# Worldwide expert agreement on updated recommendations for the treatment of systemic sclerosis

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**Running head:** recommendation-agreement in systemic sclerosis

**ABSTRACT**

Objectives. To evaluate agreement of the updated EULAR/EUSTAR recommendations for treatment of systemic sclerosis (SSc) among international experts. To determine factors that might influence agreement.

Methods. Level of agreement (10-point scale: 0=not at all, 10=completely agree) and local drug availability (yes/no) were assessed using an online survey. The weblink to the survey was shared with 481 unique email addresses and SSc networks (SCTC, ASIG, INSYNC). Level of agreement was compared between subgroups stratified for participant characteristics.

Results. In total 263 experts participated, of whom n=209 (79%) completed each single item. The majority were rheumatologists (n=200, 76%), working in Europe (n=185; 71%); 59% (n=156) were EUSTAR member, and 57% (n = 151) had > 10 years of clinical experience.

Overall level of agreement was high (mean 8.0; [SD, 2.5]). Top three highest mean agreement included: 1. ACE-inhibitors for scleroderma renal crisis (9.2[ 2.1]), 2. blood pressure control in SSc-patients treated with corticosteroids (9.0 [2.2]), 3. proton pump inhibitors to prevent reflux complications (9.0[2.2]); top three of lowest mean agreements included: 1. fluoxetine for Raynaud's phenomenon (RP) (4.6[ 2.8]), 2.hematopoietic stem cell transplantation (HSCT) for severe SSc (7.1[2.9]), 3. phosphodiesterase inhibitors-5 for RP (7.3 [2.7]). Agreement differed between Europe and non-Europe for the use of iloprost, bosentan, methotrexate, HSCT and cyclophosphamide. Treatment availability could partially explain differential agreement for iloprost, bosentan and HSCT.

Conclusions. In general, worldwide expert agreement on updated recommendations for treatment of SSc is high, supporting their value. Differences in agreement are partially explained by geographical area and treatment availability.

**INTRODUCTION**

In Systemic sclerosis (SSc), the complex pathophysiology and multiple organ involvement urge in most cases multidisciplinary therapeutic approach. Therefore, and due the disease heterogeneity, the physician needs a clear guidance in the choice of those drugs that are supported by the best clinical evidence and that may be used in practice. (1, 2)

The European League Against Rheumatism (EULAR) and European Scleroderma Trials and Research group (EUSTAR) have updated their recommendations on SSc treatment. (3) When compared to previous recommendations, the vascular area has been expanded including phosphodiesterase inhibitors-5 (PDE-5) inhibitors for the treatment of SSc-related Raynaud's phenomenon (RP) and digital ulcers (DU), and riociguat for the treatment of pulmonary arterial hypertension (PAH). Also in this area, the recommendations for the use of endothelin receptor antagonists (ERA), prostanoids and PDE-5 inhibitors for SSc-related PAH have been defined more precisely. In the area of systemic treatment, hematopoietic stem cell transplantation (HSCT) is proposed for patients with a rapidly progressive SSc course. (3, 4)

There is a great interest in how and to what extent these guidelines are considered to be useful and applicable in every day clinical practice. (5) Apart from newly added recommendations, clinical experience with regards to the drugs also highlighted in the previous set of recommendations has increased, which may have changed their perception by the physician. (6, 7)

In general, it has been shown that guidelines are not always followed for different reasons: lack of awareness, lack of familiarity, lack of agreement, outcome expectancy, and inertia towards changing previous practice. (5, 8, 9) Years of clinical experience, especially in a

narrow area of specialization, and lack of medical resources have also been suggested (1) as possibly influencing guidelines/recommendations application. Previous evaluation of agreement on the 2009 EULAR/EUSTAR recommendations on SSc treatment among 66 experts in the field showed that agreement, although in general high, differed significantly between areas. (10) Specifically, among experts from North America the agreement on iloprost treatment of active digital ulcers was low and significantly lower than for experts from Europe. In the same report, the agreement on the use of methotrexate for skin involvement in early diffuse SSc, and bosentan for recurrent digital ulcers despite treatment with iloprost and calcium antagonists were low with more than 50% of participants scoring < 7 (scale 1-9).

