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Developing a core set of outcome measure domains to study Raynaud's phenomenon and digital ulcers in systemic sclerosis: Report from OMERACT 2020

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ABSTRACT

Raynaud's phenomenon (RP) and digital ulcers (DUs) are important disease manifestations of systemic sclerosis (SSc) that can lead to significant pain and disability. It is essential when studying these disease features to utilize outcome measures that fully evaluate the complexities of RP and DUs . The Outcome Measures in Rheumatology (OMERACT) Vascular Disease in SSc Working Group is applying the OMERACT filter 2.1 to identify a core set of disease domains that encompass the full burden of SSc-related RP and DUs. Progress to date and future research plans were presented during a Special Interest Group held in December 2020.

Introduction

Systemic sclerosis (SSc, scleroderma) is a chronic autoimmune rheumatic disease characterized by vasculopathy, inflammation, and fibrosis. Patients with SSc exhibit a spectrum of digital vasculopathy ranging from reversible attacks of Raynaud's phenomenon (RP) to permanent tissue loss (e.g. digital ulcers (DU) and gangrene). Although the pathogenesis of RP has yet to be fully elucidated, it is thought to represent an integration of vascular abnormalities, abnormalities in neural control of vascular tone, and imbalances of circulating factors [1]. Regardless of disease subtype, RP affects >96% of those with SSc [2] and is associated with significant impact on daily activities [3]. Moreover, half of patients with SSc report a history of DUs with a point prevalence of 5–10% [4]. DUs usually occur early (within the first 5 years) in the course of the disease and identify patients with a likely severe disease course [5], including internal organ involvement [6].

There is a paucity of data pertaining to standardizing outcome measures for SSc-related RP and DUs for use in clinical trials. Defining and assessing these manifestations in the context of research is quite challenging [7]. RP and DUs combine multiple pathophysiologic pathways and clinical manifestations yet display several different components relating to both feel and function. Consequently, patient and physician perspectives relating to real-world experiences of RP and DU may not completely align [8]. Thus, currently available outcome measures for describing RP and DU have noteworthy limitations including inter- and intra-rater variability [9] and may not fully capture the patient-experience of these disease manifestations.

Outcome Measures in Rheumatology (OMERACT) is an international group of investigators, patient research partners, and methodologists working to improve harmonization of data-driven outcome measure collection for rheumatologic conditions [10]. The OMERACT Vascular Disease in SSc Working Group is composed of patient representatives, clinical researchers, and health professionals with an interest in SSc seeking to establish a core set of disease domains for the study of SSc-related RP and DU. The Group's significant progress and proposed research plans were presented at a virtual OMERACT Special Interest Group meeting held in December 2020.

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Methods

Composition of the working group

The OMERACT Vascular Disease in SSc Working Group is comprised of 11 individuals from North America, Europe, and Australia: 2 patient representatives with SSc, and 9 health professionals and researchers. Team progress and goals are discussed at monthly virtual meetings.

Outline of research plans

The Working Group's overarching goal is to apply the OMERACT pathway for the development of a core domain set for future trials in SSc-related RP and DUs [11]. The proposed steps to achieving this are delineated in Fig. 1. Dedicated scoping reviews of the literature on outcome measures in SSc-related RP and DUs are underway, as is a summary of qualitative research in the field completed to date. These two steps will inform the selection of candidate domains which will then be prioritized through a consensus process informed by an international Delphi exercise that will include the relevant stakeholders: patients with SSc, and health professionals and researchers with a specific interest in SSc-related RP and DU [10,11]. Results of the Delphi will be analyzed by the Working Group and lead to formulation of a draft core domain set and list of core contextual factors, that will be presented for endorsement by the OMERACT community.

Progress to date

Comprehensive literature reviews exploring the patient experience of SSc digital vasculopathy

The complex patient experience of SSc-RP and SSc-DU has been explored through comprehensive literature reviews examining the lived experience of SSc-associated digital vasculopathy [12,13]. In each review a broad range of sources were critically appraised ranging from clinical trial data, qualitative research methods and observational studies reporting practice-based evidence. This work helped determine the topic guides developed for the subsequent qualitative research.

