A PHASE II RANDOMISED CONTROLLED TRIAL OF ORAL PREDNISOLONE IN EARLY DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS (PRedSS)

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KEY WORDS

Systemic sclerosis, pain, disability, randomised controlled trial, corticosteroids

KEY MESSAGES

Whether or not corticosteroids should be prescribed in early dcSSc is highly contentious.

PRedSS is the first randomised controlled trial of moderate dose corticosteroids in early dcSSc.

PRedSS' inconclusive results indicate the need for a further randomised controlled trial.

ABSTRACT

Objectives. Although the painful and disabling features of early diffuse cutaneous systemic sclerosis (dcSSc) have an inflammatory basis and could respond to corticosteroids, corticosteroids are a recognised 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 randomised controlled trial, converted to open-label during the Covid-19 pandemic. Patients were randomised to receive either prednisolone (approximately 0.3 mg/kg) or matching placebo (or no treatment during open-label) for 6 months. Co-primary endpoints were the Health Assessment Questionnaire Disability Index (HAQ-DI) and modified Rodnan skin core (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 randomised (17 to prednisolone, 18 to placebo/control). The adjusted mean difference between treatment groups at 3 months in HAQ-DI score was -0.10 (97.5% CI -0.29 to 0.10), p=0.254, and in mRSS -3.90 (97.5% CI -8.83 to 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.

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 randomised trial.

ClinicalTrials.gov Identifier: NCT03708718

INTRODUCTION

Early diffuse cutaneous systemic sclerosis (dcSSc) is painful, disabling, and disfiguring because of (often rapidly progressive) widespread skin thickening(1) and musculoskeletal involvement. Recent publications have bench-marked 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 which 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.

PATIENTS AND METHODS

Study design

PRedSS set out as a Phase II, multicentre, double-blind, randomised, 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.

After a screening visit, patients were assessed at baseline, six weeks, three months and six months.

Randomisation. Randomisation (ensuring allocation concealment) was 1:1 to either enteric-coated prednisolone or matching placebo capsules (one active capsule = 5mg 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 three years of onset of skin thickening). Exclusion criteria are listed Table S1.

Treatment

Patients received, for six months, approximately 0.3 mg/kg of prednisolone or less (or placebo equivalent): weight <50kg = 10mg; >50kg but <60kg = 15mg; >60kg but <80kg = 20mg, >80kg but < 100kg = 25mg; >100kg = 30mg. 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 six month (final) visit, the treatment code was broken.

Outcomes

The co-primary outcome measures (examined at three months, to maximise patient retention up until the primary endpoint, 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 Table S2.

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 randomised 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 was assumed to be missing at random (MAR) and handled within the MMRM approach which remains valid given such a mechanism. Each model included the fixed categorical effects of treatment (prednisolone versus placebo), time-point (six weeks, three months and six 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 (REML) and employed Kenward and 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 three 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, 77845 USA).

Covid-19 impact on methods

On 23/3/2020 it was decided to break the code on all eleven patients currently on trial treatment (ten 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 (11/8/2020). 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 15/12/2017 and 23/3/2020 or into the open-label phase between 11/8/2020 and 31/1/2021. Twenty-five patients were randomised during the double-blind phase (13 to prednisolone) and ten during the open-label phase (four to prednisolone). Therefore 17 were randomised to prednisolone and 18 to placebo or to no treatment ('control patients'). Figure S1 shows patient progression through the study.

Supplementary Table S3 shows the number of participants and the frequency (%) of missing outcome data.

Baseline characteristics of patients

These are summarised in Table S4. The mean disease duration from onset of skin thickening was 1.7 years (SD 0.8), 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 three months, after adjustment for baseline score and anti-topoisomerase (mean difference -0.10 at three months, 97.5% CI -0.29 to 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 three months, 97.5% CI -8.83 to 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 three months were any different from the treatment effects at either of the other time-points (six weeks, six months). Neither the interaction term for the HAQ-DI nor for the mRSS were statistically significant (p-value=0.16 and 0.48 respectively).

Supplementary Figure S2 shows the trajectories of the HAQ-DI scores and mRSS for each treatment group. Figures 1a and 1b show predictive margins derived from the fitted MMRM models. Supplementary Figure S2 demonstrates how prednisolone and control groups both experienced an improvement in skin thickening between baseline and six 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 three months. For mRSS, the treatment effect at three 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 HADS anxiety scale and the 5-Item helplessness subscale of the RAI) showed a statistically significant difference between the treatment groups at three months at the 5% significant level, all in favour of the prednisolone group (Table 1). There was also a trend in favour of the SSPRO. Trajectories are illustrated in Figures 1c, 1d, 1e and 1f.