Several factors might account for differences in the level of agreement for the EULAR/EUSTAR recommendations, such as access to drugs, national insurance policy, familiarity with treatment regimen, geographical area, and years of clinical experience in the field. EUSTAR educational activity including oral presentations during EULAR and American College of Rheumatology (ACR) meetings, EUSTAR on-line and EUSTAR educational scleroderma courses, growing number of EUSTAR members and centers may influence the expertise and recommendation adherence (11); one might expect that members of EUSTAR in general could show higher agreement level with EULAR/EUSTAR guidelines than non-EUSTAR members.

In order to improve usefulness of treatment recommendations and to enable their effective implementation in every day clinical practice worldwide, deeper insight in factors that contribute to the level of agreement is needed. We performed a web based survey among SSc-experts around the world to determine the level of agreement with 2017 updated

recommendations on treatment of SSc, and assessed factors that might account for differences in agreement between experts.

## MATERIALS AND METHODS

After publication of the updated EULAR/EUSTAR recommendations on treatment of SSc in 2017 an online survey was designed using 'survey monkey'; the survey contained the 17 EULAR/EUSTAR updated recommendations (3; Appendix 1: PDF of survey questionnaire). Based on the 17 recommendations 20 specific items were derived and evaluated. An e-mail containing a web link to the survey and to the original article was sent out to international SSc-networks (Scleroderma Clinical Trials Consortium [SCTC], Australian Scleroderma Interest Group [ASIG], International Systemic Sclerosis Inception Cohort [INSYNC]) and to 481 unique email addresses of known SSc-experts including experts from South-America and Asia. In total 5 emails were sent between June 8th, and August 5th; the survey was closed on October, 1th, 2017. The participating authors had access to email addresses of possible participants through membership of organisations in the field or based on personal contact. Responses were analysed anonymously; responses could not be traced back to individual participants. In line with this, necessity for ethics approval was waived by the Medical Ethics Committee of The Leiden University Medical Center, The Netherlands.

The following characteristics of the participants were registered: geographical area; specialty; EUSTAR affiliation or membership; membership to other (national) networks; years of clinical experience in SSc field; approximate number of patients with SSc under follow-up; participation in clinical trials in the SSc field.

For each recommendation the level of agreement was determined on a 10-point scale (0=not at all; 10=completely agree). Specifically, regarding the treatment guidelines for PAH, the number of responders prescribing PAH drugs and the number of responders referring their patients to a cardiologist and/or pulmonologist for treatment of PAH was registered. Participants were asked whether they felt comfortable in answering the questions regarding treatment of PAH and were offered the possibility to skip the part of the survey concerning guidelines for PAH treatment. Local drug availability (yes/no) was assessed. The usefulness of the recommendations was assessed by a score on a 10-point scale (0=not at all; 10 =very useful).

Statistical analyses

General characteristics of participants were summarized. Mean level of agreement, mean level of usefulness and drug availability were reported for the 20 items. Mean level of agreement was compared between different subgroups stratified according to: EUSTAR membership, geographical area, drug availability, specialty (rheumatologist vs. non-rheumatologist), number of SSc patients in active follow-up (≤50 or > 50 during the past 6 months) and years of experience.

Stratification for drug availability was only performed in cases where availability was < 90 % in either Europe, outside Europe or both. Differences between different subgroups were tested for significance using 2 tailed and 2 sample T-test, with a p-value < 0.05 indicating statistical significance.

## RESULTS

### Characteristics of participants

Of the 481 unique email addresses approached a response was retrieved from n= 228 (response rate for unique email addresses 47%). Through the weblink which was shared with three SSc networks (SCTC, ASIG, INSYNC) an additional 35 responses were acquired. In total n= 263 unique persons participated in the survey of whom n= 209 (79%) completed every single item. General characteristics were compared between the completers and the non-completers and did not differ for any of the items (data not shown). Therefore, for each single question in the survey all available measurements were taken into account.

