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Factors Influencing Patient Decision-Making Concerning Treatment Escalation in Raynaud's Phenomenon Secondary to Systemic Sclerosis

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Objective. To explore patient priorities and ranking of factors influencing patient decision-making concerning treatment escalation in the management of Raynaud's phenomenon (RP) secondary to systemic sclerosis (SSc).

Methods. Patients with SSc were invited to participate in an online survey disseminated through patient-led organizations and social media platforms.

Results. Responses from 747 individuals with self-reported SSc-RP were evaluable with broad international representation. The mean ± SD age (54.7 ± 12.1 years), clinical phenotype, and disease subsets distribution (limited cutaneous SSc [402 of 747, 53.8%], diffuse cutaneous SSc [260 of 747, 34.8%], and overlap disease [85 of 747, 11.4%]) were consistent with expected demographic information. Around one-half (56.3%) of patients reported that their SSc-RP symptoms were adequately controlled. The 5 highest ranked factors (of 13) that would prompt treatment escalation for SSc-RP were as follows: 1) inability to use the fingers properly; 2) emergence of new digital ulcer on ≥1 fingers; 3) worsening pain or discomfort from RP; 4) more severe attacks; and 5) if it may help with internal problems. Despite symptoms not being adequately controlled, 47.1% were concerned about potential treatment side effects and were more likely to accept mild (~20–40%) versus severe (2%) side effects. Patients were open to different management strategies for uncontrolled RP that included adding new treatment in combination with existing treatment (52.8%), drug substitution (40.9%), increasing the current dose (28.8%), or focusing on nonpharmacologic approaches (29.7%).

Conclusion. We have identified the relative importance of different factors influencing patient preferences for treatment decision-making regarding SSc-RP. Side-effect profiles influence acceptability of drug treatments, and many patients report a preference for nonpharmacologic management of SSc-RP.

INTRODUCTION

Raynaud's phenomenon (RP) is responsible for significant pain and disability in patients with systemic sclerosis (SSc), despite the availability of a wide range of drug therapies (1,2). Furthermore, in SSc, digital vasospasm can be complicated by irreversible tissue ischemia including digital ulcers and gangrene. In addition, generalized vascular disease (vasculopathy) is a cardinal feature of SSc including visceral-based complications (e.g., pulmonary hypertension) (3). A unified vascular phenotype has been proposed in which vascular-acting therapies could be judiciously deployed as disease-modifying agents before the onset of irreversible tissue fibrosis and organ dysfunction (4).

In the absence of a validated instrument for objectively assessing SSc-RP activity/severity, the decision to both initiate and assess treatment for RP is usually based on clinician–patient discussions about symptom severity, drug tolerability, and the perceived effectiveness of existing/planned interventions (5). Treatment is given on a regular basis because patients, including those with SSc, have a limited ability to predict both the occurrence and severity of attacks of RP (2).

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SIGNIFICANCE & INNOVATIONS

- Hand function, physical symptoms, and preventing digital/internal complications influence patient decision-making in the management of systemic sclerosis (SSc)–Raynaud's phenomenon (RP).
- Side effects significantly impact on acceptability of drug treatment for SSc-RP.
- Pharmacologic and nonpharmacologic approaches toward treatment escalation should be adopted for suboptimally controlled SSc-RP.

Expert treatment recommendations for SSc-RP have been produced under the auspices of the British Society of Rheumatology, the European Alliance of Associations for Rheumatology, the UK Scleroderma Study Group, and the Scleroderma Clinical Trials Consortium/Canadian Scleroderma Research Group (6–9). In general, these have detailed the positioning of particular drug therapies but not practically how to either initiate and/or escalate drug therapies in clinical practice, including dosing strategies that could optimize drug tolerability, treatment adherence, and treatment efficacy. For example, higher (compared to lower) doses of calcium-channel blockers have been reported to be relatively more efficacious (10).

