A Phase II randomized controlled trial of oral prednisolone in early diffuse cutaneous systemic sclerosis (PRedSS)
Griffiths-Jones, Deborah J.; Garcia, Yvonne Sylvestre; Ryder, W. David; Pauling, John D.; Hall, Frances; Lanyon, Peter

Published in:
Rheumatology

DOI:
10.1093/rheumatology/kead012

Publication date:
2023

Licence:
CC BY-NC

Document Version
Publisher's PDF, also known as Version of record

Link to publication in Discovery Research Portal

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Clinical science

A Phase II randomized controlled trial of oral prednisolone in early diffuse cutaneous systemic sclerosis (PRedSS)


1Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester, UK
2Manchester Clinical Trials Unit, The University of Manchester, Manchester, UK
3Department of Rheumatology, Royal United Hospitals Bath NHS Trust, Bath, UK
4Department of Rheumatology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
5Department of Rheumatology, Nottingham University Hospitals NHS Trust, and Lifespan and Population Health, School of Medicine, University of Nottingham, Nottingham, UK
6Department of Rheumatology, Ninewells Hospital and Medical School, Dundee, UK
7Department of Rheumatology, Dudley Group NHSFT, Dudley, UK
8Rheumatology Department, North Bristol NHS Trust, and Academic Rheumatology, University of Bristol, Bristol, UK
9Department of Rheumatology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
10Lancaster Medical School, Faculty of Health and Medicine, Lancaster University, Lancaster and Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK
11Department of Rheumatology, Freeman Hospital, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
12NIHR Biomedical Research Centre and Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
13Department of Rheumatology, Aberdeen Royal Infirmary, Aberdeen, UK
14Centre for Rheumatic Diseases, Glasgow Royal Infirmary, Glasgow, UK
15NIHR Manchester Biomedical Research Centre, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
16Royal Free Hospital, London, UK
17Research Governance and Integrity, The University of Manchester, Manchester, UK
18National Heart and Lung Institute, Imperial College London, Hammersmith Hospital, London, UK
19Centre for Rheumatology, UCL Division of Medicine, Royal Free Campus, London, UK
20Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

*Correspondence to: Ariane Herrick, Centre for Musculoskeletal Research, The University of Manchester, Manchester Academic Health Science Centre, Oxford Road, Manchester M13 9PT, UK.
E-mail: ariane.herrick@manchester.ac.uk

Deceased. The authors are very grateful to the late Professor Mason for his contributions to PRedSS including his chairing of the PRedSS Trial Steering committee.

Abstract

**Objectives:** Although the painful and disabling features of early diffuse cutaneous SSc (dcSSc) have an inflammatory basis and could respond to corticosteroids, corticosteroids are a risk factor for scleroderma renal crisis. Whether or not they should be prescribed is therefore highly contentious. Our aim was to examine safety and efficacy of moderate-dose prednisolone in early dcSSc.

**Methods:** PRedSS set out as a Phase II, multicentre, double-blind randomized controlled trial, converted to open-label during the Covid-19 pandemic. Patients were randomized to receive either prednisolone (~0.3mg/kg) or matching placebo (or no treatment during open-label) for 6 months. Co-primary endpoints were the HAQ Disability Index (HAQ-DI) and modified Rodnan skin score (mRSS) at 3 months. Over 20 secondary endpoints included patient reported outcome measures reflecting pain, itch, fatigue, anxiety and depression, and helplessness. Target recruitment was 72 patients.

**Results:** Thirty-five patients were randomized (17 prednisolone, 18 placebo/control). The adjusted mean difference between treatment groups at 3 months in HAQ-DI score was \( 0.10 \) (97.5% CI: \(-0.29, 0.10\), \( P = 0.254 \), and in mRSS \( -3.90 \) (97.5% CI: \(-8.83, 1.03\), \( P = 0.070 \), both favouring prednisolone but not significantly. Patients in the prednisolone group experienced significantly less pain (\( P = 0.027 \)), anxiety (\( P = 0.018 \)) and helplessness (\( P = 0.040 \)) than control patients at 3 months. There were no renal crises, but sample size was small.

