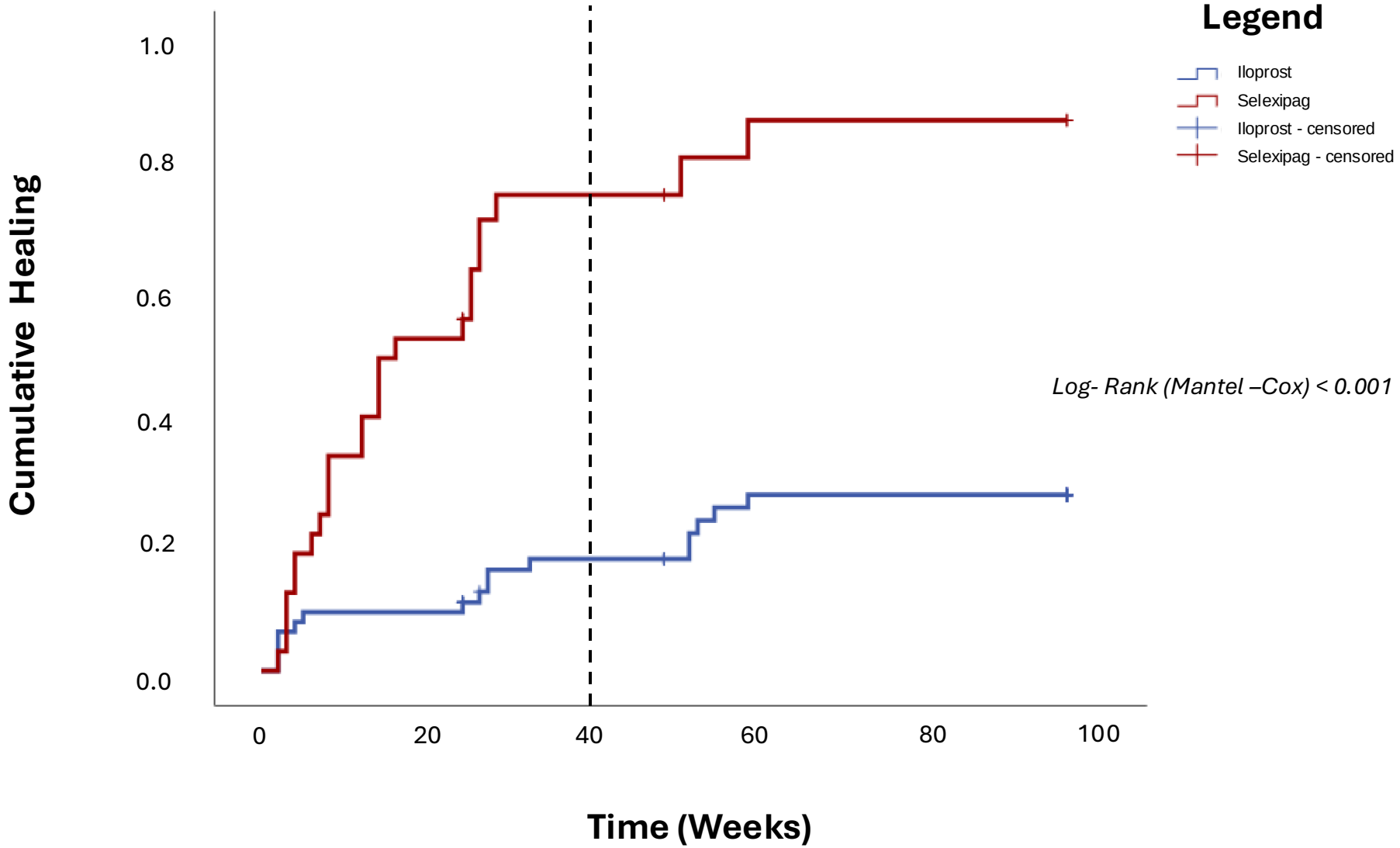

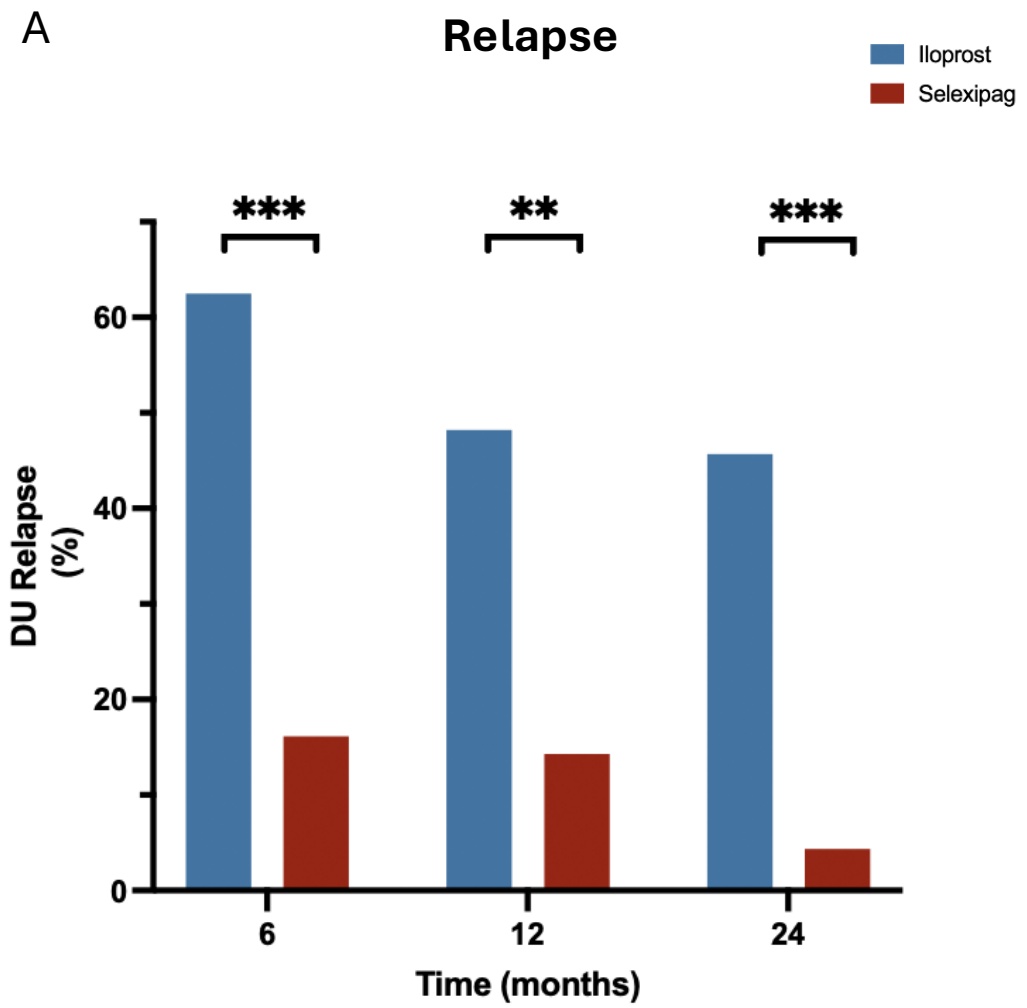

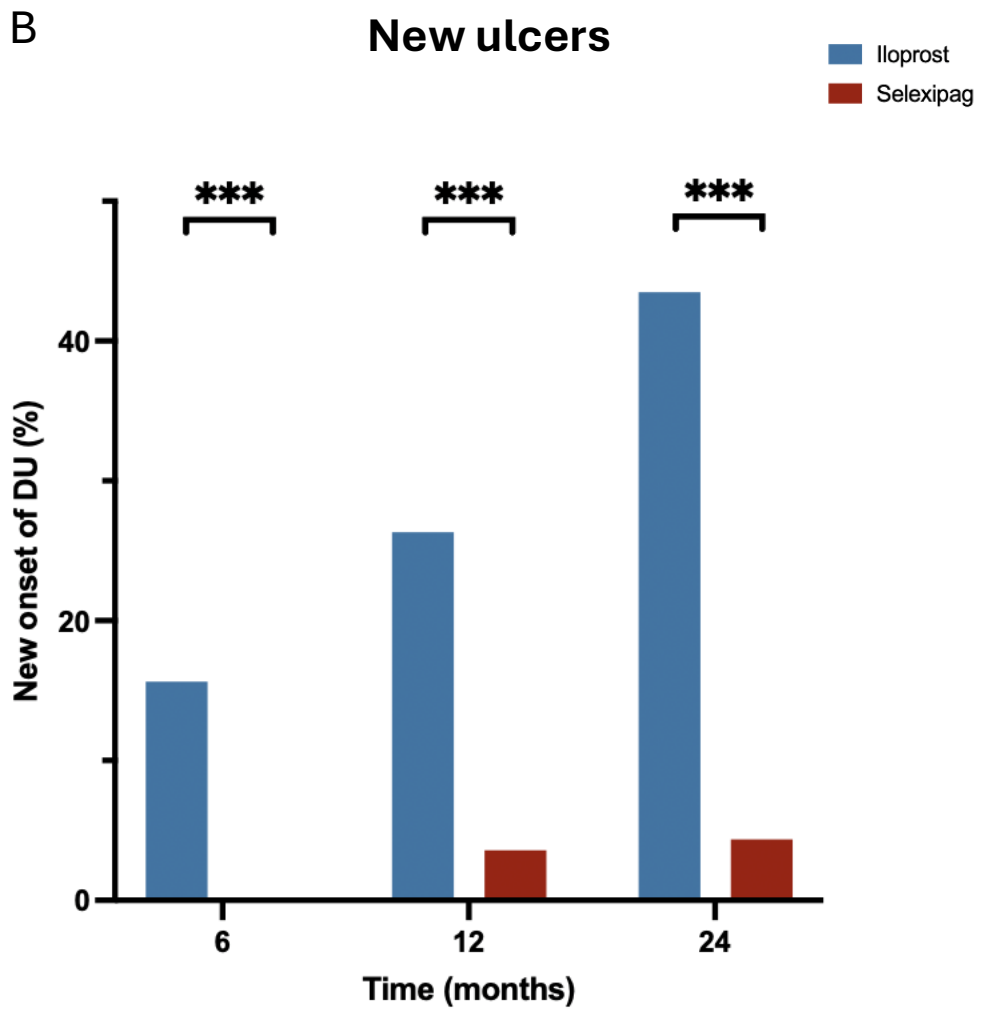

Table 1. Demographics and clinical characteristics of patients treated with iloprost or selexipag.

	Iloprost N = 64	**Selexipag** N = 32	*p-value*
Sex, F (n, %)	54 (84.4 %)	27 (84.4 %)	1
SSc variant, lcSSc (n, %)	38 (59.4%)	19 (59.4%)	1
Age, (median, IQR), years	59.7 (24.4%)	56.9 (29.2%)	0.92
Age at diagnosis (median, IQR), years	41.5 (23.1%)	38.7 (26.0%)	0.68
Smoking status (n, %)			
Non-smokers	47 (73.4%)	23 (71.9%)	0.62
Previous smokers	8 (12.5%)	6 (18.8%)	0.62
Active smokers	9 (14.1%)	3 (9.4%)	0.62
Autoantibodies (n, %)			
ANA	64 (100%)	32 (100%)	1