Treatment escalation via a treat-to-target approach has revolutionized the treatment of rheumatoid and other inflammatory arthritides and is widely used across medicine (e.g., in patients with hypertension and diabetes mellitus) (11–13). However, despite the availability of a wide range of drug therapies for RP, there is no evidence base to guide the optimal initiation and/or dose escalation, including failure after treatment, nor are the merits of different treatment approaches (e.g., initial combination versus goal-directed sequential monotherapy) considered. In addition, combination therapy is now considered the standard of care for the treatment of pulmonary hypertension, including in patients with SSc (14,15). Furthermore, little is known about the factors perceived by patients to be important in treatment escalation decision-making for SSc-RP.

Against this background, the primary aims of the current study were to explore patient priorities and ranking of factors influencing patient decision-making concerning treatment escalation in the management of SSc-RP. We also examined patient preferences regarding potential treatment strategies and acceptability of treatment side effects during treatment escalation for SSc-RP. A secondary objective was to explore whether differences existed across SSc disease subsets: diffuse and limited cutaneous SSc (dcSSc and lcSSc, respectively) and overlap SSc.

PATIENTS AND METHODS

Study design. Data were obtained from the Patient Survey of Experiences of Raynaud's Phenomenon (PASRAP) survey, the design of which has been previously described (16). In summary, the PASRAP was an international survey that sought to explore the multifaceted patient experience of RP, including approach to treatment. The link to the survey was widely distributed, including through social media (e.g., Facebook and Twitter), a scleroderma self-management website, and patient-led organizations (e.g., Scleroderma and Raynaud's UK and the Scleroderma Foundation). The survey consisted of a series of questions that included basic patient demographic and disease-related information, the impact and severity of RP and current treatments, the reasons to change current treatment and management strategies, and willingness to experience side effects. The survey questions are available online (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24710/abstract). Participants (≥18 years of age) were invited to complete the PASRAP if they had clinician-diagnosed RP and were asked to indicate their underlying diagnosis (e.g., SSc). The study was approved by the University of Michigan Institutional Review Board with exempt status (study ID: HUM00175143; OHRP IRB registration number: IRB00000246).

Statistical analysis. Demographic and baseline data, including age, sex, country, disease durations, history of diseases, medication, and treatment-related questions, were populated by scleroderma groups. Mean and SDs were reported for continuous variables; counts and percentages were reported for categorical variables. When comparing SSc groups, we performed an analysis of variance test for continuous variables that followed normal distribution, the Kruskal-Wallis test for continuous variables that did not follow normal distribution, and a chi-square test or Fisher's exact test for categorical variables. Percent of weight was calculated for different factors as follows: 1) for 13 factors in starting new treatment, assign first selected to last selected with scores 13 to 1 (i.e., assign scores in descending order) for each participant; 2) get sum of the scores for each of the reasons as numerator; 3) multiply number in the population by 13 as denominator; and 4) divide numerator (obtained weight) by denominator (sum weight) to get percent of weight (% weight).

RESULTS

Patient demographic information. The PASRAP was completed by 1,718 respondents between April 2020 and May 2020, of which 747 self-reported that their RP was secondary to SSc. Patient demographic information and disease and treatment characteristics are presented in Table 1, including for patients with lcSSc (54%), dcSSc (35%), and overlap SSc (11%). Patients' mean ± SD age was 54.7 ± 12.1 years, and the majority (93.5%) were female. More than one-half of patients reported living in the US (58.9%), and there was broad international representation including the UK (14.5%), Europe, and Australia. Patients were asked to identify when they first developed RP and were diagnosed with any underlying condition (e.g., SSc). Patient-reported median (interquartile range) disease duration for RP and SSc were 12 (5–24) and 7.0 (3.0–15.0) years, respectively.

Table 1. Patient demographic information including disease and treatment characteristics*