The majority of participants were rheumatologists (n=200, 76%), currently working in Europe (n=185; 71%); 59% (n=156) were EUSTAR member, 68% (n=183) were working in a centre affiliated to EUSTAR, and n=151 (57%) reported > 10 years of experience in the SSc field. Of all participants, 22% (n=58) were not involved in any of the official networks. Non-European geographical areas were also represented (29%): Africa n=2 (1%); Asia n=18 (7%); Australia n=13 (5%), North-America n=27(10%), South-America n=17 (6%). Other specialities that participated in the survey included internal medicine specialists (n=25), dermatologists (n=9), immunologists, and other (n=7). Forty-eight percent of participants reported to have seen up to 50 SSc-patients during the past 6 months, 19% had seen 50-100 SSc patients , and 31% had seen more than 100 patients with SSc during the past 6 months. Eighty-one percent of participants saw 0-10 patients with early SSc-patients (diagnosis < 1 year) during the past 6 months, 12% tsaw 11-25 patients with early SSc and 7% saw more than 25 patients with early SSc during the past 6 months. Regarding treatment of SSc-related PAH 208 responders completed these questions; 51% of responders stated to prescribe PAH-drugs themselves,

69% stated that they needed to refer the patient with PAH to a pulmonologist/cardiologist/another rheumatologist (example, from a tertiary centre) for treatment as well, and 21% stated to feel uncomfortable to answer the questions regarding guidelines on treatment of SSc-related PAH.

General agreement and usefulness

The mean level of agreement was 8.0 (median 9; standard deviation [SD, 2.5]). The top three highest mean agreement was reported for angiotensin converting enzyme (ACE) inhibitors for scleroderma renal crisis, blood pressure and renal function control in SSc-patients treated with corticosteroids, and treatment with proton pump inhibitors (PPI) to prevent oesophageal reflux complications (Table 1). The top three lowest mean agreement included the use of fluoxetine for Raynaud's phenomenon (RP), HSCT for rapidly progressive SSc, and PDE5-inhibitors for RP (Table 1).

The mean score for usefulness of the recommendations was in line with the level of agreement for the majority of recommendations. The top three highest level of usefulness consisted of 1. the use of ACE-inhibitors for SRC (9.2 [2.1]), 2. treatment with PPI to prevent esophageal reflux complications (8.9 [2.2]), and 3. blood pressure/renal function control in SSc-patients treated with corticosteroids (8.8 [2.4]). The top three lowest level of usefulness included 1. the use of fluoxetine (4.6 [3.0]) and 2. PDE5-inhibitors for RP (6.7 [3.0]), and 3. the performance of HSCT for rapidly progressive SSc (6.6 [3.2]). Supplementary Table 1 provides a complete overview of mean scores for agreement and usefulness for all evaluated items.

Agreement stratified for subgroups

When comparing experts from Europe to experts form other geographical areas the level of agreement differed significantly ($p< 0.05$) for the following recommendations: iloprost for RP, iloprost and bosentan for digital ulcers, methotrexate for early diffuse SSc, cyclophosphamide for SSc-related lung disease, and HSCT for severe SSc (Table 2).

Comparison of agreement between SSc experts who could dispose over the particular drug/ treatment option with agreement among experts for whom this particular drug/ treatment option was not available showed significant differences for the use of PDE5-inhibitors, bosentan and fluoxetine for RP, iloprost for digital ulcers and for RP, riociguat for PAH and HSCT (Table 3).

Only for use of bosentan to prevent digital ulcers there was a significant difference in agreement between EUSTAR members and EUSTAR non-members. For all other items the level of agreement was comparable between EUSTAR-members and non-members. There were no significant differences in the subgroups when stratified for years of clinical experience. A complete overview of all stratified analyses is provided in supplementary Tables 2 – 5.

Physicians that saw ≤ 50 SSc patients during the past 6 months (n=126) were significantly more often European (79%), and EUSTAR member (82%), and less often participated in clinical trials (50%), as compared to physicians that saw > 50 SSc patients during the past 6 months (total n=137; 62% European; 72% EUSTAR member; 86% participates in trials). Of

those with lower SSc patient numbers 53% had been involved in SSC treatment > 10 years vs. 74% of physicians that saw > 50 SSc patients during the past 6 months. However, mean agreement with the recommendations did not differ for any of the items between these two groups (data not shown).