**Conclusion:** PRedSS was terminated early primarily due to the Covid-19 pandemic, and so was underpowered. Therefore, interpretation must be cautious and results considered inconclusive, indicating the need for a further randomized trial.

**Trial registration:** ClinicalTrials.gov, https://clinicaltrials.gov, NCT03708718.
**Keywords:** SSc, pain, disability, randomized controlled trial, corticosteroids
Rheumatology key messages

- Whether or not corticosteroids should be prescribed in early dcSSc is highly contentious.
- PRedSS is the first randomized controlled trial of moderate dose corticosteroids in early dcSSc.
- PRedSS’s inconclusive results indicate the need for a further randomized controlled trial.

Introduction

Early diffuse cutaneous SSc (dcSSc) is painful, disabling and disfiguring because of (often rapidly progressive) widespread skin thickening [1] and musculoskeletal involvement. Recent publications have benchmarked this pain and disability [2, 3], increasing awareness of the need to address quality of life issues as well as survival in patients with early dcSSc.

At present there is no effective disease modifying treatment for early dcSSc. Guidelines advocate immunosuppression [4, 5], which may confer modest benefit [6], and haematopoietic stem cell transplantation may be an option in highly selected cases [7, 8]. A key question is whether corticosteroids should be prescribed. In favour of corticosteroids is that the symptoms that have a major negative impact on the everyday lives of patients with early dcSSc (tight, painful, itchy skin, and loss of function due to contractures and musculoskeletal involvement) have an inflammatory basis [9]. However, corticosteroids are a risk factor for renal crisis [10–12] of which patients with early dcSSc are already at high risk, especially when anti-RNA polymerase III positive [12].

Against this background, the aim of the PRednisolone in early diffuse SSc (PRedSS) trial was to examine safety and efficacy of moderate-dose prednisolone in patients with early dcSSc. Specific objectives were to evaluate whether moderate-dose prednisolone reduced pain and disability, and improved skin score, and whether prednisolone was safe with particular reference to renal function.

Methods

Study design

PRedSS set out as a Phase II, multicentre, double-blind randomized controlled trial (RCT) but was converted to open-label after blinded treatment with prednisolone or placebo became untenable during the Covid-19 pandemic. The trial protocol is described in detail elsewhere [13]. The study was approved by the North West–Greater Manchester South Research Ethics Committee. All participants gave written informed consent.

After a screening visit, patients were assessed at baseline, 6 weeks, 3 months and 6 months. Randomization (ensuring allocation concealment) was 1:1 to either enteric-coated prednisolone or matching placebo capsules (one active capsule = 5 mg prednisolone), stratified by anti-topoisomerase (anti-Scl70) antibody positivity. Stratification for anti-RNA polymerase III positivity (the ideal option) was not feasible because not all participating centres had access to rapid testing for anti-RNA polymerase III.

Patients

Patients from 14 UK centres were recruited. The main inclusion criteria were adults (age >18 years) with early dcSSc (skin involvement extending proximal to the elbow or knee, or involving trunk and within 3 years of onset of skin thickening). Exclusion criteria are listed in Supplementary Table S1, available at Rheumatology online.

Treatment

Patients received, for 6 months, ~0.3 mg/kg of prednisolone or less (or placebo equivalent): weight <50 kg = 10 mg; >50 kg but <60 kg = 15 mg; >60 kg but <80 kg = 20 mg, >80 kg but <100 kg = 25 mg; >100 kg = 30 mg. If a patient experienced adverse effects thought likely related to trial treatment, then the dose could be reduced. Trial treatment was additive to background treatment, including immunosuppressant therapy. A proton pump inhibitor and a calcium and vitamin D supplement were co-prescribed with the trial treatment. At the 6-month (final) visit, the treatment code was broken.