Characteristic	All SSc (n = 747)	LcSSc (n = 402)	DcSSc (n = 260)	Overlap SSc (n = 85)	*P*
Age, mean ± SD years (n = 747)	54.7 ± 12.1	55.2 ± 12.0	54.3 ± 12.0	53.2 ± 12.8	0.331
18–34	43 (5.8)	21 (5.2)	15 (5.8)	7 (8.2)	0.690
35–49	207 (27.7)	108 (26.9)	72 (27.7)	27 (31.8)	–
50–64	327 (43.8)	174 (43.3)	120 (46.2)	33 (38.8)	–
≥65	170 (22.8)	99 (24.6)	53 (20.4)	18 (21.2)	–
Sex (n = 744)					
Male	48 (6.5)	14 (3.5)	29 (11.2)	5 (6.0)	<0.001
Female	696 (93.5)	386 (96.5)	231 (88.8)	79 (94.0)	
Country (n = 747)					
Australia	34 (4.6)	22 (5.5)	9 (3.5)	3 (3.5)	0.069
Canada	26 (3.5)	12 (3.0)	11 (4.2)	3 (3.5)	–
Norway	21 (2.8)	13 (3.2)	6 (2.3)	2 (2.4)	–
UK	108 (14.5)	71 (17.7)	27 (10.4)	10 (11.8)	–
US	440 (58.9)	233 (58.0)	161 (61.9)	46 (54.1)	–
Other	118 (15.8)	51 (12.7)	46 (17.7)	21 (24.7)	–
Disease duration, median (IQR) years (n = 746)	7.0 (3.0–15.0)	8.0 (3.0–16.0)	6.0 (2.0–12.0)	9.0 (3.5–17.0)	0.014
RP duration, median (IQR) years (n = 746)	12.0 (5.0–24.0)	14.0 (6.0–27.0)	9.0 (4.0–18.0)	12.5 (6.0–28.5)	<0.001
History of DUs (n = 731)	284 (38.9)	148 (37.2)	112 (44.6)	24 (29.3)	0.028
Past gangrene (n = 284)	57 (20.1)	31 (20.9)	20 (17.9)	6 (25.0)	0.678
PAH (n = 731)	79 (10.8)	43 (10.8)	25 (10.0)	11 (13.4)	0.682
Calcium-channel blockers (n = 729)	295 (40.5)	157 (39.4)	102 (40.8)	36 (44.4)	0.699
Phosphodiesterase type 5 inhibitor (n = 729)	155 (21.3)	85 (21.4)	55 (22.0)	15 (18.5)	0.800
Endothelin receptor antagonists (n = 729)	32 (4.4)	21 (5.3)	10 (4.0)	1 (1.2)	0.252
Prostanoids (n = 729)	26 (3.6)	14 (3.5)	6 (2.4)	6 (7.4)	0.107
ACE inhibitor or angiotensin receptor (n = 729)	122 (16.7)	64 (16.1)	47 (18.8)	11 (13.6)	0.481
Fluoxetine (n = 729)	105 (14.4)	61 (15.3)	33 (13.2)	11 (13.6)	0.736

* Values are the number (%) unless indicated otherwise. ACE = angiotensin-converting enzyme; dcSSc = diffuse cutaneous systemic sclerosis; DU = digital ulcer; IQR = interquartile range; lcSSc = limited cutaneous systemic sclerosis; PAH = pulmonary arterial hypertension; RP = Raynaud's phenomenon; SSc = systemic sclerosis.

Consistent with expected prevalence of disease manifestations, there was a significant burden of digital vasculopathy, including history of ulcers (38.9%), past gangrene (20.1%), and pulmonary arterial hypertension (10.8%). Approximately one-half (40.5%) of patients were currently prescribed treatment with calcium-channel blockers. Respondents also reported treatment with phosphodiesterase type 5 inhibitors (21.3%), angiotensin-converting enzyme inhibitor, and/or angiotensin receptor blocker (16.7%) or fluoxetine (14.4%). A minority of patients were prescribed vasoactive treatment with either endothelin receptor antagonists (4.4%) or prostanoids (3.6%). Treatments for SSc-RP were similar across disease subsets (Table 1).

