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Factors influencing patient decision-making concerning treatment escalation in Raynaud's phenomenon secondary to systemic sclerosis

Running head: Patient treatment preferences for RP in SSc

Original article

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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: SSc patients were invited to participate in an online survey disseminated through patient-led organisations and social media platforms.

Results: Responses from 747 people with self-reported SSc-RP were evaluable with broad international representation. The mean age (54.7years, SD 12.1), clinical phenotype and disease subsets distribution (limited [402/747, 53.8%], diffuse [260/747, 34.8%] and overlap disease, 85/747 [11.4%]) were consistent with expected demographics. Around half (56.3%) of patients reported their SSc-RP symptoms were adequately controlled. The 5 highest-ranked (out of 13) factors that would prompt treatment escalation for SSc-RP were; 1) inability to use the fingers properly 2) emergence of new digital ulcer (DU) on one or more fingers, 3) worsening pain or discomfort of Raynaud's, 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%) vs. 'severe' (2%) side effects. Patients were open to different management strategies for uncontrolled Raynaud's that included adding new treatment in combination to existing (52.8%), drug substitution (40.9%), increasing the current dose (28.8%), or focussing on non-pharmacological approaches (29.7%).

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

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Significance and innovations

- Hand function, physical symptoms, and preventing digital/internal complications influence patient decision-making in management of SSc-RP.
- Side effects significantly impact on acceptability of drug treatment for SSc-RP.
- Pharmacological and non-pharmacological approaches toward treatment escalation should be adopted for suboptimally controlled SSc-RP.

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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 ischaemia including digital ulcers and gangrene. In addition, generalised 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 upon *clinician-patient* discussions around 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].

Expert treatment recommendations for SSc-RP have been produced under the auspices of the British Society of Rheumatology, European League against Rheumatism, UK Scleroderma Study Group, and 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,

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including dosing strategies which could optimise 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 revolutionised 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 after treatment failure, and neither are the merits of different treatment approaches (e.g., initial combination vs. goal directed sequential monotherapy) considered. In addition, combination therapy is now considered a 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 our present 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) and overlap-SSc.

Materials 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, PASRAP was an international survey which 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 organisations (e.g., Scleroderma and Raynaud's UK and the Scleroderma Foundation). The survey consisted of a series of questions that

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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 as Supplementary Material. Participants (≥18 years old) were invited to complete 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 IRB with exempt status (Study ID: HUM00175143; OHRP IRB Registration Number(s): 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. Means and standard deviations were reported for continuous variables; counts and percentages were reported for categorical variables. When comparing SSc groups, we performed ANOVA test for continuous variables that followed normal distribution, Kruskal-Wallis test for continuous variables that did not follow normal distribution, and Chi-squared test or Fisher exact test for categorical variables. Percent of weight was calculated for different factors as: 1) for 13 factors for 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; 4) divide numerator (obtained weight) by denominator (sum weight) to get percent of weight (% weight).

Results

Patient demographics

PASRAP was completed by 1718 respondents between April to May 2020, of which 747 self-reported that their RP was secondary to SSc. Patient demographics including disease and treatment characteristics are presented in Table 1, including 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. Over half of patients reported living in the USA (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

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underlying condition (e.g., SSc). Patient reported median (IQR) RP and SSc-disease duration were 12 (5-24) and 7.0 (3-16) years, respectively. Consistent with expected prevalence of disease manifestations, there was a significant burden of digital vasculopathy including history of ulcers (38.9%) and past gangrene (20.1%) and pulmonary arterial hypertension (10.8%). Around half (40.5%) of patients were currently prescribed treatment with calcium channel blockers. Respondents also reported treatment with phosphodiesterase type-5 inhibitors (21.3%), ACE 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 their level of satisfaction with their current medications to relieve their Raynaud's symptoms on ordinal scale (very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied and very dissatisfied). Only half (56.3%) of patients were satisfied that their Raynaud's 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 to start a new RP treatment

Patients were asked to indicate all the reasons (out of 13) which would make them consider starting a new treatment for Raynaud's (Table 3). The 5 highest ranked (Figure 1) reasons were 1) inability to use the fingers properly due to RP, 2) if they developed an ulcer on one or more fingers, 3) worsening pain or discomfort of Raynaud's, 4) more severe attacks, and 5) if it may help with internal problems.