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

Results for digital ulcer count, friction rubs and swollen and tender joint count at three months are shown in Supplementary Table S5. 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. During the double-blind phase, 18/25 (72%) adhered to treatment ($\geq$ 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 SAEs in two control participants: one patient suffered a myocardial infarction and haematoma secondary to endoxaban, 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 ten were open-label) fell short of the target of 72, rendering results inconclusive.

At three 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 three 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 three months was moderate (-3.9) with a MCID 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 three 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 (a) we have shown that the patient reported outcome measures in PRedSS were acceptable to patients in terms of 'questionnaire burden' and (b) 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 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.

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CONFLICT OF INTEREST STATEMENT

JD Pauling has received speaker fees from Janssen and consultancy fees from Janssen, Astra Zeneca, Permeatus Inc, Boehringher-Ingelheim and Sojournix Pharma. F Hall has received research grants from BMS, Alexion and Lilly; consultancy with Roche. P Lanyon has received consultancy fees from Pfizer and research funding from Vifor Pharma. H Gunawardena has received speaker fees from Boehringer Ingelheim. M Akil 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 Griffiths is the Chair of NHS England's Clinical Reference Group for Specialised Rheumatology. C P

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DATA AVAILABILITY STATEMENT

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 six months after publication, after approval of a proposal by the Sponsor, and the signing of a data sharing access agreement with the trial sponsor.

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REFERENCES

1. Herrick AL, Assassi S, Denton CP. Skin involvement in early diffuse cutaneous systemic sclerosis: an unmet clinical need. *Nature Reviews Rheumatol* 2022;18:276-85.

2. Peytrignet S, Denton CP, Lunt M, Hesselstrand R, Mouthon L, Silman A, et al. Disability, fatigue, pain and their associates in early diffuse cutaneous systemic sclerosis: the European Scleroderma Observational Study. *Rheumatology* 2018;57:370-81.

3. Zheng B, Nevskaya T, Baxter CA, Ramey DR, Pope JE, Baron M, et al. Changes in skin score in early diffuse cutaneous systemic sclerosis are associated with changes in global disease severity. *Rheumatology* 2020; 59:398-406.

4. Denton CP, Hughes M, Gak N, Vila J, Buch MH, Chakravarty K et al. BSR and BHPR guideline for the treatment of systemic sclerosis. *Rheumatology* 2016*;* 55:1906-10.

5. Kowal-Bielecka O, Fransen J, Avouac J,Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017*;*76**:**1327-39.

6. Herrick AK, Pan X, Peytrignet S, Lunt M, Hesslestrand R, Mouthon L, et al. Treatment outcome in early diffuse cutaneous systemic sclerosis: The European Scleroderma Observational Study (ESOS). *Ann Rheum Dis* 2017;76:1207-18.

7. Van Laar, JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA* 2014*;*311**:**2490-8.

8. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pincknev A, Welch B, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Eng J Med* 2018;378:35-47.

9. Blagojevic J, Legendre P, Matucci-Cerinic M, Mouthon L. Is there today a place for corticosteroids in the treatment of scleroderma? *Autoimmunity Reviews* 2019;18:102403.

10. Steen VD, Medsger TA. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum* 1998;41:1613-9.

11. Guillevin L, Berezne A, Seror R, Teixeira L, Pourrat J, Mahr A, et al. Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. *Rheumatology* 2012;51:460-7.

12. Hoa S, Stern EP, Denton CP, Hudson M, Scleroderma Clinical Trials Consortium Scleroderma Renal Crisis Working Group, Investigators of the Scleroderma Clinical Trials Consortium Scleroderma Renal Crisis Working Group. Towards developing criteria for scleroderma renal crisis: a scoping review. *Autoimmunity Reviews* 2017;16:407-15.

13. Herrick AL, Griffiths-Jones DJ, Ryder WD, Mason JC, Denton CP. Clinical trial protocol: PRednisolone in early diffuse cutaneous Systemic Sclerosis. *J Scleroderma Rel Disord* 2021;6:146-53.

14. Steen VD, Medsger TA. The value of the health assessment questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum* 1997;40:1984-91.

15. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardisation of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J Scleroderma Relat Disord* 2017;2:11-8.

16. Furst DE. Outcome measures in rheumatologic clinical trials and systemic sclerosis. *Rheumatology* 2008;47(Suppl 5): v29-30.

17. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 1997; 53:983-97.