Outcomes

The co-primary outcome measures (examined at 3 months, to maximize patient retention up until the primary end point, and also because any symptomatic improvement in response to prednisolone was likely to occur within a short time frame) were functional ability as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) [14] and the modified Rodnan skin score (mRSS) [15, 16]. The HAQ-DI [15] is self-administered (advantageous in the Covid-19 era) whereas the mRSS involves palpation of the skin by the examining clinician. Secondary efficacy outcomes and safety outcomes are listed in Supplementary Table S2, available at Rheumatology online.

Statistical analysis

This is discussed in full elsewhere [13], including the power calculation, which indicated that 60 patients (30 per arm) would give 82% power. We aimed to recruit 12 more patients allowing for a 17% attrition.

All statistical analyses were conducted on an intention-to-treat basis to include all randomized patients with baseline data and at least one follow-up. Continuous outcomes were analysed using mixed models for repeated measures (MMRM) to assess differences between the treatment arms. Missing data were assumed to be missing at random and handled within the MMRM approach, which remains valid given such a mechanism. Each model included the fixed categorical effects of treatment (prednisolone vs placebo), time point (6 weeks, 3 months and 6 months), whether a patient was anti-topoisomerase positive, and baseline score as well as the interactions of all fixed terms with time point. A general unstructured covariance matrix (six parameters) was used for the error terms. The models were fitted using restricted maximum likelihood and employed Kenward–Roger degrees of freedom adjustment [17].
The primary analysis focus was the contrast (adjusted mean difference in HAQ-DI and mRSS scores) between trial arms at 3 months using an adjusted two-tail 2.5% significance level. Secondary outcomes were exploratory in nature, each employing an unadjusted two-tail 5% significance level.

We conducted a sensitivity analysis by repeating the primary analysis for two different periods (i.e. ‘pre’ and ‘during’ lockdown) to help determine the extent to which the trial may have been affected by the Covid-19 pandemic.

All statistical analyses were performed using Stata/IC version 15.1, (StataCorp, College Station, TX, USA).

Covid-19 impact on methods
On 23 March 2020 the code was broken on all 11 patients currently on trial treatment (10 of whom were on immunosuppressant therapy and therefore deemed at high risk from Covid-19 if also on prednisolone) and to halt further recruitment. Ten continued on/completed the trial on an open-label basis. Because double-blind prednisolone was not going to be a viable option in the short to medium term, approvals were obtained to re-open PRedSS as an open-label study (11 August 2020). A request for extension funding to continue recruitment was declined. PRedSS closed to recruitment in February 2021.

Results
Patients were recruited into the double-blind RCT between 15 December 2017 and 23 March 2020 or into the open-label phase between 11 August 2020 and 31 January 2021. Twenty-five patients were randomized during the double-blind phase (13 to prednisolone) and 10 during the open-label phase (four to prednisolone). Therefore 17 were randomized to prednisolone and 18 to placebo or to no treatment (‘control patients’). Supplementary Fig. S1, available at Rheumatology online, shows patient progression through the study. Supplementary Table S3, available at Rheumatology online, shows the number of participants and the frequency (%) of missing outcome data.

Baseline characteristics of patients
Baseline characteristics of patients are summarized in Supplementary Table S4, available at Rheumatology online. The mean disease duration from onset of skin thickening was 1.7 (s.d. 0.8) years, reflecting an early disease cohort.

Analysis of primary outcome measures—HAQ-DI and mRSS
There was a small but not significant difference between treatment groups in HAQ-DI score at 3 months, after adjustment for baseline score and anti-topoisomerase (mean difference −0.10 at 3 months; 97.5% CI: −0.29, 0.10, P = 0.254), in favour of the prednisolone group (Table 1). Although there was no significant difference in mRSS scores between treatment groups (mean difference −3.90 at 3 months, 97.5% CI: −8.83, 1.03, P = 0.070) (Table 1), again the estimate favoured prednisolone.