Willingness to experience side effects

Patients were asked their willingness to experience side effects if a treatment was effective for RP (Table 4). Patients were much more likely to accept 'minor' vs. 'severe' side effects: headache (39.8% vs. 2.1%), nausea (22.1% vs. 2.1%), and light-headedness (28.1% vs 1.9%).

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Almost 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 Raynaud's symptoms were poorly controlled (Table 5). Around half of patients would either consider adding in 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 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 provides a number of novel insights which could be used to inform future treatment strategy guidelines.

Our study highlights the potential reasons and relative ranking (importance) that would make patients would 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 Raynaud's were considered central features of the lived patient experience of RP [17]. Patients strongly indicated that they consider treatment for Raynaud's 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

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dissatisfaction, such aspects were considered (relatively) to be less important drivers to change treatment.

Our data also further benchmarks the lived burden of Raynaud's in patients with SSc and the need for effective treatments. Only half of patients reported that their Raynaud's 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, around half of patients indicated that they would not be willing to accept *any* side effects with an effective treatment for Raynaud's. Furthermore, the magnitude (or severity) of side effects is considered to be of major importance to patients with SSc-RP. Patients were more much more likely to be willing to experience 'minor' (~20-40%) compared to 'severe' (~2%) side (headache, nausea and light-headedness) effects.

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 Raynaud's.

A key practical consideration relates to the paucity of existing evidence to inform management after treatment failure. Around half of patients would either consider substituting (52.8%) or adding in combination (40.9%) new drug therapy for RP and a 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 non-pharmacological 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 previous focussed on

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the frequency and duration of SSc-RP 'attacks' as the primary trial endpoints. Intriguingly, in our study, attack frequency/duration was not prioritised 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 more 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 multi-facetted impact and severity of digital vasculopathy in SSc, including RP [17,22–24]. Future research should also examine non-invasive 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 Raynaud's. For example, in our previous study from PASRAP, only 2% of patients (with primary and secondary RP) defined RP using 'attack' [16]. Indeed, many patients with SSc have symptoms throughout the year, and it is uncertain whether relatively *asymptomatic* colour change necessarily warrants treatment. Another major issue would likely relate to the impact of seasonal variation in environmental temperature and behavioural 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) patients with SSc that participated in the study. Another key strength is that missing responses were generally

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uncommon. Our survey population was based upon anonymously self-reported information from SSc patients anonymously and therefore not amenable to confirmatory chart review including diagnosis, subset, symptoms, and complications. However, the patient demographics, clinical phenotype and disease-subsetting suggests our cohort was representative of SSc based on previous registry analyses. For example, pulmonary arterial hypertension was reported to be present in around 10% of patients [29,30] and with past DUs in ~40% (around 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 1757 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 DUs. 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 pre-specified the 13 reasons why patients may change treatment for RP, our previous qualitative research, including a recent study from PASRAP, supports the choice of these 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 optomise treatment for SSc-RP including the need for decision analysis to help patients determine their preferences for management and to establish consensus whether such an approach should also seek to modify SSc-related digital and/or systemic vasculopathy.

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	All SSc (n=747)	**LcSSc (n=402)**	**DcSSc (n=260)**	**Overlap-SSc (n=85)**	**P-value**
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%)	
USA	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	12.0	14.0	9.0	12.5	<0.001

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[IQR] years, n=746)	(5.0, 24.0)	(6.0, 27.0)	(4.0, 18.0)	(6.0, 28.5)	
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

Table 1: Patient demographics including disease and treatment characteristics.

		All SSc n=747	**LcSSc n=402**	**DcSSc n=260**	**Overlap-SSc n=85**	**P-value**
Are your Raynaud's symptoms being adequately controlled (n=739)		416 (56.3%)	222 (55.5%)	147 (57.6%)	47 (56.0%)	0.862
How	*Very*	101	54	31	16	0.584

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satisfied are you that your current medications are relieving your Raynaud's symptoms (n=739)	*satisfied*	(13.7%)	(13.5%)	(12.2%)	(19.0%)	
	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%)	

Table 2: Perceived impact of current SSc-RP treatment.