Finally, rheumatologists were compared with non-rheumatologists. Non-rheumatologists with complete data on agreement (n=36) were more often European (85%), and more often EUSTAR member (90%). Mean level of agreement with recommendations was in general higher among rheumatologists (n=173 with complete data), and significantly higher for the following recommendations: PDE5-inhibitors for DU (mean 8.3 [SD 2.3] vs. 6.7 [3.2]), ERA for PAH (9.0[2.1] vs. 7.6 [3.2]), prostacyclin analogues for PAH (8.3 [2.5] vs. 6.6 [3.1]), MTX for skin manifestations in early diffuse SSc (7.7 [2.5] vs. 5.7 [3.6]), and HSCT for selected patients with rapidly progressive SSc (7.3 [2.8] vs. 6.0 [3.0]).

## DISCUSSION

In general, agreement among SSc experts on updated recommendations for treatment of SSc is high. Perception of the usefulness mirrors this high level of agreement. As the majority of responders is European, mean agreement for different recommendations is largely representing European SSc experts. However, by specifically comparing non-European with European physicians the data do provide insight in agreement outside of Europe as well, and show that differences in the level of agreement between continents may be partially explained by local drug or treatment option availability.

Of note, it is hard to define when a physician fulfils criteria for ‘expert in the field’. When arbitrarily using the cut-of of > 50 patients in active care during the past 6 months we did not

see a difference in level of agreement with recommendations. Possibly, this observation might be explained by the rarity and complex nature of SSc itself: physicians involved in care for these patients might more often rely on existing guidelines. In addition, by reaching out to patients through personal contacts and email addresses available through SSc networks physicians with special interest in the field were addressed and participated: the majority of responders (78%) is involved in at least one of the currently existing official SSc networks. Interestingly, agreement was in general higher among rheumatologists as compared to other specialties represented in the survey. However, these data should be interpreted with caution, as the number of physicians of other specialties was relatively low (n=36 with complete data).

When comparing our results to the results of the survey evaluating the agreement with the previous version of the EULAR/ EUSTAR recommendations, the same areas of controversy were identified: use of iloprost for RP and digital ulcers, use of bosentan for digital ulcers. Our data demonstrate that with respect to iloprost and bosentan local drug availability might at least partially account for the differences in level of agreement. In addition, for iloprost also lack of evidence and variation in regimens might result in lower level of agreement. (12) We could observe the growing level of agreement for the use of bosentan for digital ulcers over time, specifically in the European region. Among the five newly added recommendations, PDE-5 inhibitors and fluoxetine for RP, PDE-5 inhibitors for digital ulcers, riociguat for PAH and HSCT for rapidly progressive SSc, four were ranked among the recommendations with lowest agreement in general. This could not be explained by the reported strength of the recommendation. (3, 13) Still, only limited evidence is available to support use of fluoxetine for RP. (14) In addition, the fear of possible side effects or

complications might also contribute to this ranking, specifically with respect to use of HSCT for rapidly progressive SSc, which high clinical efficacy is partially counterbalanced by treatment related mortality.(15) Finally, one should acknowledge that data regarding availability could also reflect whether the drug is prescribed of-label or not. We suggest that these factors, together with low familiarity with new treatment options as a single or combined factor might explain ourobservation. Also drug availability might partially account (see supplementary tables). Interestingly, the use of methotrexate for skin involvement in early diffuse SSc gets lower level of agreement in both European and non-European responders. Clearly, this cannot be explained by a difference in drug availability or lack of familiarity.

In this survey we could assess the level of agreement which was actually high in general but the study did not evaluate the actual adherence to treatment recommendations, which might differ significantly from the agreement. This was for example shown in a study on agreement and adherence to treatment guidelines in patients with knee osteoarthritis (16): while the level of agreement with guidelines was high (97-99%), the adherence was acceptable but significantly lower (74-75%). Older patients' age and longer symptoms duration resulted in lower chance for guideline adherence; the chance for better guideline adherence increased among physicians who participated in educational events regularly and who had longer clinical experience. Interestingly, in our study, we did not observe an association between years of clinical experience with SSc and recommendation agreement.