Impact of RP and treatment. Patients were asked to indicate on ordinal scale their level of satisfaction with their current medications in relieving their RP symptoms (very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, and very dissatisfied). Only one-half (56.3%) of

Table 2. Perceived impact of current systemic sclerosis (SSc)–Raynaud's phenomenon (RP) treatment*

	All SSc	LcSSc	DcSSc	Overlap SSc	*P*
Are your RP symptoms being adequately controlled? (n = 739)	416 (56.3)	222 (55.5)	147 (57.6)	47 (56.0)	0.862
How satisfied are you that your current medications are relieving your RP symptoms? (n = 739)					
Very satisfied	101 (13.7)	54 (13.5)	31 (12.2)	16 (19.0)	0.584
Somewhat satisfied	228 (30.9)	121 (30.3)	80 (31.4)	27 (32.1)	–
Neither satisfied nor dissatisfied	253 (34.2)	139 (34.8)	87 (34.1)	27 (32.1)	–
Somewhat dissatisfied	77 (10.4)	41 (10.3)	32 (12.5)	4 (4.8)	–
Very dissatisfied	80 (10.8)	45 (11.3)	25 (9.8)	10 (11.9)	–

* Values are the number (%) unless indicated otherwise. DcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis.

Table 3. Reasons that would make patients (n = 718) with systemic sclerosis (SSc) consider starting a new treatment for Raynaud's phenomenon (RP)*

	All SSc	LcSSc	DcSSc	Overlap SSc	*P*
Hand function					
Inability to use fingers properly due to RP	502 (69.9)	276 (70.4)	174 (69.9)	52 (67.5)	0.881
Physical symptoms					
Worsening pain or discomfort from RP	461 (64.2)	257 (65.6)	161 (64.7)	43 (55.8)	0.262
More severe attacks	392 (54.6)	218 (55.6)	136 (54.6)	38 (49.4)	0.601
More frequent attacks	316 (44.0)	175 (44.6)	109 (43.8)	32 (41.6)	0.879
Worsening numbness from RP	278 (38.7)	156 (39.8)	100 (40.2)	22 (28.6)	0.153
Longer attacks	252 (35.1)	137 (34.9)	92 (36.9)	23 (29.9)	0.522
Fingers feeling colder	201 (28.0)	107 (27.3)	71 (28.5)	23 (29.9)	0.876
Worsening digital color changes from RP	189 (26.3)	98 (25.0)	74 (29.7)	17 (22.1)	0.280
Prevention of complications					
Develop an ulcer on ≥1 fingers	465 (64.8)	270 (68.9)	153 (61.4)	42 (54.5)	0.022
If it may help with internal organ problems	364 (50.7)	208 (53.1)	122 (49.0)	34 (44.2)	0.289
Develop new telangiectasia on fingers	146 (20.3)	82 (20.9)	56 (22.5)	8 (10.4)	0.064
Emotional impact					
Emotion effect of RP including annoyance, anger, frustration, and anxiety	173 (24.1)	91 (23.2)	67 (26.9)	15 (19.5)	0.343
Embarrassment and/or dissatisfaction with the appearance of fingers during attacks	100 (13.9)	45 (11.5)	42 (16.9)	13 (16.9)	0.116

* Values are the number (%) unless indicated otherwise. Grouping of items is based on previous qualitative research exploring the patient experience of RP (16,17). DcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis.

patients were satisfied that their RP symptoms were being adequately controlled. The perceived impact of current RP treatment is presented in Table 2. Patients were most likely to be either neither satisfied nor dissatisfied (34.2%) or somewhat satisfied (30.9%). Ten percent of patients were either very dissatisfied (10.8%) or somewhat dissatisfied (10.4%).

Reasons and relative ranking for starting a new RP treatment. Patients were asked to indicate all the reasons (of 13) that would make them consider starting a new treatment for RP (Table 3). The 5 highest ranked (Figure 1) reasons were as follows: 1) inability to use the fingers properly due to RP; 2) if they developed an ulcer on ≥1 fingers; 3) worsening pain or discomfort of RP; 4) more severe attacks; and 5) if it may help with internal problems.

Willingness to experience side effects. Patients were asked about their willingness to experience side effects if a treatment was effective for RP (Table 4). Patients were much more likely to accept minor versus severe side effects: headache (39.8% versus 2.1%), nausea (22.1% versus 2.1%), and light-headedness (28.1% versus 1.9%). Almost one-half (47.1%) of patients indicated that they would not be willing to experience any side effects from treatment.

Management strategies for RP. Patients were asked which management approaches they would consider if their RP symptoms were poorly controlled (Table 5). Approximately one-half of patients would either consider adding a new treatment to existing drug treatment (52.8%) or stopping existing treatment and starting a new treatment (40.9%). Approximately one-third of patients would either increase the dose of existing drug treatment (28.8%) or concentrate on non-drug approaches (29.7%).

