Treatment Recommendations for the Systemic Pharmacological Treatment of Systemic Sclerosis Digital Ulcers: results from the World Scleroderma Foundation (WSF) Ad Hoc Committee

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Abstract

Introduction

Digital ulcers (DU) are an important disease manifestation of systemic sclerosis (SSc) and are associated with significant morbidity. As such, there is an urgent need for the development of evidence-based recommendations to guide clinicians in the treatment of DU.

Methods

A steering committee of international experts was established. A systematic review of the literature pertaining to the use of pharmacologic treatments in the management of DU was performed to inform the development of treatment recommendations for SSc-DU. Consensus methodology was used to develop the final treatment recommendations.

Results

The World Scleroderma Foundation (WSF) committee agreed on eight overarching treatment principles and ten pharmacologic treatment recommendations for the management of SSc DU. Phosphodiesterase 5 inhibitors and intravenous iloprost were recommended for the management of acute DU. Bosentan was recommended for prevention of DU.

Conclusion

This study has yielded pragmatic treatment recommendations to direct treatment decisions for the management of SSc-DU. Additionally, results have highlighted areas in need of future research in order to improve patient outcomes.

Word count = 3334

Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease with prominent features of small vessel vasculopathy, which commonly presents with digital ulcers (DUs). [1] Half of patients with SSc will have a DU,[2, 3] with the risk DUs increased in patients with diffuse cutaneous SSc, anti-topoisomerase I antibody positivity, younger age at disease onset and severe respiratory involvement.[4, 5] A pattern of recurrent DUs is commonly observed, with an estimated 11% of patients having chronic SSc-DUs, defined as at least one ulcer each year.[2, 4] Patients with chronic SSc-DUs suffer from frequent serious infection including gangrene, higher rates of hospitalisation, and 16% of patients with chronic SSc-DUs will experience digital amputation.[2] The economic costs of SSc-DU are high, including reduced workforce participation,[5] and a history of SSc-DU is associated with a more severe overall disease course and poorer survival.[4]

Given the high prevalence and severe impact of SSc-DUs, systematic application of effective therapies is of critical importance. There are many potential treatment approaches to SSc-DU. Topical pharmacological therapies and dressings, surgical strategies including the debridement of ulcers, use of botulinum toxin injections or adipose tissue grafting in addition to systemic pharmacological treatments are all used in clinical practice or have been trialled to treat SSc-DU.[6-10] In an era of increasing access to multiple SSc-DU therapies and varying treatment strategies, clear guidance to physicians regarding the management of this complex disease manifestation is required. One of the objectives of the World Scleroderma Foundation (WSF) Digital Ulcer Ad Hoc Committee was to develop practical recommendations relating to the treatment of SSc-DU. These recommendations, supported by up-to-date clinical evidence and expert opinion, are designed to offer a pragmatic treatment strategy and a standardised approach to the clinical management of SSc-DU. Presented here are the WSF recommendations for the systemic pharmacological treatment of SSc-DU. Recommendations regarding local therapies will be presented elsewhere.

Methods

Research participants

A project steering committee of internationally recognised experts in the field of SSc (MH, YA, CPD, OD, TF, DEF, DK, TK, MK, MMC, JP) was established to identify the overarching research goals and select research questions to underpin the scope of the recommendations. A dedicated systemic pharmacologic treatment working group (MB, LC, NM, LR) was established to perform a systematic literature review of the systemic pharmacological treatments of SSc-DU. This group was responsible for the summary and presentation of results to the steering committee. Methodological guidance and development of the final search strategy for the systematic literature review was provided by an expert methodologist (AA) and senior medical librarian (JWS). There was no involvement of third parties in the development of these recommendations.

Systematic literature review

A systematic literature review was performed to ascertain the current level of evidence for systemic pharmacological treatment of SSc-DU. [11] The steering committee agreed that data pertaining to the efficacy of systemic pharmacological treatments, descriptions of treatment regimens and dosing of treatments, international variation in treatment practices and the safety and cost effectiveness of treatments should be extracted to inform the development of the treatment recommendations.

