Article:
Mongin, D., Matucci-Cerinic, M., Walker, U.A. et al. (16 more authors) (2024) Oral glucocorticoids for skin fibrosis in early diffuse systemic sclerosis: a target trial emulation study from the European Scleroderma Trials and Research group database. Arthritis Care & Research. ISSN 2151-464X

https://doi.org/10.1002/acr.25469

Mongin Denis (Orcid ID: 0000-0002-4801-8395)
Distler Oliver (Orcid ID: 0000-0002-2413-1959)
Vonk Madelon (Orcid ID: 0000-0002-2266-9907)
Del Galdo Francesco (Orcid ID: 0000-0002-8528-2283)
Iudici Michele (Orcid ID: 0000-0001-5871-8806)

Oral glucocorticoids for skin fibrosis in early diffuse systemic sclerosis: a target trial emulation study from the European Scleroderma Trials and Research group database.

Denis MONGIN[1], PhD, Marco MATUCCI-CERINIC[2,3], Prof, Ulrich A. WALKER[4], Prof, Oliver DISTLER[5], Prof, Radim BECVAR[6], MD, Elise SIEGERT[7], MD, Lidia P. ANANYEVA[8], Prof, Vanessa SMITH[9], MD PhD, Juan Jose ALEGRE-SANCHO[10], MD, Sule YAVUZ[11], MD, Massimiliano LIMONTA[12], MD, Gabriela RIEMEKASTEN[13], Prof, Elena REZUS[14], Prof, Madelon VONK[15], Prof, Marie-Elise TRUCHETET[16], Prof, Francesco DEL GALDO[17], Prof, Delphine S. COURVOISIER[1], Prof, Michele IUDICI[1], Prof; EUSTAR collaborators.

Author affiliations

[1] Geneva University Hospitals, Geneva, Switzerland

[2] IRCCS San Raffaele Scientific Institute, Milan, Italy, IRCCS San Raffaele Hospital, Milan Italy

[3] Vita-Salute San Raffaele University, Milan, Italy,

[4] University Hospital Basel, Basel, Switzerland

[5] University Hospital Zurich, Zurich, Switzerland

[6] University, Prague, Czech Republic

[7] Charité University Hospital, Berlin, Germany

[8] V.A. Nasonova Research Institute of Rheumatology Russian Federation, Moskow, Russia

[9] Ghent University, Ghent, Belgium; Ghent University Hospital, Ghent, Belgium; VIB Inflammation Research Center (IRC), Ghent, Belgium

[10] Hospital Universitario Dr. Peset, Valencia, Spain

[11] Istanbul Bilim University, Altunizade-Istanbul, Turkey

[12] ASST Papa Giovanni XXIII, Begamo, Italy

[13] Klinik Für Rheumatologie Und Klinische Immunologie, Universitätsklinikum Schleswig-Holstein, Lübeck, Germany

[14] Grigore T. Popa University of Medicine and Pharmacy Iasi, Rehabilitation Hospital Iasi, Romania

[15] Radboud University Medical Center, Nijmegen, The Netherlands

[16] National Reference Center for Systemic Autoimmune Rare Diseases, Bordeaux University Hospital, Hôpital Pellegrin, place Amélie-Raba-Léon, Bordeaux, France

[17] Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/acr.25469

Corresponding author: Michele IUDICI, MD, PhD, MPH, Division of Rheumatology, Department of Medicine, Geneva University Hospitals, Switzerland. Tel. +41 0223723520; Fax. +41 0223723535. **email**. michele.iudici@hcuge.ch. ORCID ID. orcid.org/0000-0001-5871-8806

Word count: 2762
Tables. 2
Figures. 1

Keywords: systemic sclerosis; treatment; glucocorticoids; diffuse systemic sclerosis.

Running head: Glucocorticoids for skin fibrosis in early diffuse SSc

Funding, grant/award info. This work was funded by the Project Recherche & développement (PRD) from Geneva University Hospitals.

Abstract

Objectives. The objective of this study is to evaluate whether adding oral glucocorticoids to immunosuppressive therapy improves skin scores and ensures safety in patients with early diffuse cutaneous systemic sclerosis (dcSSc).

Methods. We performed an emulated randomized trial comparing the changes from baseline to 12±3 months of the modified Rodnan skin score (mRSS: primary outcome) in early dcSSc patients receiving either oral glucocorticoids (≤20 mg/day prednisone-equivalent) combined with immunosuppression (treated), or immunosuppression alone (controls), using data from the European Scleroderma Trials and Research Group. Secondary endpoints were the difference occurrence of progressive skin or lung fibrosis, and scleroderma renal crisis. Matching propensity score was used to adjust for baseline imbalance between groups.

Results. We matched 208 patients (age 49 years; 33% male; 59% anti-Scl70), 104 in each treatment group, obtaining comparable characteristics at baseline. In the treated group, patients received a median prednisone dose of 5 mg/day. Mean mRSS change at 12±3 months was similar in the two groups (decrease of 2.7 [95% CI 1.4 - 4.0] in treated vs. 3.1 [95% CI 1.9 - 4.4] in control, p = 0.64). Similar results were observed in patients with shorter disease duration (≤ 24 months) or with mRSS ≤22. There was no between-group difference for all prespecified secondary outcomes. A case of scleroderma renal crisis occurred in both groups.

Conclusions. We did not find any significant benefit of adding low-dose oral glucocorticoids to immunosuppression for skin fibrosis, and at this dosage, glucocorticoid did not increase the risk of scleroderma renal crisis.

Significance & Innovation

- The effect of oral glucocorticoids in addition to immunosuppression on skin fibrosis progression in early diffuse cutaneous systemic sclerosis patients is not known.
- This study managed to emulate a randomized control trial of 208 patients with early diffuse cutaneous systemic sclerosis, of which 104 are treated with oral glucocorticoids and immunosuppression.
- Our results suggest that the use of oral glucocorticoids is not needed to slow down skin fibrosis in early diffuse cutaneous systemic sclerosis patients.

INTRODUCTION

Systemic sclerosis (SSc) is a complex, multisystemic autoimmune disease characterized by high mortality and morbidity [1]. The two main recognized disease subsets, i.e. limited (lc-) and diffuse (dc-) cutaneous SSc [2], present different evolution and prognosis. Patients with diffuse cutaneous systemic sclerosis (dcSSc) manifest fibrotic complications and decline in organ function early during the disease course, resulting in poor quality of life, and leading to a mortality rate that is five to eight times higher than that observed in the general population [3]. Currently, available treatment offers limited benefit, and hematopoietic stem cell transplantation should be considered in selected cases [4]. Guidelines recommend that immunosuppression (mycophenolate mofetil, rituximab, cyclophosphamide) should be promptly introduced to control symptoms and prevent fibrotic complications [5–7].