Differences between SSc disease subsets. There was no significant difference in the impact or perceived benefit of current treatment for SSc-RP between disease subsets (Table 2). Patients with lcSSc ranked digital ulcers as the highest reason to change treatment for RP (Table 3). There were subtle differences in the lowest ranking reasons between disease subsets (Figure 1). There was no difference between SSc subsets in willingness to experience side effects (Table 4) or management approaches (Table 5).

DISCUSSION

To our knowledge, this is the first study to examine patients' beliefs and preferences about treatment escalation for SSc-RP, and it provides a number of novel insights that could be used to inform future treatment strategy guidelines. Our study highlights the potential reasons and relative ranking (importance) that would make patients consider starting a new treatment for RP. Inability to use the fingers properly due to RP was the highest ranking reason to start a new treatment for RP. Physical symptoms including pain and the severity of attacks of RP were considered central features of the lived patient experience of RP (17). Patients strongly indicated that treatment for RP should also seek to positively modify digital ulcer (ranked second) and internal organ-based (ranked fifth) complications of the disease. Although RP is associated with broad emotional impact including fear, anxiety, embarrassment, and dissatisfaction, such aspects were considered (relatively) to be less important drivers to change treatment.

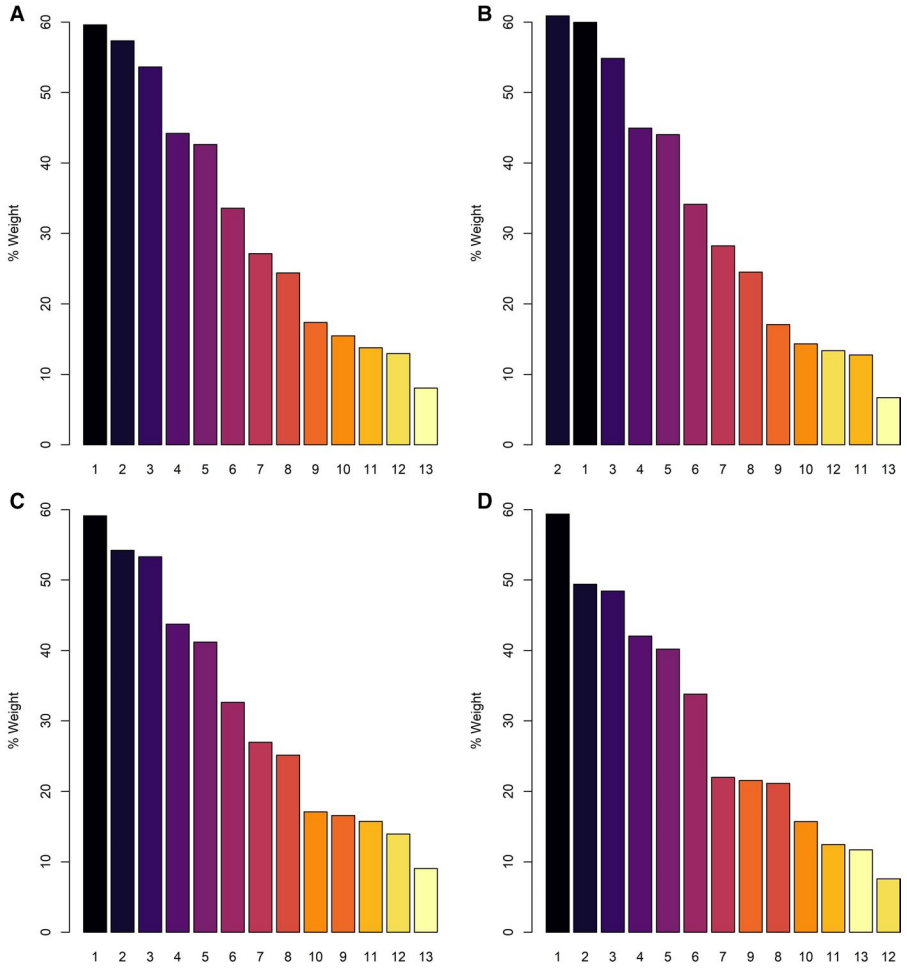

Figure 1. Ranked reasons why patients with systemic sclerosis (SSc) would consider starting a new treatment for Raynaud's phenomenon (RP) for all patients with SSc (**A**), those with limited cutaneous SSc (lcSSc) (**B**), those with diffuse cutaneous SSc (dcSSc) (**C**), and those with overlap SSc (**D**). 1 = inability to use fingers properly due to RP; 2 = develop an ulcer on ≥1 fingers; 3 = worsening pain or discomfort from RP; 4 = more severe attacks; 5 = if it may help with internal organ problems; 6 = more frequent attacks; 7 = worsening numbness from RP; 8 = longer attacks; 9 = fingers feeling colder; 10 = worsening digital color changes from RP; 11 = emotion effect from RP including annoyance, anger, frustration, and anxiety; 12 = develop new telangiectasia on fingers; 13 = embarrassment and/or dissatisfaction with the appearance of fingers during attacks.

Our data also further benchmark the lived burden of RP in patients with SSc and the need for effective treatments. Only one-half of patients reported that their RP symptoms were being adequately controlled. However, there is evidence of clear discordance between patients' expectations about the goals of treatment against their willingness to experience side effects. For example, approximately one-half of patients indicated that they would not be willing to accept any side effects with an effective treatment for RP. Furthermore, the magnitude (or severity) of side effects is considered to be of major importance to patients with SSc-RP.