18. Khanna D, Clements PJ, Volkmann ER, Wilhalme H, Tseng C, Furst DE, et al. Minimally clinically important differences for the modified Rodnan skin score: result from the Scleroderma Lung Studies (SLS-I and SLS-II). *Arthritis Res Ther* 2019;21:23.

19. Spierings J, Ong V, Denton CP. PASTUL questionnaire: a tool for self-assessment of scleroderma skin during the COVID-19 pandemic. *Ann Rheum Dis* 2021;80:819-20.

FIGURE LEGEND

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.

Table 1: Treatment effects of the continuous outcomes at 3 months

	N	Difference (s.e.)	97.5% CI	p-value	Effect in favour of
Co-primary outcomes					
HAQ-DI	34	-0.10 (0.08)	(-0.29 to 0.10)	0.254	Prednisolone
mRSS	31	-3.90 (2.05)	(-8.83 to 1.03)	0.070	Prednisolone
Sensitivity Analyses					
HAQ-DI					
Period I (Pre-Lockdown)	23	-0.12 (0.14)	(-0.48 to 0.23)	0.383	Prednisolone
Period II (Lockdown)	25	-0.07 (0.11)	(-0.33 to 0.19)	0.506	Prednisolone
Period III (Post-Lockdown)	34	-0.10 (0.08)	(-0.29 to 0.10)	0.254	Prednisolone
mRSS					
Period I (Pre-Lockdown)	23	-1.38 (2.41)	(-7.41 to 4.66)	0.576	Prednisolone
Period II (Lockdown)	23	-1.38 (2.41)	(-7.41 to 4.66)	0.576	Prednisolone
Period III (Post-Lockdown)	31	-3.90 (2.05)	(-8.83 to 1.03)	0.070	Prednisolone
Secondary outcomes	**N**	**Difference (s.e.)**	**95% CI**	**p-value**	**Effect in favour of**
SHAQ VAS scales					
Pain	34	-0.49 (0.21)	(-0.93 to -0.06)	0.027	Prednisolone
Intestinal problems	34	0.38 (0.24)	(-0.11 to 0.87)	0.121	Control
Breathing	34	-0.00 (0.24)	(-0.48 to 0.48)	0.995	Prednisolone
Raynaud's phenomenon	34	-0.12 (0.31)	(-0.75 to 0.51)	0.704	Prednisolone
Finger ulcers	33	-0.13 (0.21)	(-0.55 to 0.30)	0.550	Prednisolone
Overall disease activity	32	-0.16 (0.24)	(-0.65 to 0.33)	0.505	Prednisolone
11 point scleroderma functional index	34	-0.41 (1.84)	(-4.17 to 3.36)	0.827	Prednisolone
SSPRO	27	-12.66 (6.26)	(-25.59 to 0.26)	0.055	Prednisolone
5-D Itch	22	-1.17 (1.74)	(-4.80 to 2.46)	0.509	Prednisolone
CHFS	32	-0.21 (2.86)	(-6.08 to 5.66)	0.942	Prednisolone
FACIT	34	4.22 (3.00)	(-1.91 to 10.34)	0.170	Prednisolone
HADS: Anxiety	34	-2.05 (0.82)	(-3.73 to -0.37)	0.018	Prednisolone
HADS: Depression	34	0.91 (0.69)	(-0.50 to 2.32)	0.197	Control
RAI: Helplessness	34	-1.54 (0.72)	(-3.01 to -0.07)	0.040	Prednisolone
SF-36: Physical component	34	1.83 (1.89)	(-2.04 to 5.69)	0.343	Prednisolone
SF-36: Mental component	34	-1.65 (3.55)	(-8.91 to 5.62)	0.647	Control
EQ 5D 3L: Health Utility	34	0.15 (0.09)	(-0.03 to 0.32)	0.098	Prednisolone
EQ 5D 3L Health State: VAS	34	5.31 (7.06)	(-9.14 to 19.75)	0.459	Prednisolone
Patient Global Assessment	31	0.84 (0.68)	(-0.56 to 2.24)	0.230	Prednisolone
Physician Global Assessment	32	-0.63 (0.73)	(-2.13 to 0.87)	0.396	Prednisolone

Results generated from the MMRM models adjusting for anti-topoisomerase and baseline values of the associated outcome. Difference = Prednisolone-Control. P-values of <0.025 are statistically significant for the co-primary outcomes. P-values of <0.05 are statistically significant for the secondary outcomes

Sensitivity analyses time periods: Period I includes all available data up to the 22nd March 2020, just before the recruitment was halted due to a national lockdown. Period II includes all available data from the start of the trial until the 11th August 2020 when trial recruitment resumed following the national lockdown. Period III is the primary analysis, includes all available data for the 35 randomised participants (I.e., pre, lockdown and post lockdown data).

