Management Practices for Raynaud's Phenomenon in Patient's with Systemic Sclerosis: A Real-World Data from Community-Based Practices in the United States

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ABSTRACT

Background/Purpose: Raynaud's phenomenon (RP) and the complex vasculopathy of systemic sclerosis (SSc) can lead to chronic digital ischemia, ulcerations, and necrosis with significant pain and hand function loss. Being not only the most common SSc manifestation, SSc-RP is one of the highest patient-reported disease impacts on quality-of-life. Early interventions for RP can have an important impact on altering the disease course by preventing ischemia-reperfusion injury and subsequent oxidative stress with further endothelial dysfunction and fibrosis in SSc. However, it is unknown how adequately RP medications are utilized in real-world, community-based settings, while avoiding RP-worsening medications. We aimed to assess RP management patterns in SSc patients among the United States community-based rheumatologists.

Methods: We used FORWARD, The National Databank for Rheumatic Diseases study, which consists of rheumatologist diagnosed patients. We identified adult SSc patients who participated in FORWARD between 1999 and 2023 for this study. Data is collected semi-annually with questions on disease characteristics, comorbidities, medications, and patient-reported outcomes (health assessment questionnaire, patient global assessment, pain) and validated using medical records. Medications that can improve or worsen RP were identified. Descriptive statistics were used to assess RP management patterns.

Results: The study included 270 SSc patients (~83% diffuse) with a mean symptom duration of 12.1 (10.6) years (30%, ≤5 years of symptoms) at enrollment (Table 1). The median (IQR) follow-up was 3.4 (1.3-7.8) years. During follow-up, 61% of patients used a medication for RP, which was most frequently calcium channel blockers (CCBs) (48%). About 13% and 20% of patients received RP-worsening medications while receiving or not receiving medications for RP, respectively (Table 2). Second-line agents (phosphodiesterase-5 inhibitors [PD5i], endothelin 1 receptor antagonists, or prostaglandin analogs) were ever utilized only in 15% of the patients. Moreover, only ~29% of the patients remained on medications for RP throughout their follow-up. While patients who had hypertension or were on immunomodulatory medications were more likely to be on RP medications, patients who had early disease (≤2 years), were current smokers, or black were less likely to be on RP medications (Figure). From 2000 to 2023, CCBs remained stably the most common RP medication prescribed. PD5i have been increasing since 2019, but utilization of non-CCB RP medication remained <10% (Figure).

Conclusion: Medications for RP, especially non-CCB, remain underutilized for SSc-RP in community-based practice. Less than one-third of patients stay on RP medications long-term. A significant number of patients continue to be on RP-worsening medications even while not on medication for RP, which emphasizes the importance of carefully reviewing medications in SSc patients. Given that early intervention for RP can reduce complications, further endothelial damage, and fibrosis, more vigorous awareness programs should be implemented about RP management in the community practice.

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BACKGROUND

- Raynaud's phenomenon (RP) is the most common and earliest manifestation of systemic sclerosis (SSc) which theoretically contributes to ongoing disease pathogenesis via recurrent ischemia-reperfusion injury.
- SSc-RP is also the highest ranked SSc symptom affecting quality of life and is independently associated with hand function loss and psychologic morbidity.
- Therefore, early interventions for SSc- RP may have an important impact on morbidity, quality of life and even disease course and mortality in SSc.

OBJECTIVE

- To describe RP management patterns for SSc patients amongst United States (US) community-based rheumatologists

METHODS

- **Study cohort**: Adult SSc patients who were diagnosed by a rheumatologist and participated in FORWARD* between 1999 and 2023
  *FORWARD: A multi-disease registry that enrolls participants by referral from US rheumatologists providing diagnoses
- **Data collection:** Sociodemographic, disease characteristics, comorbidities, medications and patient reported outcomes (PROs) were collected via semiannual questionnaires.
- **Exposures:**
  - **Medications for RP**: Calcium channel blockers (CCBs), renin angiotensin system inhibitors (RASi: losartan or lisinopril), fluoxetine, topical nitroglycerin, phosphodiesterase 5 inhibitors (PDE5i), endothelin receptor antagonists (ERAs), prostaglandin analogs (PGA), others (pentoxifylline, dipyridamole and prazosin)
  - **Medications worsening RP** : β-blockers, amphetamine derivatives, migraine medications (triptans and ergotamine derivatives), decongestants and dopaminergic agents
- **Statistical analysis:** Frequencies of RP improving or worsening medication use, management practices according to patient characteristics, trends of different RP medication use over time, and persistence use of RP medications were assessed using descriptive statistics.