Table 4. Patients' (n = 701) willingness to experience side effects if a treatment was effective for systemic sclerosis (SSc)–Raynaud's phenomenon*

	All SSc	LcSSc	DcSSc	Overlap SSc	*P*
Mild headache	279 (39.8)	146 (38.2)	100 (41.7)	33 (41.8)	0.654
Severe headache	15 (2.1)	10 (2.6)	4 (1.7)	1 (1.3)	0.618
Mild nausea	155 (22.1)	80 (20.9)	54 (22.5)	21 (26.6)	0.538
Severe nausea	15 (2.1)	10 (2.6)	5 (2.1)	0 (0.0)	0.342
Mild light-headedness	197 (28.1)	117 (30.6)	65 (27.1)	15 (19.0)	0.101
Severe light-headedness	13 (1.9)	10 (2.6)	3 (1.3)	0 (0.0)	0.275
None	330 (47.1)	183 (47.9)	109 (45.4)	38 (48.1)	0.817

* Values are the number (%) unless indicated otherwise. DcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis.

Table 5. Management approaches that patients (n = 701) with systemic sclerosis (SSc) would consider if their Raynaud's phenomenon symptoms were poorly controlled*

	All SSc	LcSSc	DcSSc	Overlap SSc	*P*
Add a new treatment to existing drug treatment	370 (52.8)	194 (50.8)	135 (56.3)	41 (51.9)	0.408
Increase the dose of existing drug treatment	202 (28.8)	120 (31.4)	66 (27.5)	16 (20.3)	0.118
Stop existing treatment and start a new treatment	287 (40.9)	146 (38.2)	109 (45.4)	32 (40.5)	0.206
Focus on non-drug approaches	208 (29.7)	122 (31.9)	62 (25.8)	24 (30.4)	0.265

* Values are the number (%) unless indicated otherwise. DcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis.

Patients were much more likely to be willing to experience minor (~20–40%) compared to severe (~2%) side effects (headache, nausea, and light-headedness).

Other novel findings were the lack of any impact of disease subsets on existing RP treatments and priorities for treatment escalation. However, patients with lcSSc indicated that the highest ranking reason to change treatment was for digital ulcer disease. Furthermore, there were some subtle changes in the ranking of the lowest ranking reasons between disease subsets. Irrespective of disease subset, there was significant unwillingness to accept side effects for an effective treatment for RP.

A key practical consideration relates to the paucity of existing evidence to inform management after treatment failure. Approximately one-half of patients would either consider substituting (52.8%) or adding in combination (40.9%) new drug therapy for RP, and one-third (28.8%) would increase the dose of current treatment. This is of interest because experts from the Scleroderma Clinical Trials Consortium and the Canadian Scleroderma Research Group, in general, propose an additive approach (with drugs used in combination) for the treatment of SSc-RP (9). One-third (29.7%) of patients also indicated that they are keen to consider nonpharmacologic approaches to management, although the evidence base to support these interventions at present are limited (18).