Recommendations

Using the results of the systematic literature review, a summary of evidence for each of the identified systemic pharmacologic treatments for SSc-DU were developed by NM and LR and treatment recommendations were drafted. The level of evidence supporting each recommendation was defined according to the indications of the Centre for Evidence-Based Medicine (http://www.cebm.net); Level 1: systematic review of randomised controlled trial

(RCT), individual RCT (high quality); Level 2: systematic review of cohort studies, individual cohort study (including low quality RCT); Level 3: systematic review of case-control studies, individual case-control study; Level 4: case series, poor quality cohort and case-control study; Level 5: expert opinion without critical appraisal. [12]

Draft recommendations were presented to the steering committee and discussed at an online consensus meeting. A subsequent draft of systemic pharmacological treatment recommendations, that incorporated the feedback from the consensus meeting, was distributed via email and final consensus was reached via an iterative process of feedback from steering committee members. A survey of the 16 Digital Ulcer Ad Hoc Committee members was performed to assess the level of agreement with the proposed recommendation statements, using the REDCap electronic data capture tools hosted at The University of Melbourne. Participants were asked to rate their level of agreement with each of the recommendation statements on a numerical rating scale from 1 (strongly disagree) to 9 (strongly agree). The level of agreement for each statement is presented as the mean (with standard deviation) score.

Results

Systematic literature review

The results of the systematic literature review have been previously published.[10] In summary, 1,507 citations were screened with 140 reports undergoing full text review with 47 articles included in the final review. Data pertaining to efficacy of systemic pharmacological therapies for management of acute digital ulcers and prevention of future digital ulcers were available and have been summarised elsewhere.[10] Owing to limitations of the data available, it was not possible to describe any geographic variation in SSc-DU management practices or evaluate the cost effectiveness or relative efficacy of various treatment strategies or dosing regimens. Clinical trials of SSc-DU were marked by significant heterogeneity in patient selection, study methodology and use of background vasoactive treatments.

Treatment recommendations

We developed eight overarching treatment principles (Table 1) and ten treatment recommendations (Table 2) for the systemic pharmacological management of SSc-DU. The final recommendations were grouped as treatments for active DU and treatments for prevention of DU. Fourteen (97.5%) complete survey responses were received to calculate the level of agreement with each of the treatment recommendations.

(1) Phosphodiesterase 5 inhibitors (PDE5i) are recommended for the management of digital ulcers. (LoE 2,3)

Results from one RCT and one crossover study demonstrated that PDE5i treatment leads to accelerated healing of DU. [13-15] Three observational studies [16-18] at moderate risk of bias (RoB) showed efficacy of PDE5i in the treatment of acute DU. PDE5i were generally well tolerated by study participants with a favourable risk-benefit profile.

Despite the moderate quality of evidence supporting use of sildenafil, and the frequent use of other vasoactive agents in clinical studies of PDE5i potentially biasing these results, the steering committee deemed it appropriate to recommend the use of PDE5i for management of SSc-DU.

(2) Intravenous (IV) iloprost is conditionally recommended for the management of digital ulcers. (LoE 2-3)

Two RCTs evaluated the efficacy of IV iloprost for management of Raynaud's phenomenon and assessed the treatment efficacy for SSc-DU as a secondary endpoint [19, 20], suggesting improved healing of DU with IV iloprost. Observational data suggests improvement in DU healing with use of IV iloprost. Therefore, in the absence of RCTs of iloprost assessing DUs as a primary endpoint, the expert committee conditionally recommend the use of IV iloprost for the management of acute DU.

(3) Atorvastatin may be considered for the treatment of digital ulcers (LoE 2)

Atorvastatin may be considered an additional therapeutic approach for SSc-DU based on the results of one small RCT, including DU data as a secondary endpoint.[21] However, owing to the paucity of other data, there is insufficient evidence to support the use of atorvastatin as an alternative to vasodilator therapy.