Mixed-methods research on the patient experience of SSc-related RP and DUs

Prospective qualitative research studies where undertaken utilizing focus groups of patients with SSc and analyzed using inductive thematic analysis [14–16]. Given the anticipated impact of geographic variation and ethnic diversity on the patient experience of SSc-RP, focus groups were conducted with patients with SSc (n = 40) enrolled from 3 English-speaking SSc units in varying climates in the UK and US (Bath, Pittsburgh, and New Orleans). In the expectation that the lived experience of SSc-DU was less strongly linked to climate and geographic variation, the focus groups for SSc-DU (n = 29 with history of DU) were based at UK sites, although both studies (RP and DU) applied a purposive sampling framework to ensure broad representation in terms of sex, ethnicity, disease duration, and disease sub-setting [14–16]. The planned Delphi exercise will further broaden patient participation in determining domains of importance in SSc-associated digital vasculoapthy (see below). Conceptual frameworks encapsulating the lived experience of SSc-RP and SSc-DU have been devised from this work (Fig. 2) and have revealed similarities and differences between the patient experiences of both SSc-RP and SSc-DUs.

Parallel cross-sectional studies to explore the patient experience of SSc-RP has reported that patients can identify different patterns of RP, which may relate to progression of the obliterative vasculopathy in SSc [17]. Coping strategies also influence patient perceptions of SSc-RP severity [18]. Patients can predict the development of new DUs, experience varying symptoms of ulcers changing with evolution and healing [19], and utilize rich narrative devices to describe their ulcer pain. [20] These findings are helping to broaden an understanding of the patient experience of SSc-associated digital vasculopathy and identify domains considered important by patients that may not be captured with existing outcome measures.

Scoping literature reviews to determine domains of SSc-RP and SSc-DU

Parallel scoping literature reviews pertaining to SSc-related RP and DU are underway. The aim of these reviews is to evaluate the domains of illness studied, and the range of outcome measures used, in clinical studies of RP and DUs in patients with SSc. Search strategies were developed, and reference search performed in February 2020. Abstract, full-text screening and data extraction were performed by two authors (NM, MH). Evidence will be described and synthesized to inform the eventual next steps delineated in the working group's research plan.

Planned Delphi exercise

Identification of candidate domains of illness for the study of SSc-related RP and DUs will be ascertained through careful analysis of the

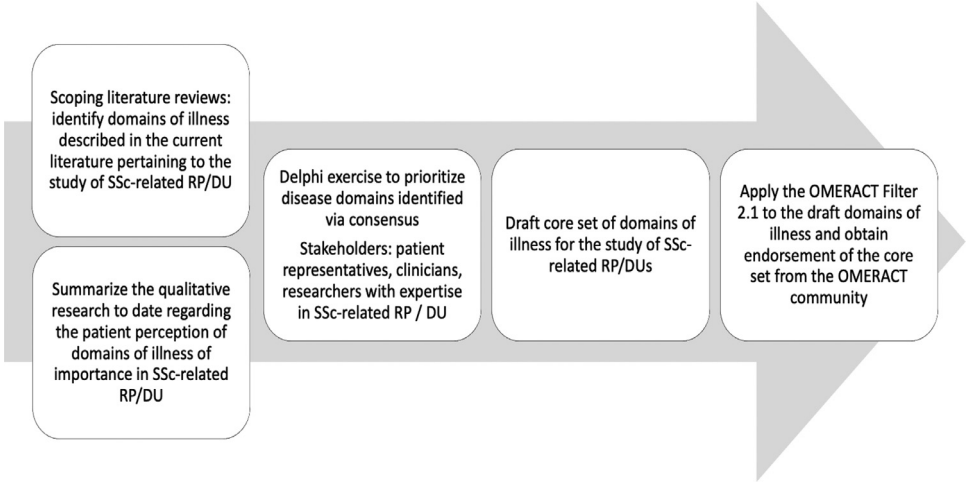

Fig. 1. Outline of OMERACT Vascular Disease in Systemic Sclerosis Working Group research plan. The Group's ultimate goal is the development of core domain sets for systemic sclerosis (SSc)-related Raynaud's phenomenon (RP) and digital ulcers (DUs).