This study has a few disadvantages that should be taken into account. First, the exact number of physicians that received the link to the survey is not known, as a web link was shared with SCTC, INSYNC and ASIG who shared the survey with their members which

yielded an additional 35 responders. By reaching out to personal contacts of the authors as well as using all email addresses available through SSc networks we tried to extend the group of responders beyond the networks itself. Still, the majority of responders (78%) was involved in any of the official SSc networks, indicating that practising rheumatologists outside of SSc networks are underrepresented. . As responders participated anonymously, no comparison between responders and non-responders could be made. Nevertheless, 79% of responders fully completed the survey and general characteristics did not differ between completers and non-completers. Also, due to anonymous participation authors on the guidelines might have participated but could not be identified and compared to the remainder of the responders, which is a limitation of the study. However, the original article included 37 authors, which indicates a maximum of 14% of responders being author on the guideline manuscript. Also, the comparison of agreement between EUSTAR- members and EUSTAR non-members did not show large differences. Unfortunately, rheumatologists from Europe were overrepresented in our survey despite all our efforts to recruit specialists from other geographical areas and specialists from other backgrounds into the project. Results of the current study show that specific geographical area and local drug availability are of importance, and probably as a consequence, adherence to treatment recommendations is influenced by these factors. It could be suggested, that increased EULAR/EUSTAR educational activity and advocacy of newly published clinical trials results or observational studies may significantly improve recommendations availability and adherence; we can assume that close contacts with local regulatory authorities may influence the promotion of unmet needed drugs or treatment options and justify their registration to the health basket. Still, in the treatment of SSc areas remain that need to be clarified such as the correct use of corticosteroids, treatment of calcinosis, treatment of severe gastro-intestinal motility

dysfunction and gastric antral vascular ectasia, and use of biological therapies. (17, 18) Given lack of evidence in these areas these complications were not addressed in the recommendations and consequently were not part of the survey as well.

In conclusion, the level of agreement on EULAR/EUSTAR recommendations for treatment of SSc worldwide is in general high. Differences in agreement are partially explained by geographical area and local drug/treatment option availability. To ensure the effective implementation of treatment recommendations for SSc worldwide it is necessary to expand the network of educational efforts in the field of SSc, to learn more on local drug/treatment option availability and to put effort in improvement of treatment providing with recruitment of decision-makers in order to merge real treatment options and existing recommendations. More steps should be done in order to implement recommendations for treatment of SSc in every day clinical practice in particular looking at the new wave of drugs and expanding drug indications that are now under investigation in clinical trials and that may enter in clinical practice in the near future. (19)

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Table 1. Recommendations for treatment of systemic sclerosis; mean level of agreement among SSc experts (n=209)

| Recommendation | Agreement (mean, SD) |
|---|---|
| CCB should be considered as first-line therapy for SSc-RP | 8.2 (2.7) |
| PDE-5I should be considered in treatment of SSc-RP | 7.3 (2.7) |
| Fluoxetine might be considered in treatment of SSc-RP attacks | 4.6 (2.8) |
| Intravenous Iloprost should be considered for severe SSc-RP | 7.9 (2.7) |
| Intravenous iloprost should be considered in the treatment of DU in SSc-patients | 8.7 (2.3) |
| PDE- 5I should be considered in the treatment of DU in SSc-patients | 8.0 (2.5) |
| Bosentan should be considered for reduction of number of new DU in SSc patients | 7.9 (2.8) |
| ERA should be considered to treat SSc-related PAH* | 8.8 (2.4) |
| PDE-5I should be considered to treat SSc-related PAH* | 8.9 (2.3) |
| Riociguat should be considered to treat SSc-related PAH* | 7.4 (2.8) |
| Intravenous epoprostenol should be considered for treatment of patients with severe SSc-related PAH* | 8.3 (2.5) |
| Prostacyclin analogues should be considered to treat SSc-related PAH* | 8.0 (2.7) |
| MTX may be considered for skin manifestations of early diffuse | 7.4 (2.8) |

| | |
|---|---|
| SSc | |
| Cyclophosphamide should be considered for treatment of SSc-ILD, in particular for patients with progressive ILD | 8.0 (2.6) |
| HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure | 7.1 (2.9) |
| Experts recommend immediate use of ACEI in the treatment of SRC | 9.2 (2.1) |
| Blood pressure and renal function should be carefully monitored in SSc patients treated with glucocorticoids | 9.0 (2.2) |
| PPI should be used for the treatment of SSc related GERD, and prevention of oesophageal ulcers and strictures | 9.0 (2.2) |
| Prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances | 8.0 (2.4) |
| Intermittent or rotating use of antibiotics to treat symptomatic small intestine bacterial overgrowth in patients with SSc | 8.5 (2.1) |

*N= 166: of n=209 complete responders 21% did not complete the questions regarding PAH specific drugs because they stated to feel uncomfortable to answer the questions regarding guidelines on treatment of SSc-related PAH.