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	All SSc	**LcSSc**	**DcSSc**	**Overlap**	**P-value**

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	(n=747)	(n=402)	(n=260)	-SSc (n=85)	
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 of Raynaud's	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 of Raynaud's	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%)	0.521
Fingers feeling colder	201 (28.0%)	107 (27.3%)	71 (28.5%)	23 (29.9%)	0.876
Worsening digital color changes of Raynaud's	189 (26.3%)	98 (25.0%)	74 (29.7%)	17 (22.1%)	0.280
Prevention of compations					
Develop an ulcer on one or more 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

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Embarrassment/dissatisfaction with the appearance of fingers during attacks	100 (13.9%)	45 (11.5%)	42 (16.9%)	13 (16.9%)	0.116

Table 3. Reasons that would make patients with SSc consider starting a new treatment for Raynaud's. Grouping of items based on previous qualitative research exploring the patient experience of RP [16,17].

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	All SSc (n=747)	**LcSSc (n=402)**	**DcSSc (n=260)**	**Overlap - SSc (n=85)**	**P-value**
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

Table 4: Willingness to experience side effects if a treatment was effective for SSc-RP.

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	All SSc (n=747)	LcSSc (n=402)	DcSSc (n=260)	Overlap - SSc (n=85)	P-value
Adding in 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

Table 5. Management approaches that patients with SSc would consider if their Raynaud's symptoms were poorly controlled.

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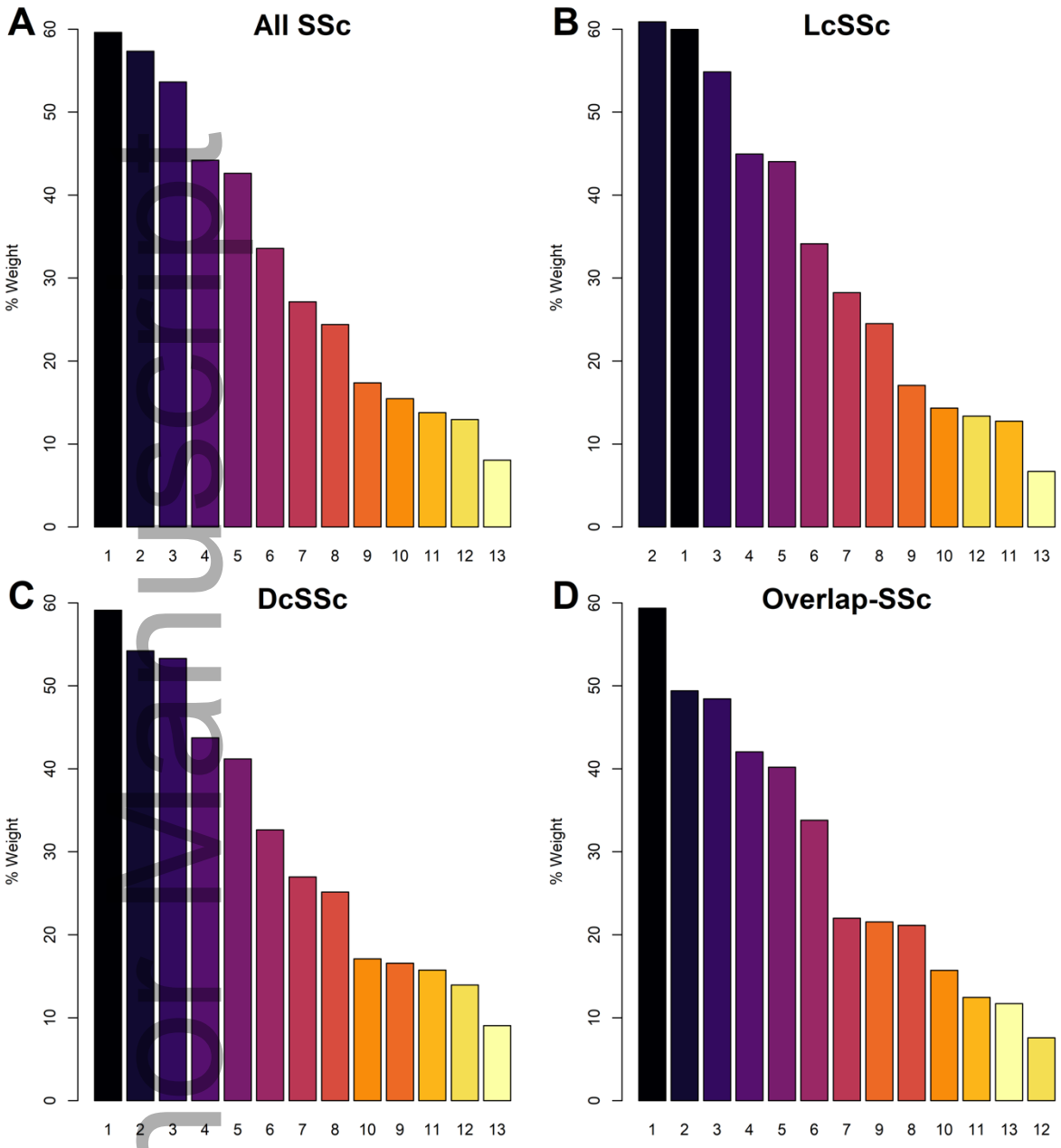