We also tested the interaction treatment-by-time to assess whether treatment effects at 3 months were any different from the treatment effects at either of the other time points (6 weeks, 6 months). Neither the interaction term for the HAQ-DI nor that for the mRSS was statistically significant (P = 0.16 and 0.48, respectively).

Supplementary Fig. S2, available at Rheumatology online, shows the trajectories of the HAQ-DI scores and mRSS for each treatment group. Fig. 1A and B shows predictive margins derived from the fitted MMRM models. Supplementary Fig. S2 demonstrates how prednisolone and control groups both experienced an improvement in skin thickening between baseline and 6 months, with the prednisolone group starting from a lower baseline.

Sensitivity analyses results for the primary endpoints are shown in Table 1. Results based on the datasets for the different time periods were similar for the HAQ-DI, yielding the same conclusion, i.e. no significant effect of prednisolone on functional ability at 3 months. For mRSS, the treatment effect at 3 months increased from −1.38 to −3.90 when period III (post-lockdown) results were included.

Analysis of secondary outcome measures
Three of the secondary outcomes (VAS pain, the Hospital Anxiety and Depression Scale [HADS] anxiety scale and the 5-item helplessness subscale of the Rheumatology Attitudes Index [RAI]) showed a statistically significant difference between the treatment groups at 3 months at the 5% significant level, all in favour of the prednisolone group (Table 1). There was also a trend in favour of the Scleroderma Skin Patient Reported Outcome (SSPRO). Trajectories are illustrated in Fig. 1C–F.

The interaction treatment-by-time (6 weeks, 3 months, 6 months) was not significant for any of the secondary outcomes.

Results for digital ulcer count, friction rubs and swollen and tender joint count at 3 months are shown in Supplementary Table S5, available at Rheumatology online. Few patients had these on physical examination.

Treatment adherence
Treatment adherence and a description of how this was calculated is given in Supplementary Data S1, available at Rheumatology online. During the double-blind phase, 18/25 (72%) adhered to treatment (≥80% treatment adherence with missing information in 5/25 (20%)). During the open-label phase, 3/4 (75%) patients adhered to treatment with missing information in 1/4 (25%).

Adverse events
There were a total of 44 adverse events from 15 participants, 22 in the prednisolone group and 22 in the control group. There were four serious adverse events in two control participants: one patient suffered a myocardial infarction and haematoma secondary to edoxaban, and the other developed pulmonary arterial hypertension and cardiac failure secondary to pulmonary hypertension. There were two cases of new hypertension, both in patients on prednisolone, and two cases of worsening of existing hypertension, both in control participants. There were no cases of scleroderma renal crisis, no serious infections and no new diabetes.

Discussion
PRedSS was a casualty of the Covid-19 pandemic and was halted early. The major limitation of the study was that the...
35 patients recruited (of whom 10 were open-label) fell short of the target of 72, rendering results inconclusive.

At 3 months, trajectories for both co-primary endpoints (the HAQ-DI and the mRSS) favoured prednisolone, although there were no statistically significant differences between groups and the estimated benefit of prednisolone on functional ability, as gauged by the adjusted mean HAQ-DI at 3 months, was small (−0.10). The assessment of the mRSS was hampered with the move away from face-to-face follow-up assessments necessitated by the COVID-19 pandemic, and open-label assessments had the potential of observer bias. Bearing in mind these limitations, the estimated benefit of prednisolone on the adjusted mean mRSS at 3 months was moderate (−3.9) with a minimally clinically important difference of −5 [18] lying within the confidence interval.

The large number of secondary outcomes (over 20) means that interpretation of these results should be even more cautious. However, it is worth noting the benefits of prednisolone over placebo at 3 months in pain and in helplessness (and also in anxiety). Treatment with prednisolone appeared safe. Specifically there were no renal crises, although patient numbers were small and it is also possible that longer durations of prednisolone therapy might increase renal crisis risk.