There was significant heterogeneity and ranking (of importance) of the reasons why patients would consider changing current treatment. SSc-RP clinical trials have previously focused on the frequency and duration of SSc-RP attacks as the primary trial end points. Intriguingly, in our study, attack frequency/duration was not prioritized by patients as factors that would lead them to consider treatment escalation. We observed impaired hand function (i.e., inability to use the hands properly due to RP) as the highest ranked factor that might prompt change of treatment. The Raynaud's Condition Score (RCS) is a validated outcome measure that assesses the level of difficultly due to RP and captures broader aspects of the patient experience including digital ulcers and numbness (19,20). However, concerns have been raised by experts in SSc-RP about the limitations of the RCS diary, which might impede on drug development programs (21). Ongoing collaborative international research is seeking to develop novel patient-reported outcome measures to assess the multifaceted impact and severity of digital vasculopathy in SSc, including RP (17,22–24). Future research should also examine noninvasive microvascular (e.g., structural and function) imaging to assess the impact of treatment on microangiopathy in SSc, in particular, in early phase studies of SSc-RP.

Consensus must be achieved with relevant stakeholders, including patients, about whether treatment escalation for SSc-RP should also seek to positively modify digital ulcer disease (occurrence and healing) and/or systemic vasculopathic complications. Another important aspect related to treatment must explore the concept of discrete attacks of RP. For example, in our previous study using the PASRAP, only 2% of patients (with primary and secondary RP) defined RP using the word 'attack' (16). Indeed, many patients with SSc have symptoms throughout the year, and it is uncertain whether relatively asymptomatic color change necessarily warrants treatment. Another major issue would likely relate to the impact of seasonal variation in environmental temperature and behavioral factors because these are associated with greater severity of SSc-RP (25,26). Patients with RP are increasingly using internet-based information to learn more about their condition, including approaches to treatment; however, the overall quality and readability is poor (26,27). Therefore, there is a need to develop disease-specific and accessible information to inform patient decision-making for SSc-RP (27,28).

A major strength of our study was the large number (~750) of patients with SSc who participated in the study. Another key strength is that missing responses were generally uncommon. Our survey population was based on anonymously self-reported information from patients with SSc and therefore was not amenable to confirmatory chart review, including diagnosis, subset, symptoms, and complications. However, the patient demographic information, clinical phenotype, and disease subsetting suggest that our cohort was representative of SSc based on previous registry analyses. For example, pulmonary arterial hypertension was reported to be present in ~10% of patients (29,30) and past digital ulcers in ~40% (approximately one-half of patients with SSc report a history of ulcers) (4,31,32). Past gangrene was reported by ~20–25% of patients, which is higher than previously reported. For example, in a study from the European Scleroderma Trials and Research Group database, which included 1,757 patients, 8.9% had current or previous digital gangrene (33). In our study, patients were

only asked about gangrene if they indicated that they had previously developed digital ulcers. Therefore, it could be expected that gangrene would be more common/overrepresented in patients with SSc and established digital vasculopathy (i.e., history of ulcers). Calcium-channel blockers were the most commonly indicated drug therapy, followed by phosphodiesterase type 5 inhibitors, which reflects current clinical practice (7,9). Although we prespecified the 13 reasons why patients may change treatment for RP, our previous qualitative research, including a recent study from the PASRAP, supports the choice of these reasons, including how patients define their RP (16,17).

In conclusion, our study provides a number of novel insights into patient's beliefs and preferences about treatment escalation for SSc-RP. These include the reasons (and relative ranking) why patients would change their current treatment and possible therapeutic strategies. Side effects significantly impact on acceptability of drug treatment for SSc-RP. Future research is required to optimize treatment for SSc-RP, including the need for decision analysis to help patients determine their preferences for management and to establish consensus as to whether such an approach should also seek to modify SSc-related digital and/or systemic vasculopathy.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Hughes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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