(4) Endothelin receptor antagonists are not recommended in the management of acute digital ulcers. (LoE 2)

Evidence from RCTs indicates that endothelin receptor antagonists are not associated with accelerated healing of acute DUs. [22-24] Therefore, the Ad Hoc Committee supports a recommendation against the use of endothelin receptor antagonists in the treatment of acute SSc-DU.

(5) There is insufficient evidence to recommend in favour or against calcium channel antagonists, immunosuppression, plasmapheresis, N-acetylcysteine and ketanserin, for the treatment of digital ulcers. (LoE 3-4).

The efficacy of nifedipine has been prospectively evaluated in two studies of a total of 13 patients, published in the 1980s.[25, 26] Given the limited data available to assess the efficacy of calcium channel antagonists, no robust conclusions could be drawn about the use of this class of medication. There is insufficient data to draw any conclusions regarding the efficacy of oral prostacyclin analogues such as Treprostinil, beraprost or selexipag in the prevention of SSc-DU. [27-29] Other compounds have been explored in small observational studies at high RoB. [30-35] Conclusions about the efficacy or otherwise of these other agents cannot be made due to the limitations of available evidence.

(6) There is no evidence to support the use of antiplatelet agents in the treatment of digital ulcers, with one study suggesting worsening of digital ulcers with use of clopidogrel. (LoE 2-3)

No data shows treatment efficacy of anti-platelet agents in the treatment of SSc-DU and one study suggested a worsening of DU with the use of clopidogrel. [36, 37] Therefore the steering

committee agreed there is no evidence to support the use of antiplatelet agents in the management of SSc-DU.

Prevention of SSc-DU

(1) Bosentan is recommended for the prevention of future digital ulcers. There is no evidence to support other endothelin receptor antagonists for the prevention of digital ulcers. (LoE 2)

Two RCTs have demonstrated effective prevention of new SSc-DU associated with the use of bosentan. Conversely, two RCTs showed that macitentan did not prevent the occurrence of new SSc-DU. Bosentan was generally well tolerated in both RCTs and in other observational studies with a favourable risk profile. [22, 24, 30]

Despite the moderate quality of evidence supporting use of bosentan, and the frequent concurrent use of other vasoactive agents reported in studies of ERA treatments potentially biasing results, the steering committee deemed it appropriate to recommend the use of bosentan for patients with recurrent DU.

(2) IV iloprost is conditionally recommended for the prevention of future digital ulcers. (LoE 2-3)

Data from one RCT at moderate RoB suggested use of IV iloprost reduces the number of future DU, with SSc-DU data collected as a secondary outcome. [19] This recommendation can only be conditionally made as there is no study of IV iloprost with SSc-DU as primary endpoint, limiting the robustness of the evidence supporting the use of IV iloprost as a preventative treatment of SSc-DU.

(3) PDE5i are conditionally recommended for the prevention of future digital ulcers. (LoE 2-3)

Two RCTs with a small sample size at moderate RoB and observational data suggests that PDE5i may be effective in reducing the number of future SSc-DU. [14-17] Therefore, the steering committee conditionally recommend the use of PDE5i to prevent future SSc-DU.

(4) There is insufficient evidence to recommend in favour or against calcium channel antagonists, and oral prostacyclin analogues for the prevention of digital ulcers. (LoE 2,3)

There are no large studies that assess the efficacy of calcium channel antagonists as a treatment for SSc-DU, meaning no recommendation either in favour or against use of these compounds can be made. [11] There is insufficient data to draw any conclusions regarding the efficacy of oral prostacyclin analogues such as treprostinil, beraprost or selexipag in the prevention of SSc-DU. [27-29]

Discussion

In SSc, DU are an important manifestation associated with significant morbidity.[5] As the treatment armamentarium expands, there is a need for practical recommendations to guide treatment decisions.[38] This report summarizes expert opinion and available literature and has established ten recommendations pertaining to the systemic pharmacological treatment and prevention of DU in SSc. In addition to systemic therapy, this committee recommends local therapy as part of the treatment strategy for all SSc-DUs. These recommendations are designed to complement recently published recommendations for local treatments strategies for SSc-DU.