RESULTS

- 270 patients with SSc (~83% dcSSc, 88% female and white, mean (SD) symptom duration 12 (10) years, 30% ≤5 years of symptoms, ~50 % on immunomodulatory agents)
- Follow-up (median [IQR]): 3.4 (1.3-7.8) years
- **61%** use of any RP medication use (*Table)*
  - CCBs most common (48%), followed by losartan (11%), lisinopril (6%)
- Advanced therapy use (PDE5i, ERA, PGA): **15%;** combination use: **20%**
  - Combinations: CCB+losartan (5.6%), CCB+PDE5i (5.2%) and CCB+ERA (3.7%)
- Statin use: **~23%;** antiplatelet use **~43%** throughout the follow-up

Table 1. Medication utilized for SSc-RP

	At enrollment	Throughout the follow-up
Utilization of medications for RP, %	47.0	61.1
Calcium channel blockers	45.4	48.1
Losartan	6.7	11.5
Lisinopril	2.1	6.3
Fluoxetine	2.9	5.9
Topical nitroglycerin	0	0.4
Phosphodiesterase 5 inhibitors	4.2	8.9
Endothelin receptor antagonists	3.9	7.4
Prostaglandin analogues	0	1.1
Prazosin	0.4	0.4
Pentoxifylline	2.9	4.4
Use of advanced therapies (PDE5i, ERA or PGA), %	12.2	15.0
Maintenance of RP medications, %		
Throughout the entire follow-up (100%)	-	28.9
70-99% of the visits	-	10.7
50-69% of the visits	-	10.0
30-49% of the visits	-	5.6
1-30%	-	5.9
None	-	38.9
Use of RP worsening medications, %	13.3	25.6
Decongestants	0.9	5.2
Migraine medications (triptans, ergotamines)	2.2	3.7
Amphetamine derivatives	0.4	1.5
Beta blockers	11.8	17.4
Dopaminergic agents	1.3	1.4
Concomitant RP improving & worsening medication use, %	15.0	13.2
RP worsening medication use without RP medications, %	11.9	20.2

- Less frequent RP medication use in patients who did not have HTN, have early disease, were black or current smokers than others (*Figure 1A*)
- No seasonal change in RP medication use but more frequent RP medication use in West and Southwest climate zones of US (*Figure 1B*)
- Stable trend of RP medication use from 2000 to 2023 (CCBs, most common) with a decline in CCB use and an increase in PDE5i use since 2019 *(Figure 1C)*
- **Only ~1/3 persistently remained on an RP medication** (*Table 1*)
- 20% of patients receiving at least one RP-worsening medication while not on a medication for RP
- Management of GERD with PPI/H2RB significantly better than RP management (80% vs. 61%, p<0.001)

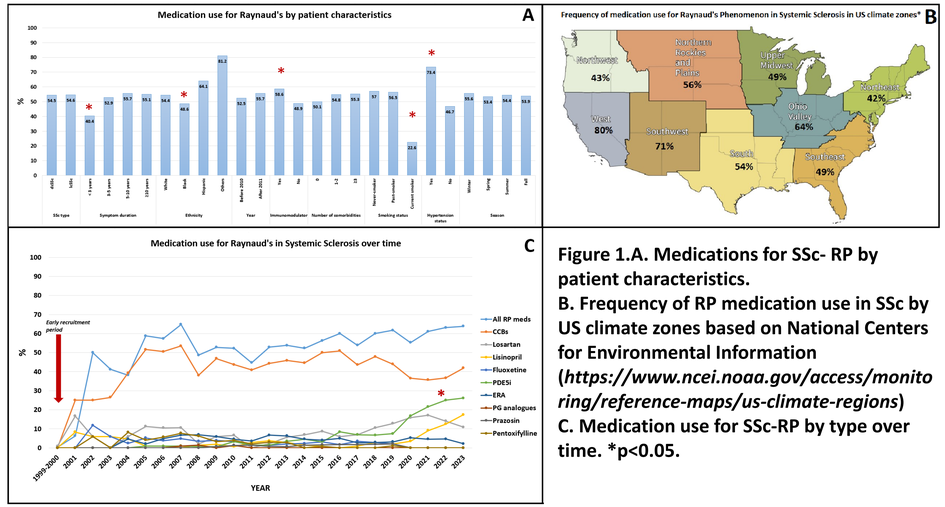

Figure 1.A. Medications for SSc- RP by patient characteristics.
B. Frequency of RP medication use in SSc by US climate zones based on National Centers for Environmental Information (*https://www.ncei.noaa.gov/access/monitoring/reference-maps/us-climate-regions*)
C. Medication use for SSc-RP by type over time. *p<0.05.

CONCLUSIONS

- Although CCBs are commonly used for SSc-RP among community-based rheumatology practices, overall SSc- RP management appears neglected (even worse than GERD management) with low maintenance rates, low advanced therapies and combination regimen use, and significant concomitant use of RP-worsening medications.
- The increase in PDE5i use beginning in 2019 and corresponding to generic PDE5i availability, provides face-validity to this real-world data.
- Patients with high risk for RP complications (black individuals, smokers, or those with early disease) treated for RP less than others.
- Limitations: No data on RP severity, digital ulcers or pulmonary hypertension (PH) (RP medication use may actually be worse than found given that some of these medication might be used for PH
- Besides FDA non-approval of advanced therapies (PDE5i, ERA or PGA) for SSc-RP or its complications, lack of experience and guidelines for the management of SSc-RP, its complications and associated impact on quality-of-life play a significant role in the care gap of SSc-vasculopathy in community-based rheumatology practices.

FORWARD
The National Databank for Rheumatic Diseases