Whether adding oral glucocorticoids to immunosuppression is beneficial to slow down skin fibrosis progression in early dcSSc patients is a matter of debate [8–10]. In past years, research has failed to define the exact role of these compounds for this indication, mainly because of limitations in study design (nonrandomized studies [11], small randomized studies at high risk of bias [10,12]). Recently, a randomized controlled trial investigating the impact of adding oral glucocorticoids to routine care on skin fibrosis progression and quality of life ended prematurely for insufficient patient accrual due to COVID-19 pandemic [13].

In the absence of clear evidence, glucocorticoids are being widely and often for long period prescribed to patients with dcSSc [8,9,14,15], with the consequent risk of drug toxicity and treatment-related damage accrual.

In the context of a rare disease where conducting a randomized controlled trial is difficult and may not succeed, comparative effectiveness studies on large sample of routinely collected data can provide guidance for management. Target trial emulation can help reduce bias in the effect estimates derived from observational analyses [16].

This study aims to evaluate whether adding oral glucocorticoids to immunosuppression for skin fibrosis improved skin score at 1-year and was safe in terms of risk of scleroderma renal crisis.

METHODS

Ethics and regulations

This study was conducted in compliance with the Helsinki Declaration. Local ethic committee permission for each EUSTAR centre and informed consent, where appropriate according to local ethic regulations, were obtained prior to EUSTAR enrolment.

Specification of the target trial

This observational analysis was designed to emulate a target trial (ie, a hypothetical pragmatic trial that would have answered the causal question of interest [17]) on the use of immunosuppression plus oral glucocorticoids vs immunosuppression alone to improve skin fibrosis in patients with early diffuse SSc (see eligibility criteria below). Main outcome was the between-arm difference in skin fibrosis change at one year from baseline.

EUSTAR database

This analysis was based on data from SSc patients enrolled in The European Scleroderma Trials and Research Group (EUSTAR) [1,18]. This international database prospectively collects data from SSc patients seen in routine care at least annually from > 200 centers from all the continents. For inclusion, patients have to meet the 2013 ACR/EULAR classification criteria for SSc [19].

Eligibility criteria

We included SSc patients aged 18 years or more, presenting a dcSSc subset according to Leroy et al. [2], a modified Rodnan skin score (mRSS) ≥ 7, with ≤ 5 years disease duration since the 1st non-Raynaud symptom, who had started either immunosuppression monotherapy or immunosuppression plus oral glucocorticoids ($\leq$ 20 mg of prednisone equivalent per day) at inclusion between January 2009 and December 2020. The criterion of mRSS ≥7 equals the minimal score that is required to qualify as diffuse cutaneous and was deliberately chosen not to miss early patients who will become progressive later on. We excluded patients with a previous renal crisis; patients receiving daily > 20 mg prednisone equivalent at inclusion; patients receiving or had received pulse methylprednisolone within 6 weeks from the inclusion; patients with an associated connective tissue disease; patients who had received hematopoietic stem cell transplantation, lung or heart transplantation.

Interventions

We compared the following two treatment strategies at inclusion: 1) Immunosuppression alone. Patients in this group could have received in the timeframe considered intravenous or oral cyclophosphamide, methotrexate, mycophenolate mofetil, azathioprine, rituximab, tocilizumab, without concomitant glucocorticoids ('control group'). 2) Immunosuppression (as defined above) plus oral glucocorticoids at a daily dose $\leq$ 20 mg prednisone equivalent ('treated group').

Primary and secondary outcomes

The primary outcome measure was the between-group mean difference of mRSS at 12 ± 3 months from baseline. EUSTAR centers are advised that the same investigator is performing the mRSS on follow-up visits in individual patients, and EUSTAR investigators are trained on a regular basis on how to perform the mRSS [20,21]. The follow-up time of 12 months was selected since it is considered a relevant timeframe to detect significant changes in mRSS, and is therefore used in many clinical studies [22,23]. Secondary endpoints, evaluated at 12 ± 3 months from baseline, were:

- Development of progressive skin fibrosis (increase in mRSS of 5 points and ≥25% from baseline)
- Development of progressive lung fibrosis (either decrease in either forced vital capacity - FVC ≥10%, or both decrease of FVC ≥5% and decrease in diffusing capacity of the lung for carbon monoxide - DLCO ≥15%)
- Development of progressive skin fibrosis and development of progressive lung fibrosis [21,24,25]
- Incidence of scleroderma renal crisis

Subgroup analyses

We performed two subgroup analyses for the primary outcome. The first focused on patients with a disease duration from non-Raynaud's onset ≤ 24 months, who are those with more active inflammation and therefore more likely to respond to glucocorticoids [21,26]. These patients are also more likely to have worsening skin and lung disease [27]. The second included the subset of patients with a mRSS value below 22, in order to enrich the sample of patients with the highest likelihood to have a progressive skin disease [21]. Imputation and matching of the groups were re-performed for each subgroup analysis (see next section).

Statistical analyses

Two sets of analysis were performed for each outcome: the main one included patients having at least a measured outcome difference at 12 ± 3 months. The second one was a sensitivity analysis considering all the patients fulfilling the eligibility criteria. In this analysis, we addressed missing data for the main outcome by incorporating them along with the covariates during the imputation process for missing variables. For both sets of analysis, treatment groups were first matched using propensity score matching with a 1:1 ratio using nearest neighbor matching. The propensity score was assessed using logistic multivariable regression with use of glucocorticoids as dependent variable and a set of covariates as independent variables. These were identified by the analysis

of the literature on the topic [21,26–29] and discussion among some of the authors (DM, MI, DSC, FDG). Priority was given to prognostic variables, whereas variables strongly associated with treatment but not - or weakly - with the outcome (instrumental variables) can induce unstable weights with little or no gain in terms of bias reduction. We included in the model age, sex, disease duration (from the first non-Raynaud's onset), baseline mRSS, presence of joint synovitis, immunosuppression treatment type (cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab, other), anti-topoisomerase and anti-RNA polymerase III status, presence of tendon friction rubs, smoking status, year of enrolment. Missing covariates were handled using multiple imputation with chained equation, with 50 samples and 10 iterations, considering all covariates and the outcome in the imputation model. The predicted propensity score was the mean of the predicted scores of each sample.

Descriptive statistics used paired t test for continuous variables and mcNemar or Friedman tests for dichotomous variables, to account for the matching of the groups.

The difference in outcomes between the two matched groups was analyzed using linear regression predicting the main outcome or logistic regression predicting the secondary outcomes, as a function of the baseline use of glucocorticoids and with a random intercept on the matched patients account for the matching of the groups.

For the sensitivity analysis, matching was performed the same way. The outcome was imputed considering the outcome and all covariates in the imputation model. The estimation of the effect of baseline use of glucocorticoids was then pooled from regression estimates following Rubin's rules [30]. The analyses were computed using R software version 4.0.3 [31], with mice library for the multiple imputation [32].