Figure 1. Reasons and ranking why patients with SSc would consider starting a new treatment for Raynaud's. All patients with SSc (A), limited (B) and diffuse (C) disease, and overlap-SSc (D). **1**. Inability to use fingers properly due to RP, **2**. Develop an ulcer on one or more fingers, **3**. Worsening pain or discomfort of Raynaud's, **4**. More severe attacks, **5**. If it may help with internal organ problems, **6**. More frequent attacks, **7**. Worsening numbness of Raynaud's, **8**. Longer attacks, **9**. Fingers feeling colder, **10**. Worsening digital colour changes of Raynaud's, **11**. Emotion effect of RP including annoyance, anger, frustration, and anxiety, **12**. Develop new telangiectasia on fingers, **13**. Embarrassment/dissatisfaction with

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the appearance of fingers during attacks.

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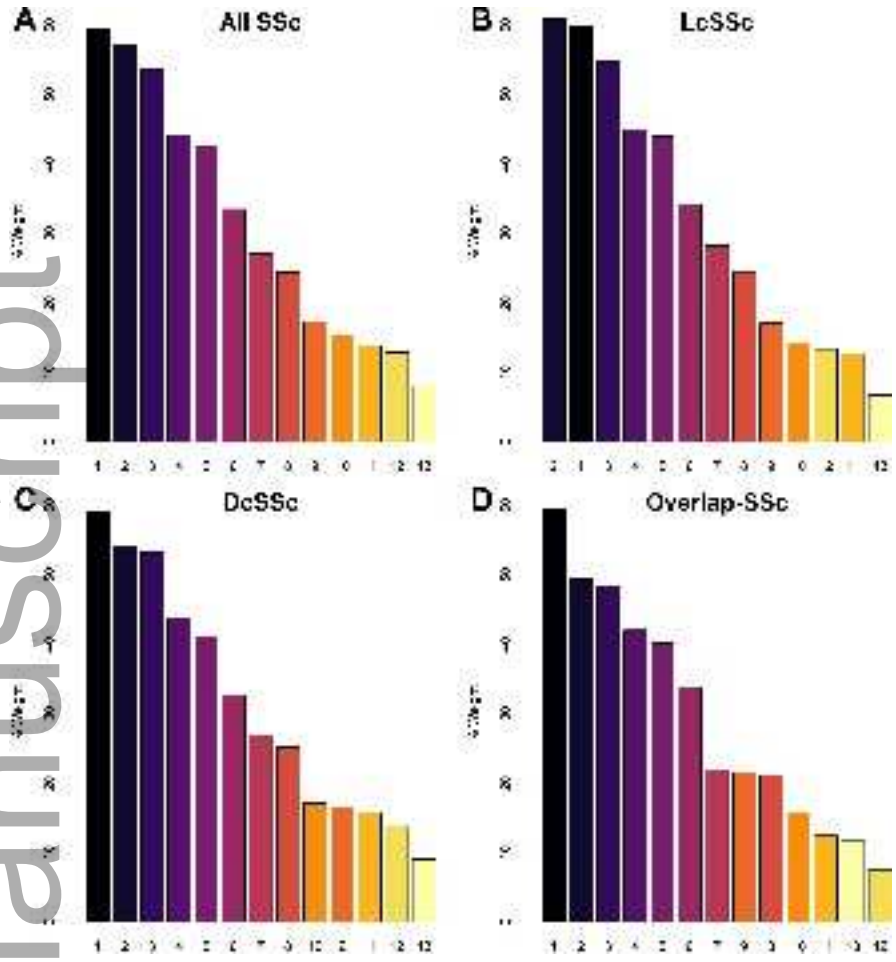

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