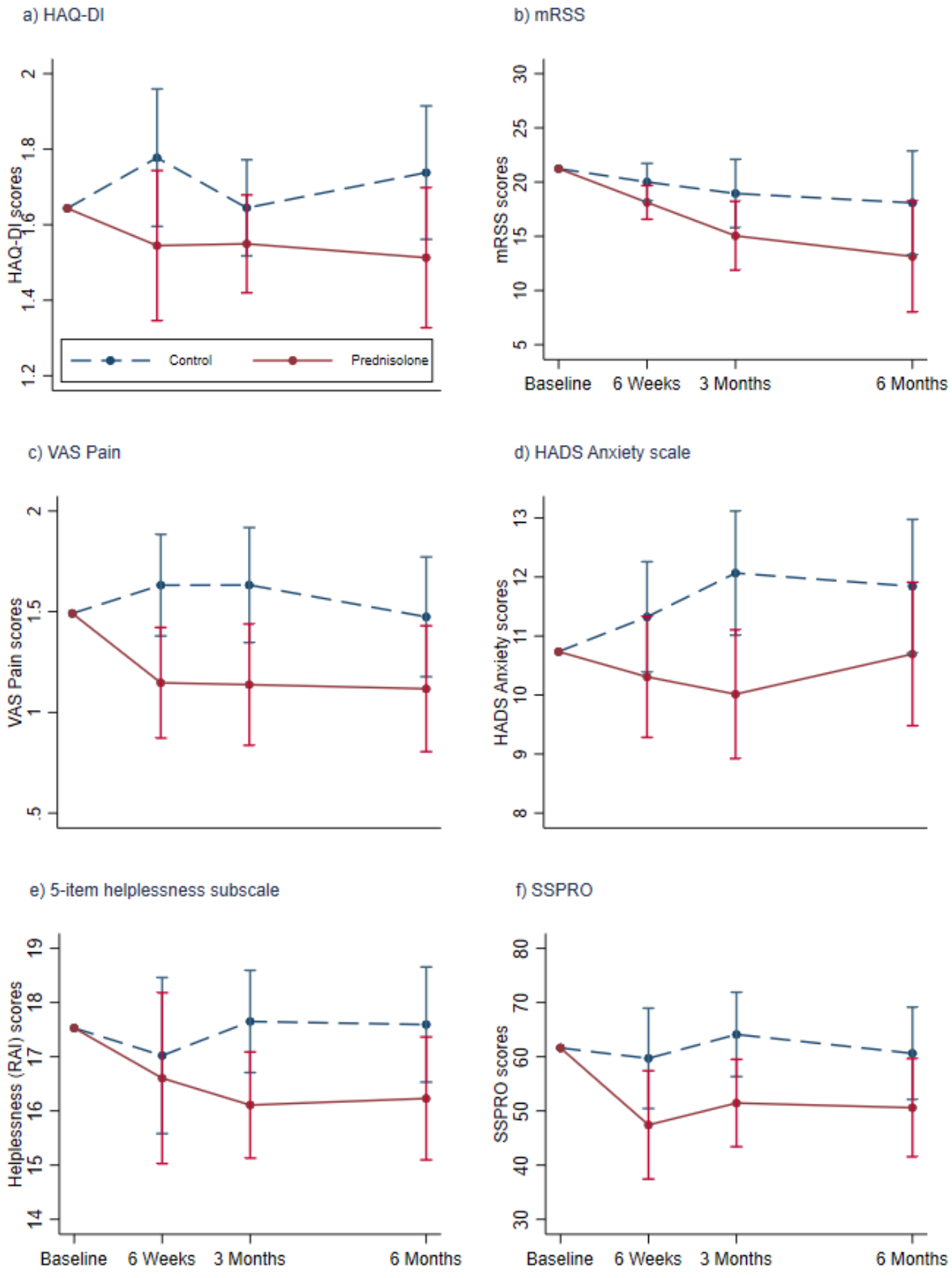

Figure 1: Primary and secondary outcomes. Predictive margins (mean scores) at follow-up times with 97.5% CIs for the HAQ-DI and mRSS and 95% CIs for the remaining outcomes. These are predictions for a set of cases "like" (in terms of baseline and anti-topoisomerase values) the combined sample if all were treated with the intervention or all as control respectively. The combined group baseline mean scores are also displayed.