Data sharing statement. Data are available on reasonable request.

RESULTS

Study population

Among 20761 SSc patients of the EUSTAR database assessed for eligibility, 745 had at least one visit with the information proving they had a disease duration < 5 years, received immunosuppression and were adult patients. An additional 515 patients did not meet inclusion criteria (see Flow-chart in figure 1). Of the 230 patients who met the eligibility criteria (see Supplementary Table 1 for key characteristics), we successfully performed 1:1 matching for 208 patients: 104 received immunosuppression without glucocorticoids, and 104 received a combination of immunosuppression and glucocorticoids. The two groups of patients had similar baseline characteristics (Table 1): 67% were females, with a mean age 49 years, a mean disease

duration of 2.5 years and a median mRSS of 18, with 43% of the patients having interstitial lung disease identified by lung Xray or high-resolution computed tomography. At baseline, median daily prednisone dose was 5 mg/day, and 13 (12.5%) patients received more than 15 mg/day of prednisone. The patients were mainly treated with methotrexate (38%) and mycophenolate mofetil (35.1%) at baseline, 9% of them receiving a combination of immunosuppressive therapy. Over follow-up, 42 (20.2%) patients switched to another immunosuppressive treatment, with no significant between-group difference.

Primary outcome analyses

Difference in mRSS at 12 ± 3 months were similar between the 2 groups (treated group: decrease of 2.7 [95% CI 1.4 - 4.0] vs. control group: 3.1 [95% CI 1.9 – 4.4], p = 0.64) (see **Figure 2** and **Table 2**). Results were similar when considering patients with missing mRSS at 12 $\pm$ 3 months in the analysis (see supplementary table 2), when the analysis was restricted to the subgroup of patients with a shorter disease duration ($\leq$ 24 months, see supplementary table 3), and when considering patients with baseline mRSS inferior to 22 (see supplementary table 4).

Secondary outcome analyses

Within the previous matched cohort of 208 patients, no significant difference was observed between control and treated groups for all secondary outcomes (see Table 2).

When performing matched analysis for each of these outcomes, we found no effect of treatment on progressive skin fibrosis at 12 $\pm$ 3 months (OR = 1.3 [0.6, 3.0], p = 0.53), nor on progressive lung fibrosis (OR = 1.0 [0.5, 2.0], p = 1), progressive skin and lung fibrosis (OR = 1.3 [0.7, 2.4], p = 0.43) or renal crisis (OR = 1.0 [0.1, 7.2], p = 1, see supplementary table 5). In line with these findings, we did not find any difference in the subgroups of patients with missing outcomes at 12 $\pm$ 3 months (see supplementary Table 5), in those with a shorter disease duration ($\leq$ 24 months) (see supplementary table 6), or with a baseline mRSS inferior to 22 (see supplementary table 7).

DISCUSSION

This target trial emulation study showed no difference on skin fibrosis progression between early dcSSc patients treated with immunosuppression monotherapy and those receiving immunosuppression plus oral glucocorticoids. In both groups, we observed a similar improvement in skin induration at 1-year, with no clinically or statistically significant between-group difference. Two cases of scleroderma renal crisis occurred, one in each treatment group. The proportion of patients with progressive skin disease, progressive lung disease, and regressive skin and lung disease was similar in patients receiving or not glucocorticoids.

Data from randomized trials and observational studies reveal widespread use of glucocorticoid in dcSSc patients (40% of dcSSc patients from EUSTAR database were on prednisone in 2018 [15]). While it's widely accepted that a short course of low-dose prednisone can help with fatigue, musculoskeletal pain, or itch [5,6,9,13,33,34], its effectiveness for controlling skin fibrosis is more controversial. Even among experts, glucocorticoids prescribing practices for this indication vary widely [8]. Recent research intended to address this important point but could not provide a definite answer. The PRedSS study, a double-blind randomized controlled trial, converted to open-label and terminated early during the COVID-19 pandemic [13] assessed versus placebo the impact of adding moderate dose of prednisolone (0.3 mg/Kg) to immunosuppression on skin fibrosis and disability at 3 months (2 co-primary endpoints). The two co-primary endpoints were not met, but the study was underpowered since only 35 patients could be randomized. In this context of uncertainty, we designed this emulated trial to answer such research question difficult to study in randomized studies. Emulated target trials are particularly useful when the randomized study that would answer our causal question - the target trial - is not feasible, ethical, or timely [16]. We found no benefit of adding oral glucocorticoids to immunosuppression on skin fibrosis progression. We examined this aspect in a large sample of patients with a disease duration ≤ 5 years, as well as in those with a shorter disease duration (≤ 24 months) or with a mRSS between 7 and 22 who are potentially at higher risk to progress and more responsive to anti-inflammatory treatment [21,25,26,28]. In all the cases, we did not observe any significant impact of prednisone on skin, suggesting that, if an effect of glucocorticoids exists, it is very likely below clinical significance [35]. While our study has design limitations, it strongly questions the utility of prescribing oral glucocorticoids at the dose investigated for better skin fibrosis control in patients with early dcSSc.

Our data seems suggest that the use of low-dose prednisone in early dcSSc is not a major risk factor for scleroderma renal crisis. In this study, where patients started with a median prednisone dose of 5 mg/day, scleroderma renal crisis occurred in 2 patients, of whom only one was in the glucocorticoid-treated group. Our data are in keeping with previous literature [36] and with the results from Griffiths-Jones et al, where no case of scleroderma renal crisis was observed in 17 early dcSSc patients treated with daily 0.3 mg/Kg prednisolone [13]. However, our results should be interpreted with caution, as our sample size may not have been sufficiently powered to answer this research question.

About one-third of patients from both treatment groups experienced progressive lung fibrosis. This suggests that adding prednisone to immunosuppression may not be beneficial for interstitial lung disease in early dcSSc. However, our study's primary focus was not on assessing lung outcomes,

and adjustments for confounding were primarily tailored to the main primary endpoint. Therefore, these results should be interpreted with caution. Further research is required to address this clinically significant question.

Our study has major strengths. The EUSTAR database collects the clinical characteristics and outcomes of a large number of patients, enabling analysis of a rare disease phenotype difficult to target in a randomized controlled trial. Analyses benefited from multiple methods to address potential confounding by indication and subgroup and sensitivity analyses were concordant for the primary outcome results, bolstering confidence in the main results. The international composition of the database allowed inclusion of patients from different countries potentially heterogeneous for treatment, racial background, and disease severity. This study summarizes the results of a potential pragmatic trial where patients have received treatment in routine care setting. As a result, we were able to include patients likely to have more severe disease, multiple comorbidities, and possibly greater treatment resistance - patients who are generally less represented in randomized trials.