The development of these treatment recommendations has highlighted a number of areas in need of further study to clarify the optimal treatment approach to SSc-DU. Future research should focus on whether a class effect from use of PDE5i is observed, or whether only sildenafil has efficacy in the management of SSc-DU. Although the above recommendations imply a benefit of PDE5i as a pharmacologic class in the management of DU, we note that the evidence supporting sildenafil specifically is more robust. [13, 14] Tadalafil has only been applied in a Raynaud's phenomenon study where DU outcomes were collected as a secondary outcome.[15] Comparable effects of bosentan and macitentan have not been observed in previous RCTs suggesting no class effect from the use of ERAs.[17-19] Therefore, it will be important to more robustly assess the efficacy of tadalafil as a treatment for SSc-DU. There is

no evidence to support the efficacy of oral prostacyclin analogues in the treatment of DU. Three RCTs evaluated the use of oral prostacyclin analogues. There was no improvement in DU burden demonstrated with the use of treprostinil, beraprost or selexipag. [27-29] Additional important areas of future research include the role of combination systemic pharmacological therapy and more rigorous assessment of the role of non-pharmacologic therapies, both in isolation and in combination with systemic pharmacologic therapy.

There are few studies investigating the use of immunosuppression in the treatment of DU. One case report described improvement of DUs in a patient that received rituximab. [30] In a small case series exploring the effect of treatment with cyclosporin, one patient experienced healing of DU.[31] However, the use immunosuppressants must be carefully balanced with the risk of infection, including osteomyelitis.[39, 40] Our previous systematic literature review [11] included a post-hoc analysis of the Scleroderma Lung Study which found no improvement in SSc-DU outcomes for those participants treated with oral cyclophosphamide. [41] A pilot study (n=66) comparing the use of tofacitinib to methotrexate for skin disease suggested a greater improvement in SSc-DU healing in the tofacitinib arm compared to methotrexate.[33] However, this small study was not powered to assess treatment effect on SSc-DU, therefore, it is not possible to make any treatment recommendation either in favour or against tofacitinib for the treatment of SSc-DU. Based upon current knowledge, there is no conclusive evidence that use of immunosuppressive agents are effective in the treatment of acute DU or prevention of future DU.

Since the publication of our systematic literature review, there have been further studies evaluating systemic pharmacological treatments in large SSc cohorts. A validation study of a prognostic prediction model (DU-VASC) analysed data from the European Scleroderma Trials and Research group registry and suggested that the use of antiplatelet agents is associated with less frequent DU.[42] Calcium channel antagonist use was not associated with a reduction in future risk of SSc-DU in the Australian Scleroderma Cohort Study.[43] Both of these studies report notable findings for consideration in the treatment of SSc-DU, however they were not

included in our previous publication as they were retrospective analyses of data and therefore did not meet the review inclusion criteria.[10] Additionally, caution needs to be applied when making conclusions about treatment efficacy using observational data owing to the high risk of selection and information bias, measurement error and confounding associated with cohort studies.

The European Alliance of Associations for Rheumatology (EULAR) published updated recommendations for the treatment of SSc in 2024.[44] EULAR recommendations were made on the basis of evidence from RCTs only and included recommendations for the treatment of acute SSc-DU with PDE5i and, or IV iloprost. Bosentan was recommended for the prevention of future new DU.[44] Whilst there are many similarities in the both the EULAR and WSF SSc-DU treatment recommendations, the WSF recommendations represent a more cautious interpretation of findings recommending the use of IV iloprost. This was felt appropriate because the data supporting the use of IV iloprost is derived from secondary endpoint data of Raynaud's phenomenon clinical trials and therefore these studies were not adequately powered to assess DU outcomes. These guidelines make a conditional recommendation for the use of atorvastatin based on the result of one RCT. However, the low level of agreement with this recommendation acknowledges that the use of statins for management of SSc-DU requires further study before stronger recommendations either in favour of, or recommending against, the use of statins can be made. These treatment recommendations include guidance based on expert opinion intentionally, as it is recognised there remain significant knowledge gaps about important aspects of SSc-DU treatment.[10] Hence, these guidelines include an expert opinion recommendation for the use of systemic pharmacological treatment in combination with local therapy and wound care. Our proposed treatment recommendations build on the EULAR guidelines by offering a detailed summary that incorporates data from observational studies, while also highlighting the need for targeted research to develop more effective treatments for SSc-DU.