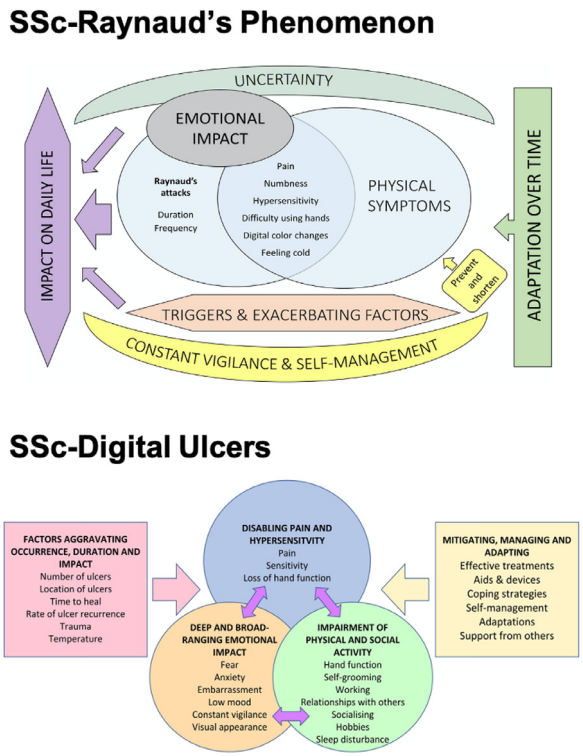

Fig. 2. Conceptual maps comprising the major inter-related themes and subthemes that constitute the patient experience of systemic sclerosis (SSc)-related Raynaud's phenomenon (RP) and digital ulcers (DUs) [14,15]. There is significant overlap between RP and DUs, including physical symptoms, in particular, pain which is a cardinal feature of both. There are broad-ranging psychological and functional impacts and patients live with great fear and uncertainty and adapt over time by using a number of mitigating strategies. Reproduced with permission from Pauling et al. [14] and Hughes et al. [15] (Full documentation of authorisation available on request).

results of the above-described scoping literature reviews and qualitative patient research completed to date. Key domains will be identified through consensus. These candidate domains will then be evaluated through a Delphi exercise, expected to involve 3 rounds of questionnaires, and include as participants patient representatives, and health professionals and researchers with experience in the field of SSc-related RP and DU. Recognizing the need to explore and approach SSc across a range of populations, and to assure more comprehensive input, the Delphi will involve participants from many countries on several continents. It is anticipated that the Delphi exercise will facilitate achieving a high level of consensus among participants about the major domains to study in RP and DUs.

OMERACT 2020 special interest group

A virtual Special Interest Group was held in December 2020 with the goal of obtaining viewpoints from key stakeholders regarding the Working Group's progress to date and future research plan. In addition to the members of the Working Group, 60 participants (listed in the Acknowledgements) contributed to the discussion and polls, including patients, clinicians, investigators, and methodologists. A summary of the Working Group's progress and next steps was presented.

During the OMERACT session several important issues and questions were brought forward for discussion in addition to poll questions which were answered virtually and anonymously. Firstly, 38/50 (76%) participants agreed with only inviting individuals with a specific interest, experience, and expertise in SSc-related RP and DU for the proposed Delphi exercise. Nonetheless, it was suggested that methodologists with experience in developing outcome measures be included in the Delphi exercise, given the challenge in discerning differences in domains and their associated instruments. Given the complexity of the overall constellation of factors at play, the key importance of assuring a patient-centered approach was highlighted.

In addition, participants recognized the importance of studying RP and DUs separately, despite broad recognition that these disease manifestations are linked both clinically and pathophysiologically. Highlighting this, the Working Group's patient representatives described that in their own experience, they are able to separately distinguish between the pain and disability arising from both RP and DUs. Participants acknowledged that for convenience and practicality, SSc-related RP and DUs have often been studied concurrently with similar outcome measures. The majority (41/44) of session participants agreed with the Working Group's plan to study these vascular manifestations in parallel. The challenge of developing more objective outcome measures for RP and DUs was also discussed. For example, many participants suggested exercising some caution when applying non-invasive outcome measures, in particular, pertaining to perfusion, as there is currently limited understanding in how these reflect the patient experience.

In summary, the discussion points and poll questions were quite helpful in directing the Working Group's future research plan and next steps.

Discussion

The OMERACT Vascular Disease in SSc Working Group's proposed research plan is well underway with significant progress made to date. Following OMERACT methodology[10], the group is working towards drafting a core domain set for SSc-related RP and DU that incorporates all important aspects of disease burden. Given the complex pathophysiologic and clinical interplay between these disease manifestations, the group has opted to perform parallel studies and analyses for RP and DUs. In addition to recent qualitative research completed exploring the multi-faceted patient experience of SSc-RP and DUs, scoping literature reviews will further inform the group's next steps, including achieving consensus through the planned Delphi exercise and subsequent OMERACT endorsement through voting on core domain sets for both SSc-RP and DU (provisionally scheduled for 2022). The Working Group is strongly encouraged by the positive and valuable feedback obtained during the Special Interest Group held in December 2020.

Conclusion

RP and DUs are salient manifestations of SSc. The OMERACT Vascular Disease in SSc Working Group aims to develop a core set of domains for SSc-related RP and DUs that captures the full burden of these disease manifestations.

Declaration of Competing Interest

Dr Hughes reports speaking fees from Actelion Pharmaceuticals, Eli Lilly and Pfizer, outside of the submitted work.

Dr. Pauling reports grants and personal fees from Janssen, outside the submitted work; Dr Pauling reports personal fees from Boehringer Ingelheim, Sojournix Pharma and Permeatus, Inc.

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