Some limitations need to be acknowledged. First, as in any observational analysis, assignment to a particular treatment was not randomized. Thus, residual confounding cannot be entirely ruled out. For example, although patients were matched for all known factors associated with skin fibrosis progression in early diffuse SSc, a higher proportion in the treatment group received cyclophosphamide. While this could indicate greater disease severity, it may also reflect differences in physician' experience, healthcare system, treatment availability, and cost considerations. However, it is important to note that the adjustments made in the analysis aimed to minimize such potential effect, and all subgroup analyses were consistent with the main finding. Second, selection bias could play a role since we studied patients with information on skin involvement and disease duration. Third, we had no information about the precise duration, dose modification over the study period, and adherence to glucocorticoid intake in our sample. While this imprecision may represent information bias, it also enhances the generalizability of our findings since our aim was to emulate a pragmatic trial where no additional measures to assess treatment adherence are carried out, and the analysis was performed as an intention-to-treat. Intention-to-treat analysis helps minimize selection bias by including all participants as originally assigned, regardless of whether they strictly adhere to the treatment protocol. This approach accounts for subjects who may switch between experimental and control groups or prematurely discontinue treatment, ensuring that the results reflect real-world variations in treatment adherence [37]. Moreover, the EUSTAR database does not provide information about the reasons

leading physicians to prescribe treatment (either glucocorticoids or immunosuppression), limiting our ability to determine whether the outcome investigated (skin fibrosis) was intended to be targeted by the drugs prescribed. Another potential limitation is that we considered exploring the efficacy of glucocorticoid monotherapy but were unable to do so due to the very low number of patients receiving this treatment in the EUSTAR database. Finally, we were not able to assess the impact of glucocorticoid treatment on other patient-relevant outcomes such as pain, disability, quality of life, because of unavailable data.

In conclusion, the results of this target trial emulation study on patients with an early dcSSc seen in routine care, showed no benefit on skin of adding oral (≤ 20 mg/day) glucocorticoids to immunosuppression. Our findings question the utility of prescribing low-dose of these compounds for this indication, thus adding further knowledge to a debated subject [8,10,33,34,38]. Whether short course of low-dose steroids could contribute to improve fatigue, pain, itch was not the object of the present study and remains to be further investigated. However, the lack of an excess of renal complication in glucocorticoid-treated patients and clinical experience provide supports for these drugs to be used for symptom control, while emphasizing the crucial need for monitoring early signs of kidney disfunction. Our results should be interpreted with caution due to the limitations of our observational study design.

Acknowledgments.

Ethical approval information, institution(s) and number(s): This study was conducted in compliance with the Helsinki Declaration. Local ethic committee permission for each EUSTAR centre and informed consent, where appropriate according to local ethic regulations, were obtained prior to EUSTAR enrolment.

Contributorship.

Considering the following criteria:

Criterion 1: a) Substantial contributions to study conception and design; and/or b) Substantial contributions to acquisition of data; and/or c) Substantial contributions to analysis and interpretation of data.

Criterion 2: Drafting the article or revising it critically for important intellectual content

Criterion 3: Final approval of the version of the article to be published

The contribution of each author is as follow:

- Denis MONGIN: 1a, 1c, 2, 3
- Marco MATUCCI-CERINIC: 1b, 2, 3
- Ulrich A. WALKER: 1b, 2, 3

- Oliver DISTLER: 1b, 2, 3
- Radim BECVAR: 1b, 2, 3
- Elise SIEGERT: 1b, 2, 3
- Lidia P. ANANYEVA: 1b, 2, 3
- Vanessa SMITH: 1b, 2, 3
- Juan Jose ALEGRE-SANCHO: 1b, 2, 3
- Sule YAVUZ: 1b, 2, 3
- Massimiliano LIMONTA: 1b, 2, 3
- Gabriela RIEMEKASTEN: 1b, 2, 3
- Elena REZUS: 1b, 2, 3
- Madelon VONK: 1b, 2, 3
- Marie-Elise TRUCHETET: 1b, 2, 3
- Francesco DEL GALDO: 1b, 2, 3
- Delphine S. COURVOISIER: 1a, 1c, 2, 3
- Michele IUDICI: 1a, 1b, 1c, 2, 3

Patient and Public Involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

EUSTAR collaborators: Florenzo Iannone (Bari (Italy));; Otylia Kowal Bielecka (Bialystok (Poland)); Carmen Pizzorni (Genova (Italy)); Francesco Ciccia (Naples (Italy));; Simona Rednic (Cluj-Napoca (Romania)); P. Vlachoyiannopoulos (Athens (Greece)); Jiri Stork (Prague (Czech Republic)); Murat Inanc (Capa, Istanbul (Turkey)); Patricia E. Carreira (Madrid (Spain)); Srdan Novak (Rijeka (Croatia)); Laszlo´ Czirjak (Pecs (Hungary));; Eugene J. Kucharz (Katowice (Poland)); Katja Perdan-Pirkmajer (Ljublijana (Slovenia)); Bernard Coleiro (Balzan (Malta)); Gianluca Moroncini (Ancona (Italy)); Dominique Farge Bancel (Paris (France)); Fabian A Mendoza (Philadelphia (USA)) Roger Hesselstrand (Lund (Sweden)); Mislav Radic (Split (Croatia)); Alexandra Balbir-Gurman (Haifa (Israel)); Andrea Lo Monaco (Ferrara (Italy)); Raffaele Pellerito (Torino (Italy)); Alessandro Giollo (Verona (Italy)); Jadranka Morovic-Vergles (Zagreb (Croatia)); Christopher Denton (London (United Kingdom));; Nemanja Damjanov (Belgrade (Serbia & Montenegro)); Jörg Henes (Tübingen (Germany)); Vera Ortiz Santamaria (Granollers, Barcelona (Spain)); Stefan Heitmann (Stuttgart (Germany)); Dorota Krasowska (Lublin (Poland)); Paul Hasler (Aarau (Switzerland)); Barbara Russo (Geneva (Switzerland)); Michaela Kohm (Frankfurt am Main (Germany)); Ivan Foeldvari (Hamburg (Germany)); Gianluigi Bajocchi (Reggio Emilia (Italy)); Maria Joao Salvador (Coimbra (Portugal)); Bojana Stamenkovic (Niska Banja (Serbia and Montenegro)); Carlo Francesco Selmi (Rozzano, Milano (Italy)); Mohammed Tikly (Johannesburg (South Africa)); Ariane Herrick (Salford (United Kingdom)); Ulf Muller-Ladner (Bad Nauheim (Germany)); Klaus Søndergaard (Aarhus N (Denmark)); Francesco Puppo (Genova (Italy)); Merete Engelhart (Hellerup (Denmark)); Gabriela Szu¨ cs (Debrecen (Hungary)); Carlos de la