PRedSS provides valuable information to take forward to a future clinical trial. First, a double-blind trial of prednisolone is complex, due to the need to adjust corticosteroid dose during intercurrent illness and therefore increasing the likelihood of code-breaks, particularly during the Covid-19 era. Second, remote visits are feasible, reducing the need for patients to travel to hospital (a major advantage during the Covid-19 era) because (i) we have shown that the patient reported outcome measures in PRedSS were acceptable to patients in terms of ‘questionnaire burden’ and (ii) skin score can now be self-assessed through development of the Patient self-Assessment of Skin Thickness in Upper Limb (PASTUL) questionnaire [19]. Third, our experience with PRedSS will inform power calculations and likely recruitment rates for a future study. And so although PredSS has not provided a definitive answer
Figure 1. Primary and secondary outcomes. Predictive margins (mean scores) at follow-up times with 97.5% CIs for the HAQ-DI and mRSS and 95% CIs for the remaining outcomes. These are predictions for a set of cases ‘like’ (in terms of baseline and anti-topoisomerase values) the combined sample if all were treated with the intervention or all as control respectively. The combined group baseline mean scores are also displayed. HADS: Hospital Anxiety and Depression Scale; HAQ-DI: HAQ Disability Index; mRSS: modified Rodnan skin score; RAI: Rheumatology Attitudes Index; SSPRO: Scleroderma Skin Patient Reported Outcome; VAS: visual analogue scale.
as to whether or not corticosteroids should be prescribed in patients with early dCSSc, it provides critical insights for future studies addressing this important clinical question, and perhaps also provides support for the view of many clinicians that it is not unreasonable to prescribe short-term moderate dose prednisolone for symptom control, always remembering the importance of careful monitoring of blood pressure and renal function.

**Supplementary material**

**Supplementary material** is available at *Rheumatology* online.

**Data availability**

De-identified participant data and a data dictionary (as well as the study protocol and the statistical analysis plan) will be available to qualified researchers 6 months after publication, after approval of a proposal by the sponsor, and the signing of a data sharing access agreement with the trial sponsor.

**Funding**

This work was supported by Versus Arthritis (grant number 21021).

**Disclosure statement:** J.D.P. has received speaker fees from Janssen and consultancy fees from Janssen, Astra Zeneca, Permeatus Inc., Boehringer-Ingelheim and Sojournix Pharma. F.H. has received research grants from BMS, Alexion and Lilly; consultancy with Roche. P.L. has received consultancy fees from Pfizer and research funding from Vifor Pharma. H.G. has received speaker fees from Boehringer Ingelheim. M.A. has received consultancy fees from Gilead, Nordic pharma, speaker fees from Janssen and sponsorship to attend meetings from GSK, Eli Lilly, Roche and AstraZeneca. B.G. is the Chair of NHS England’s Clinical Reference Group for Specialized Rheumatology. C.P.D. reports grants and personal fees from Arena, Boehringer Ingelheim, Corbus, CSL Behring, Galapagos, GalixoSmithKline, Horizon, Roche, and Abbvie; all outside the submitted work. A.L.H. has received consultancy fees from Arena, Boehringer-Ingelheim, Camurus, CSL Behring and Gesynta Pharma, speaker fees from Actelion and Janssen, and research funding from Actelion and Gesynta Pharma.

**Acknowledgements**

PRedSS was funded by Versus Arthritis. The study was supported by the United Kingdom Clinical Research Collaboration-registered King's Clinical Trials Unit at King's Health Partners, which is part funded by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London and the NIHR Evaluation, Trials and Studies Coordinating Centre. We are grateful to the members of the independent data monitoring committee: Lorraine Harper, Luc Mouthon and Melissa Bucknall. Also, to Rachel Jones and Svetlana Tishkovskaya for their contributions as members of the Trial Steering Committee. We are also grateful to Dr Robert Layfatis for allowing us to use SSPRO and to Dr Marlyn Mayo for permission to use the S-D Itch Questionnaire.

**References**