Anti-Scl70	33 (51.6%)	15 (46.9%)	0.33
ACA	27 (42.2%)	17 (53.1%)	0.38
DUs-therapy latency, years (median, IQR)	1.1 (3.4%)	5.6 (6.7%)	0.14
N° of DUs at baseline (median, IQR)	2 (2%)	2 (2%)	0.55

F = Female; SSc = Systemic Sclerosis; lcSSc = limited cutaneous Systemic Sclerosis; IQR = Interquartile Range; ANA = Antinuclear Antibodies; Scl70: Antitopoisomerase-I; ACA = Anticentromere Antibodies; DUs = Digital Ulcers;

Table 2. Concomitant medications of patients treated with iloprost or selexipag.

	Iloprost N = 64	**Selexipag** N = 32	p-value
PDE5i (n, %)	22 (34.4%)	15 (46.9%)	0.270
ERA (n, %)	34 (53.1%)	22 (68.8%)	0.189
CCB (n, %)	32 (50.0%)	14 (43.8%)	0.666
No vasoactive therapy (n, %)	7 (10.9%)	3 (9.4%)	0.268
Therapy with 1 vasoactive agent (n, %)	27 (42.2%)	10 (31.3%)	0.268
CT with 2 vasoactive agents (n, %)	29 (45.3%)	16 (50.0%)	0.268
CT with 3 vasoactive agents (n, %)	1 (1.6%)	4 (9.4%)	0.268
Anti-platelet therapy (n, %)	29 (19.7%)	10 (31.3%)	0.875
Statin (n, %)	15 (23.4%)	6 (18.8%)	0.430
Immunosuppressive therapy (n, %) Methotrexate Mycophenolate Tocilizumab Rituximab	33 (51.6%) 11(17.2%) 17 (26.6%) 4 (6.3%) 6 (9.4%)	18 (56.3%) 3 (9.4%) 7 (21.9%) 3 (9.4%) 4 (12.5%)	0.664 0.370 0.617 0.579 0.637

PDE5i = Phosphodiesterase type 5 inhibitors; ERA = Endothelin Receptor Antagonists; CCB = Calcium Channel Blockers; CT = Combination Therapy;