Puente (Madrid (Spain)); Valeria Riccieri (Roma (Italy)); Ruxandra Maria Ionescu (Bucharest (Romania)); Ami Sha (Baltimore (USA)); Ana Maria Gheorghiu (Bucharest (Romania)); Cord Sunderko¨ tter (Mu¨ nster (Germany)); Joörg Distler (Erlangen (Germany)); Francesca Ingegnoli (Milano (Italy)); Luc Mouthon (Paris (France));; Francesco Paolo Cantatore (Foggia (Italy)); Susanne Ullman (Copenhagen (Denmark)); Carlos Alberto von Muhlen (Porto Alegre (Brazil)); Maria Rosa Pozzi (Monza (Italy)); Kilian Eyerich (Munich (Germany)); Piotr Wiland (Wroclaw (Poland)); Marie Vanthuyne (Brussels (Belgium));; Kristine Herrmann (Dresden (Germany)); Ellen De Langhe (Leuven (Belgium)); Branimir Anic, Marko Baresic, Miroslav Mayer (Zagreb (Croatia)); Maria U¨ prus, Kati Otsa (Tallin (Estonia));; Brigitte Granel (Marseille (France)); Carolina de Souza Mu¨ller (Curitiba (Brazil)); Svetlana Agachi (Chisinau (Republic of Moldova)); Simon Stebbings (Dunedin (New Zealand)); Alessandro Mathieu, Alessandra Vacca (Monserrato (CA) (Italy)); Percival D. Sampaio-Barros (S~ao Paulo (Brazil)); Lisa Stamp (Christchurch (New Zealand)); Kamal Solanki (Hamilton (New Zealand)); Douglas Veale (Dublin (Ireland)); Esthela Loyo, Carmen Tineo (Santiago (Dominican Republic)); Sergio Toloza (Catamarca (Argentina)); Mengtao Li (Beijing (China)); Walid Ahmed Abdel Atty Mohamed (Alexandria (Egypt)); Jacek Olas (Crakow (Poland)); Fahrettin Oksel, Figen Yargucu (Bornova, Izmir (Turkey)); Cristina-Mihaela Tanaseanu (Bucharest (Romania)); Rosario Foti (Catania (Italy)); Codrina Ancuta (Iasi (Romania)); Daniel E. Furst (Los Angeles (USA)); Britta Maurer (Bern (Switzerland)); Jacob van Laar (Middlesbrough (United Kingdom)); Marzena Olesinska (Warsaw (Poland)); Cristiane Kayser (S~ao Paulo (Brazil)); Nihal Fathi (Assiut (Egypt)); Paloma Garcıa de la Pena Lefebvre, Jorge Juan Gonzalez Martin (Madrid (Spain)); ~ Patrick Carpentier, Bernard Imbert (Grenoble (France)); Camille France`s, Patricia Senet (Paris (France)); Jean Sibilia (Strasbourg (France)); Ira Litinsky (Tel Aviv (Israel)); Jean Luc Sene´cal, Martial Koenig, France Joval, Grodzicky Tamara (Montreal (Canada));; Goda Seskute (Vilnius (Lithuania)); Lesley Ann Saketkoo (New Orleans (USA)); Eduardo Kerzberg (Buenos Aires (Argentina)); Washington Bianchi, Breno Valdetaro Bianchi (Rio de Janeiro (Brasil)); Ivan Castellvı (Barcelona (Spain)); Jasminka Milas-Ahic, Roberta Visevic (Osijek (Croatia));; Doron Rimar (Haifa (Israel)); Maura Couto (Viseu (Portugal)); Franc¸ois Spertini (Lausanne (Switzerland)); Antonella Marcoccia (Roma (Italy)); Sarah Kahl (Bad Bramstedt (Germany)); Vivien M. Hsu (New Brunswick (USA)); Thierry Martin (Strasbourg (France)); Sergey Moiseev, Pavel Novikov (Moscow (Russia)); Lorinda S. Chung (Stanford (USA)); Tim Schmeiser (WuppertalElberfeld (Germany)); Dominik Majewski (Poznan (Poland)); Zbigniew Zdrojewski (Gdansk (Poland)); Julia MartınezBarrio (Madrid (Spain)); Dinesh Khanna (Ann Arbor, Michigan (USA)); Vera Bernardino (Lisboa (Portugal)); Lelita Santo (Coimbra (Portugal)); Yair Levy (Kfar Saba (Israel));; Omer Nuri Pamuk (Edirne (Turkey)); Daniel Brito de Araujo (Pelotas, RS (Brasil)); Piercarlo Sarzi Puttini (Milano (Italy)); Marek Brzosko (Szczecin (Poland)); Hadi Poormoghim (Tehran (Iran)); Marta Maman (Buenos Aires (Argentina)); Ina Ko¨

tter (Hamburg (Germany)); Giovanna Cuomo (Naples (Italy)); Francis Gaches (Toulouse (France)); Laura Belloli (Milano (Italy)); Petros Sfikakis (Athens (Greece)); Juliana Markus (Uberlandia (Brazil)); Daniel Furst (Los Angeles (USA)); AnaMaria Ramazan (Constanta City (Romania)); Patrick Jego (Rennes (France)); Lorenzo Dagna (Milano (Italy)); JM van Laar (Utrecht (The Netherlands)); Lidia Rudnicka (Warsaw (Poland)); Susana Oliveira (Amadora (Portugal)); Fabiola Atzeni (Messina (Italy)); Masataka Kuwana (Tokyo (Japan)); Arsene Mekinian (Paris (France)); Mickae¨l Martin (Poitiers (France)); Yoshiya Tanaka (Kitakyushu (Japan)); Hidekata Yasuoka (Aichi (Japan)); Carmen-Pilar Simeo´ n-Aznar (Barcelona (Spain)); Tatsuya Atsumi (Sapporo (Japan)); Magda Parvu (Bucharest (Romania)); Ines Cordeiro (Lisboa (Portugal)); Nicoletta Del Papa (Milano (Italy)); Thomas Karonitsch (Vienna (Austria)); Anna Bazela-Ostromecka (Grunwaldzka (Poland)); Enrico Selvi (Siena (Italy)); Yasushi Kawaguchi (Tokyo (Japan)); Tomas Soukup (Hradec Kralove (Czech Republic)); Ignasi Rodriguez-Pinto (Barcelona (Spain)); Marija Geroldinger-Simic (Linz (Austria)); Gerard Espinosa (Barcelona (Spain)); Karen Voigt (Hamburg (Germany)); Torsten Kubacki (Ko¨ln (Germany)); Olena Garmish (Kiev (Ukraina)); Marta Mosca (Pisa (Italy)); Ulrich Gerth (Rheinfelden (Switzerland)); Ludmila Antonenko (Kiev (Ukraina)).