One goal of the WSF Digital Ulcer Ad Hoc Committee was to evaluate the treatment costs associated with SSc-DU. It was not possible to achieve this aim as there has not been a formal health economic assessment of any specific SSc-DU management strategy. A study from Australia showed that patients with SSc-DU have a higher healthcare utilisation and increased direct health costs compared to SSc patients without DU.[5] However cost effectiveness analysis of individual therapies has not been performed and it is yet to be shown that use of systemic pharmacological therapies, some of which are high-cost medications or require admission to hospital for administration, is associated with a reduction in health care costs. Similarly, we were unable to determine any geographic variation in treatment practices given the lack of studies comparing treatment regimens between various regions around the world.

The development of these treatment recommendations is not without limitations. The results of this consensus process must be interpreted with consideration of the methodological limitations of the studies used to inform these recommendations. SSc-DU studies are generally constrained by heterogeneous DU classification and definitions, variability in participant baseline characteristics and the lack of standardised outcome measures to assess treatment effect. Furthermore, the concomitant use of other vasodilator therapy, local wound care and baseline DU severity is often not accounted for in studies of SSc-DU. Several studies failed to meet the *a priori* defined primary endpoint, and DU data have been extracted from the reporting of secondary RCT outcomes. Additionally, RCTs are characterised by short follow-up times, whereas observational studies suggest that improvement in SSc-DU can only be observed over a period of many months. Any RCT completed over a 12 or 16 week follow up period might well be unable to detect significant improvement from a given intervention due to an inadequate duration of follow up. Therefore, the evidence upon which any group can make treatment recommendations for management of SSc-DU is limited.

These recommendations for pharmacological management strategies should be used as a guide based on physician opinion only. The broad-ranging multidisciplinary expertise of the WSF Digital Ulcer Ad Hoc Committee was sought to inform the development of these

recommendations. Whilst consideration was given to geographic representation to ensure a breadth of clinical perspectives in the formation of this committee, it is a potential limitation of these recommendations that the broader perspectives of the SSc community were not included. A larger consensus-building exercise was outside the scope of this project but remain an important consideration for the development of treatment recommendations/updates in the future, when higher quality evidence is available.

Additionally, there was no patient-research partner involvement in the development of the systematic literature research questions, or the assessment of the final treatment principles and recommendations. Any future treatment recommendations should include patient perspectives to ensure the acceptability of recommendations to patients as well as to ensure that treatments address the aspects of SSc-DU management that are of importance to patients. The patient experience of SSc-DU includes disabling pain, impaired physical and social activity and significant daily adaptation to mitigate symptoms and manage the impact of SSc-DUs.[45] These important aspects of SSc-DU management were not explicitly addressed in these recommendations. We have previously reported that effect of systemic pharmacological treatment on patient-reported outcomes is only variably reported in clinical trials of systemic pharmacological therapy, with little data supporting improvement in patient symptoms with any of the recommended systemic pharmacological therapies.[10] Robustly designed, Interventional studies are required to investigate the efficacy of treatments to alleviate SSc-DU symptom burden so as future treatment recommendations can better address patients' priorities for the management of SSc.

Conclusion

The proposed recommendations reflect current available evidence and international expert opinion pertaining to the management of SSc-DU. These recommendations are designed to help guide clinicians in the treatment of this important and often difficult to treat disease manifestation of SSc.

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