Abbreviations: systemic sclerosis –SSc, standard deviation – SD, Dihydropyridine-type calcium channel blockers – CCB, phosphodiestherase-5 inhibitors – PDE-5I, angiotensin converting enzyme inhibitor - ACEI, proton pump inhibitors - PPI, Raynaud's phenomenon – RP, digital ulcers – DU, endothelin receptor antagonists – ERA, pulmonary artery hypertension – PAH, methotrexate – MTX, interstitial lung disease – ILD, hematopoietic stem cells transplantation –

HSCT, scleroderma renal crises- SRC, gastroesophagal reflux disease – GERD, nonsignificant.

Table 2: Treatment recommendations with different agreement between European SSc experts and non-European SSc experts; mean (standard deviation)

| | European experts N= 157 | Non European experts N= 63 | P value |
|---|---|---|---|
| Intravenous Iloprost should be considered for severe SSc-RP | 8.5 (2.2) | 6.5 (3.1) | <0.0001 |
| Availability (%) | 90 | 55 | |
| Intravenous iloprost should be considered in the treatment of DU in SSc-patients | 9.0 (1.9) | 7.4 (2.7) | <0.0001 |
| Availability (%) | 93 | 59 | |
| Bosentan should be considered for reduction of number of new DU in SSc patients | 8.5 (2.3) | 6.3 (3.2) | <0.0001 |
| Availability (%) | 86 | 57 | |
| MTX may be considered for skin manifestations of early diffuse SSc | 7.9 (2.7) | 6.8 (3.0) | <0.05 |
| Availability (%) | 95 | 92 | |
| Cyclophosphamide should be considered for treatment of SSc-ILD, in | 8.3 (2.4) | 7.4 (2.9) | <0.05 |

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|---|---|---|---|
| particular for patients with progressive ILD | | | |
| Availability (%) | 99 | 100 | |
| HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure | 7.3 (2.7) | 6.4 (3.2) | <0.05 |
| Availability (%) | 66 | 66 | |

Abbreviations: SD: standard deviation; SSc: systemic sclerosis; RP: Raynaud's phenomenon; DU: digital ulcers; MTX: methotrexate; ILD: interstitial lung disease; HSCT: hematopoietic stem cell transplantation;

Table 3: Treatment recommendations with different agreement between experts stratified according to drug / treatment option availability; mean (standard deviation)

| | Drug available | Drug not available | P value |
|---|---|---|---|
| PDE-5 inhibitors should be considered in treatment of SSc-RP | 7.9 (2.5) n=129 | 6.4 (2.7) n=88 | <0.0001 |
| Fluoxetine might be considered in treatment of SSc-RP attacks | 4.9 (2.9) n=138 | 4.1 (2.5) n=81 | <0.05 |
| Intravenous Iloprost should be considered for severe SSc-RP | 8.3 (2.6) n=170 | 6.8 (2.7) n=44 | <0.001 |
| Intravenous iloprost should be considered in the treatment of DU in SSc-patients | 8.8 (2.2) n=176 | 7.5 (2.6) n=37 | <0.0001 |
| Bosentan should be considered for reduction of number of new DU in SSc patients | 8.3 (2.4) n=165 | 6.5 (3.0) n=48 | <0.0001 |
| Riociguat should be considered to treat SSc-related PAH | 8.1 (2.4) n=99 | 6.6 (3.0) n=66 | <0.0001 |
| HSCT should be considered for treatment of selected patients with | 7.4 (2.8) n=136 | 6.5 (2.8) n=71 | <0.05 |

rapidly progressive SSc at risk of organ

failure

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Abbreviations: SD: standard deviation; PDE-5: phosphodiestherase-5; SSc: systemic sclerosis; RP: Raynaud's phenomenon; DU: digital ulcers; PAH: pulmonary arterial hypertension; HSCT: hematopoietic stem cell transplantation;

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