ORCID iD

Michele IUDICI https://orcid.org/0000-0001-5871-8806

J.J. Alegre-Sancho: 0000-0003-1641-0875

Elena REZUS: https://orcid.org/0000-0002-8175-2583

References

1. Meier FM, Frommer KW, Dinser R, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. *Ann Rheum Dis*. 2012;71(8):1355-1360. doi:10.1136/annrheumdis-2011-200742

2. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol*. 1988;15(2):202-205.

3. Herrick AL, Assassi S, Denton CP. Skin involvement in early diffuse cutaneous systemic sclerosis: an unmet clinical need. *Nat Rev Rheumatol*. 2022;18(5):276-285. doi:10.1038/s41584-022-00765-9

4. van Laar JM, Farge D, Sont JK, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA*. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368

5. Denton CP, Hughes M, Gak N, et al. BSR and BHPR guideline for the treatment of systemic sclerosis. *Rheumatology (Oxford)*. 2016;55(10):1906-1910. doi:10.1093/rheumatology/kew224

6. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017;76(8):1327-1339. doi:10.1136/annrheumdis-2016-209909

7. Galdo FD, Lescoat A, Conaghan PG, et al. Op0234 2023 Update of Eular Recommendations for the Treatment of Systemic Sclerosis. *Annals of the Rheumatic Diseases*. 2023;82(Suppl 1):154-155. doi:10.1136/annrheumdis-2023-eular.1383

8. Fernández-Codina A, Walker KM, Pope JE, Scleroderma Algorithm Group. Treatment Algorithms for Systemic Sclerosis According to Experts. *Arthritis Rheumatol*. 2018;70(11):1820-1828. doi:10.1002/art.40560

9. Hunzelmann N, Moinzadeh P, Genth E, et al. High frequency of corticosteroid and immunosuppressive therapy in patients with systemic sclerosis despite limited evidence for efficacy. *Arthritis Res Ther*. 2009;11(2):R30. doi:10.1186/ar2634

10. Iudici M, van der Goes MC, Valentini G, Bijlsma JWJ. Glucocorticoids in systemic sclerosis: weighing the benefits and risks - a systematic review. *Clin Exp Rheumatol*. 2013;31(2 Suppl 76):157-165.

11. Calguneri M, Apras S, Ozbalkan Z, et al. The efficacy of oral cyclophosphamide plus prednisolone in early diffuse systemic sclerosis. *Clin Rheumatol*. 2003;22(4-5):289-294. doi:10.1007/s10067-003-0733-2

12. Sharada B, Kumar A, Kakker R, et al. Intravenous dexamethasone pulse therapy in diffuse systemic sclerosis. A randomized placebo-controlled study. *Rheumatol Int*. 1994;14(3):91-94. doi:10.1007/BF00300808

13. Griffiths-Jones DJ, Garcia YS, Ryder WD, et al. A Phase II randomised controlled trial of oral prednisolone in early diffuse cutaneous systemic sclerosis (PRedSS). *Rheumatology (Oxford)*. Published online January 13, 2023. doi:10.1093/rheumatology/kead012

14. Iudici M, Fasano S, Iacono D, Russo B, Cuomo G, Valentini G. Prevalence and factors associated with glucocorticoids (GC) use in systemic sclerosis (SSc): a systematic review and meta-analysis of cohort studies and registries. *Clin Rheumatol*. 2014;33(2):153-164. doi:10.1007/s10067-013-2422-0

15. Iudici M, **Mongin D**, Siegert E, et al. Glucocorticoids prescribing practices in systemic sclerosis: an analysis of the EUSTAR database. *Rheumatology*. Published online September 13, 2022:keac533. doi:10.1093/rheumatology/keac533

16. Dickerman BA, García-Albéniz X, Logan RW, Denaxas S, Hernán MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med*. 2019;25(10):1601-1606. doi:10.1038/s41591-019-0597-x

17. Matthews AA, Danaei G, Islam N, Kurth T. Target trial emulation: applying principles of randomised trials to observational studies. *BMJ*. 2022;378:e071108. doi:10.1136/bmj-2022-071108

18. Walker UA, Tyndall A, Czirják L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis*. 2007;66(6):754-763. doi:10.1136/ard.2006.062901

19. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum*. 2013;65(11):2737-2747. doi:10.1002/art.38098

20. Galluccio F, Walker UA, Nihtyanova S, et al. Registries in systemic sclerosis: a worldwide experience. *Rheumatology (Oxford)*. 2011;50(1):60-68. doi:10.1093/rheumatology/keq355

21. Maurer B, Graf N, Michel BA, et al. Prediction of worsening of skin fibrosis in patients with diffuse cutaneous systemic sclerosis using the EUSTAR database. *Ann Rheum Dis*. 2015;74(6):1124-1131. doi:10.1136/annrheumdis-2014-205226

22. Khanna D, Clements PJ, Furst DE, et al. Recombinant human relaxin in the treatment of systemic sclerosis with diffuse cutaneous involvement: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2009;60(4):1102-1111. doi:10.1002/art.24380

23. Pope JE, Bellamy N, Seibold JR, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum*. 2001;44(6):1351-1358. doi:10.1002/1529-0131(200106)44:6<1351::Aid-art227>3.0.Co;2-i

24. Hoffmann-Vold AM, Allanore Y, Alves M, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis*. 2021;80(2):219-227. doi:10.1136/annrheumdis-2020-217455

25. Wu W, Jordan S, Becker MO, et al. Prediction of progression of interstitial lung disease in patients with systemic sclerosis: the SPAR model. *Ann Rheum Dis*. 2018;77(9):1326-1332. doi:10.1136/annrheumdis-2018-213201

26. Herrick AL, Peytrignet S, Lunt M, et al. Patterns and predictors of skin score change in early diffuse systemic sclerosis from the European Scleroderma Observational Study. *Ann Rheum Dis*. 2018;77(4):563-570. doi:10.1136/annrheumdis-2017-211912

27. Amjadi S, Maranian P, Furst DE, et al. Course of the modified Rodnan skin thickness score in systemic sclerosis clinical trials: analysis of three large multicenter, double-blind, randomized controlled trials. *Arthritis Rheum*. 2009;60(8):2490-2498. doi:10.1002/art.24681

28. Dobrota R, Maurer B, Graf N, et al. Prediction of improvement in skin fibrosis in diffuse cutaneous systemic sclerosis: a EUSTAR analysis. *Ann Rheum Dis*. 2016;75(10):1743-1748. doi:10.1136/annrheumdis-2015-208024

29. Mihai C, Dobrota R, Assassi S, Mayes MD, Distler O. Enrichment Strategy for Systemic Sclerosis Clinical Trials Targeting Skin Fibrosis: A Prospective, Multiethnic Cohort Study. *ACR Open Rheumatol*. 2020;2(8):496-502. doi:10.1002/acr2.11165

30. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons, Ltd; 1987. doi:10.1002/9780470316696.fmatter

31. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2019. https://www.R-project.org

32. Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*. 2011;45:1-67. doi:10.18637/jss.v045.i03

33. 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(12):102403. doi:10.1016/j.autrev.2019.102403

34. Iudici M. What should clinicians know about the use of glucocorticoids in systemic sclerosis? *Mod Rheumatol*. 2017;27(6):919-923. doi:10.1080/14397595.2016.1270796

35. Khanna D, Furst DE, Hays RD, et al. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. *Ann Rheum Dis*. 2006;65(10):1325-1329. doi:10.1136/ard.2005.050187

36. 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(9):1613-1619. doi:10.1002/1529-0131(199809)41:9<1613::Aid-art11>3.0.Co;2-o

37. McCoy CE. Understanding the Intention-to-treat Principle in Randomized Controlled Trials. *West J Emerg Med*. 2017;18(6):1075-1078. doi:10.5811/westjem.2017.8.35985

38. van den Hombergh WMT, Kersten BE, Knaapen-Hans HKA, et al. Hit hard and early: analysing the effects of high-dose methylprednisolone on nailfold capillary changes and biomarkers in very early systemic sclerosis: study protocol for a 12-week randomised controlled trial. *Trials*. 2018;19(1):449. doi:10.1186/s13063-018-2798-x

Figure legend.

Figure 1: Flowchart of the selection process of the target population from the EUSTAR database.

Figure 2: Panel A: modified Rodnan skin score (mRSS) at baseline and after 12 ± 3 months for patients receiving immunosuppression alone ('control') and those receiving immunosuppression plus glucocorticoids ('treatment')- Panel B: distribution of the mRSS difference between12 ± 3 months and baseline for the two groups.

Table 1. Patients' characteristics at baseline. P values are provided by paired t test for continuous variables, paired Wilcoxon tests for the modified Rodnan and score, and McNemar test for categorical variables with 2 categories, Friedman test for categorical variable with more than 2 categories.

	Overall	Control group		Treated group		p
		value	% missing data	value	% missing data	
N patients	208	104		104		
Male, n, %	68 (33)	36 (35)	0.0	32 (31)	0.0	0.66
Age (year), mean (SD)	49 (12)	50 (14)	0.0	49 (11)	0.0	0.97
Smoking ever, n (%)	62 (36)	31 (38)	22	31 (35)	14	0.24
Immunosuppressant treatment, n (%)						
methotrexate	84 (40.4)	45 (43.3)	0.0	39 (37.5)	0.0	0.46
rituximab	20 (9.6)	13 (12.5)	0.0	7 (6.7)	0.0	0.24
cyclophosphamide	43 (20.7)	16 (15.4)	0.0	27 (26.0)	0.0	0.06
mycophenolate mofetil	73 (35.1)	38 (36.5)	0.0	35 (33.7)	0.0	0.76
other	6 (2.9)	4 (3.8)	0.0	2 (1.9)	0.0	0.62
Combination of immunosuppressant treatment, n (%)	19 (9.1)	12 (11.5)	0.0	7 (6.7)	0.0	0.30
Daily prednisone dose, mg/day, median (IQR)	----	----		5.0 [5.0, 10.0]	5.8	
Disease duration (years), mean (SD)	2.4 (1.4)	2.5 (1.3)	0.0	2.3 (1.5)	0.0	0.34
Baseline mRSS, median [IQR]	18.0 [12.0, 23.0]	18.0 [12.0, 23.0]	0.0	19.0 [12.8, 23.0]	0.0	0.76
Forced vital capacity (% predicted), mean (SD)	84 (20)	84 (22)	14	84 (19)	11	0.99
Diffusing capacity of the lung for carbon monoxide, mean (SD)	62 (18)	64 (21)	20	59 (15)	18	0.11
Joint synovitis, n (%)	37 (18)	15 (15)	4	22 (22)	2	0.16
Anti-topoisomerase positive, n (%)	112 (59)	54 (56)	8	58 (61)	9	0.75
Anti-RNA polymerase III positive, n (%)	30 (25)	17 (30)	44	13 (20)	38	0.41
Presence of tendon friction rubs, n (%)	33 (17)	15 (16)	8	18 (18)	5	0.83
Interstitial lung disease*	100 (43.5)	51 (40.5)	0.0	49 (47.1)	0.0	0.38
Baseline year, n (%)			0.0		0.0	0.83
2013	36 (17)	20 (19)		16 (15)		

	Overall	Control group		Treated group		p
		value	% missing data	value	% missing data	
2014	45 (22)	19 (18)		26 (25)		
2015	44 (21)	20 (19)		24 (23)		
2016	25 (12)	13 (12)		12 (11)		
2017	17 (8)	10 (10)		7 (7)		
2018	33 (16)	17 (16)		16 (15)		
2019	8 (4)	5 (5)		3 (3)		

* at lung X-ray or high-resolution computed tomography

Table 2. Primary and secondary outcomes for the main. P values are provided by paired t test for continuous variables and McNemar test for categorical variables.

	Overall	Controls		Treatment		p
		value	% missing data	value	% missing data	
Primary outcome						
mRSS difference	-2.9 (7.4)	-3.2 (6.8)	0	-2.6 (8.0)	0	0.55
Secondary outcomes						
Progressive skin fibrosis, n (%)	25 (12)	10 (10)	0	15 (14)	0	0.39
Progressive lung fibrosis, n (%)	41 (27)	23 (29)	23	18 (26)	34	0.83
Regressive skin and lung fibrosis, n (%)	83 (49)	41 (47)	15	42 (51)	21	0.48
Renal crisis, n (%)	2 (1)	1 (1)	0	1 (1)	0	0.99

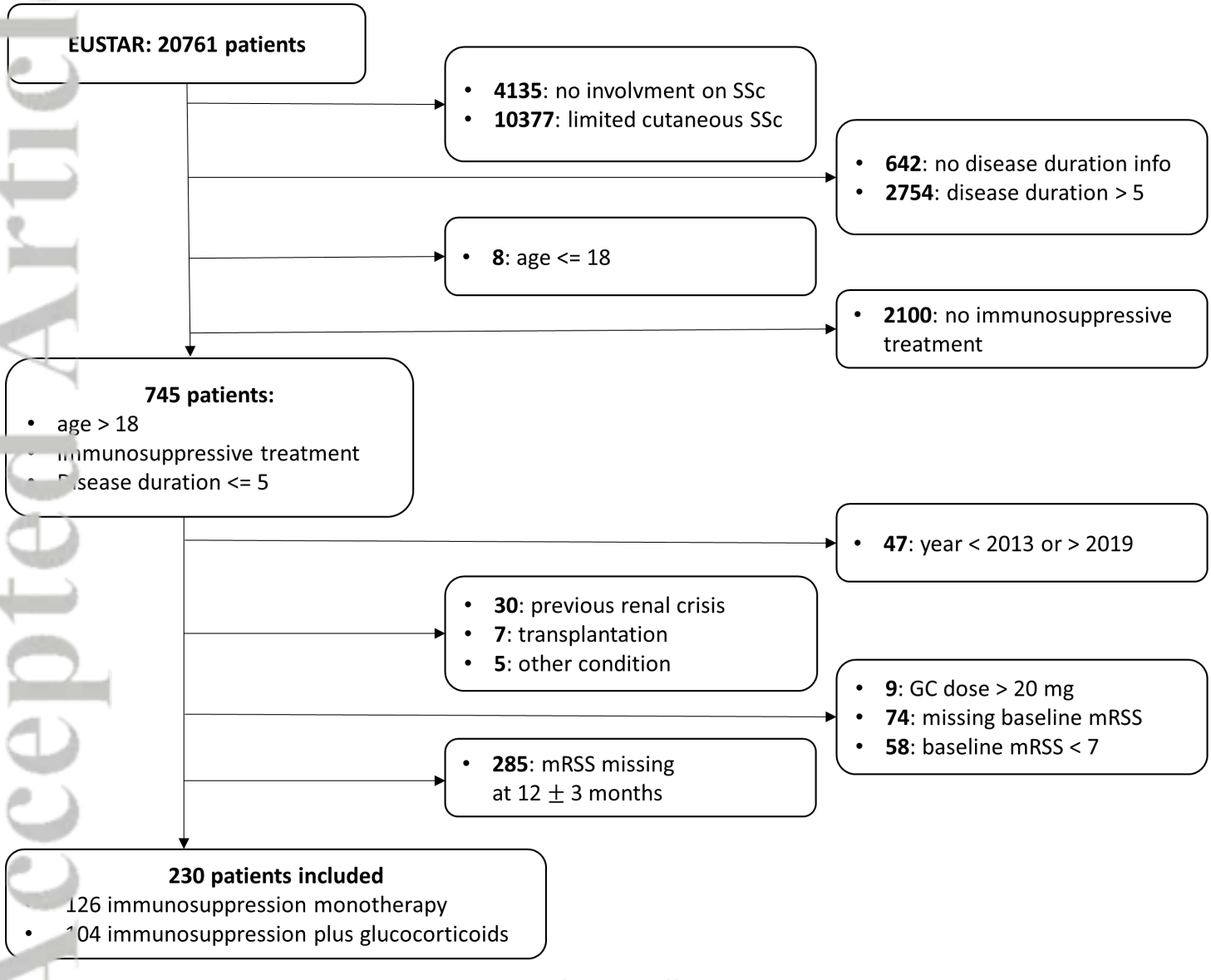

figure1.tiff

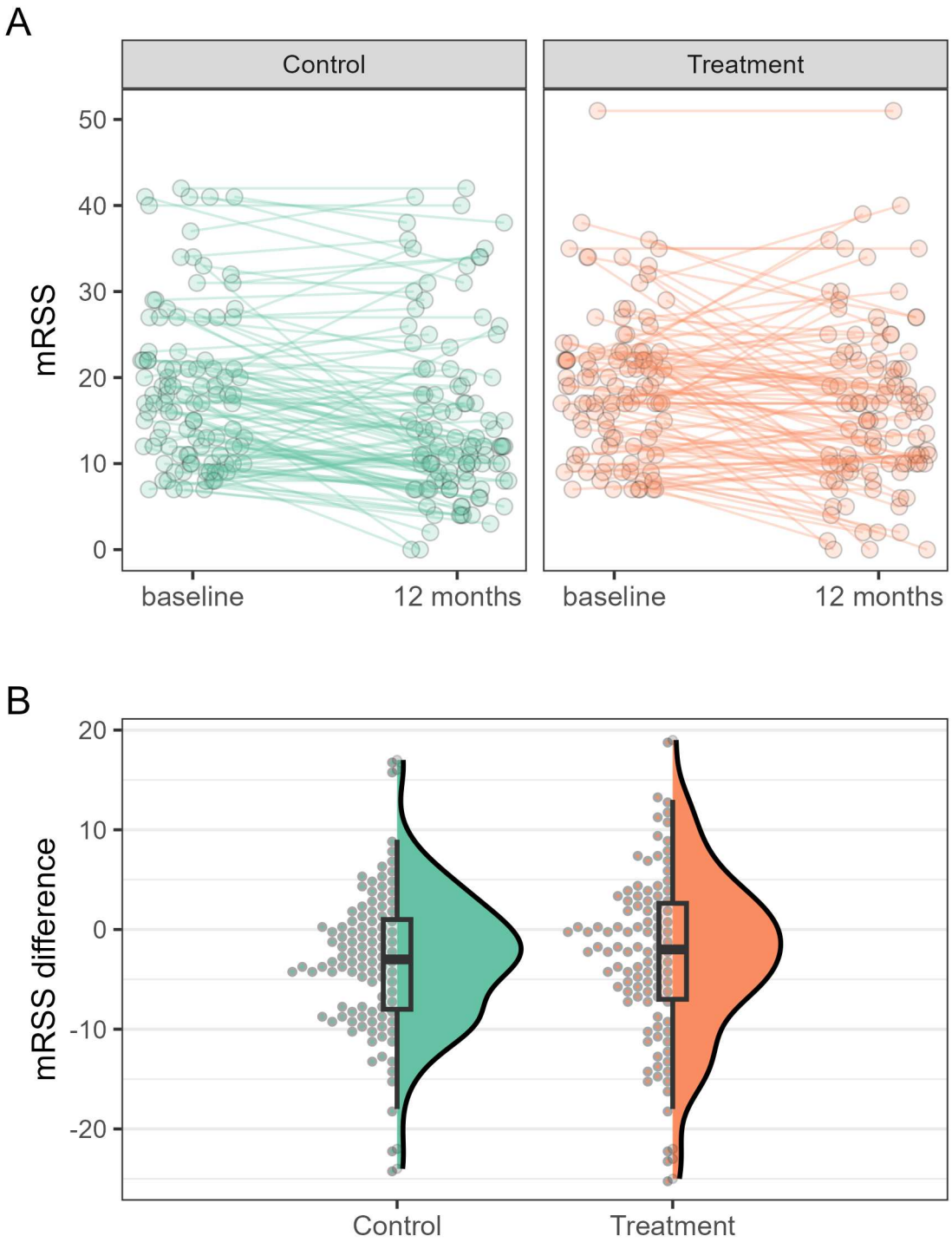

figure2.tiff