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Glucocorticoids prescribing practices in systemic sclerosis: an analysis of the EUSTAR database.

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Abstract

Objectives. To estimate the long-term exposure to glucocorticoids (GC), the factors associated with, and the variations in prescribing practices over time and across recruiting countries.

Methods. We included patients with systemic sclerosis (SSc) having a visit in the EUSTAR database from January 2013 onward. We analyzed the prevalence and the main features of GC users, the exposure to GC over time, and the respective dosages. Multivariable linear regression analysis identified factors associated with GC intake duration. Time trends, and variations in GC utilization across recruiting countries were explored. Missing data were imputed using multiple imputation with chained equations.

Results. The 9819 patients included were mostly females (85%), lcSSc (73%), median age 58 years. At baseline, 34% of patients (n = 2769/8109) (48% dcSSc vs. 29% lcSSc) were on GC, median dose 7.5 mg/day. GC users were more frequently males, dcSSc, anti-Scl70 positive, with a more severe disease. On average, GC users spent 25% of their follow-up time (median 33.2 months) on GC, with no significant between-subsets difference. Notably, 33% (n= 971/2959) and 22% (n= 647/2959) of patients followed-up for >1 year, had received GC for >6 and >12 months, respectively. In multivariable analysis, patient and disease's characteristics poorly explained the variability of GC exposure (adjusted-R^2 = 0.06, P<0.001). GC utilization varied within and across countries, and gradually decreased over time (36% in 2013 vs. 23% in 2018).

Conclusions. GC are widely and long-term prescribed in SSc, with significant between- and within-country(ies) differences. A gradual decrease in their utilization is observed.

Keywords. systemic sclerosis, glucocorticoids, epidemiology

Key messages

- Glucocorticoids are widely and long-term prescribed in SSc.
- Glucocorticoids users spent 25% of their follow-up time on these agents.
- Glucocorticoids utilization is variable within and across countries, and has gradually decreased over time.

Introduction

Although glucocorticoids are largely prescribed in rheumatology for their anti-inflammatory and disease-modifying action, their role in systemic sclerosis (SSc) is not well established (1, 2), along with the magnitude of their use in daily care.

The rationale for prescribing glucocorticoids comes from the evidence that SSc patients with early disease present an inflammatory component that can theoretically respond to steroids (3, 4). Perivascular and tissue inflammatory infiltrates consisting of mononuclear cells and mainly CD4+ lymphocytes are observed in the skin of early diffuse SSc (5, 6). Moreover, corticosteroids can decrease vascular leak, and the expression of adhesion molecules on endothelial cells (7), mechanisms involved in the early phase of SSc pathogenesis. Glucocorticoids are also prescribed to control symptoms. Experience accumulated in clinical setting suggests that they are useful to resolve musculoskeletal inflammatory manifestations, and SSc patients receiving corticosteroids often report improvement of itchiness, fatigue and appetite (1, 2).

However, the use of glucocorticoids remains controversial in SSc because of the lack of solid evidence demonstrating their anti-fibrotic efficacy when administered alone or in

combination with other immunosuppressive drugs. Additionally, important arguments against their use are the established association with scleroderma renal crisis and additional, SSc-independent, general adverse events (1, 8). Possible harmful effects of glucocorticoids include the inhibition of prostaglandins and the amplification of responses to vasoconstrictive substances like catecholamines (1-7). These actions could potentially be dangerous in SSc, in which vascular damage can result in Raynaud's phenomenon, digital ulcers, pulmonary hypertension and scleroderma renal crisis (1-7).

Despite these limitations, it seems that use of especially low dose glucocorticoids is widespread in SSc. Data from cross-sectional studies (9-12) and physician's survey (13) suggest that up to one-third of limited cutaneous SSc (lcSSc) and up to half diffuse cutaneous SSc (dcSSc) patients are on corticosteroids at a given time point. However, differently from other systemic rheumatic diseases, no study has investigated the utilization of long-term glucocorticoids in SSc. Estimating glucocorticoids exposure, and understanding the main features associated with their long-term use, is pivotal to achieve a better and more reasoned prescription, avoid related harms, and identify potential targets for improvement of quality management.

Herein, using data from a large international database, we have estimated to what extent SSc patients are exposed to glucocorticoids over time, identified the main features of patients receiving long-term glucocorticoids, and explored variations in prescribing patterns across countries and over time.

Methods

EUSTAR database, inclusion criteria and ethics

This study used prospectively collected data from the EUSTAR database. The structure of the EUSTAR database and minimum essential dataset have been described previously (11, 14). A set of demographics, clinical, imaging, and treatment data are collected at least yearly for each patient. We included all patients having at least one visit from January 1st, 2013 to May, 17th 2019, and available data on glucocorticoids in at least one observation. The EUSTAR database collects at each visit information on the use and dose of oral glucocorticoids, expressed as daily dose (milligrams) of prednisone-equivalent.

Local ethic committee permission for each EUSTAR centre and informed consent, where appropriate according to local ethic regulations, were obtained prior to EUSTAR enrolment.

Prevalence of glucocorticoids at study entry, time-trends, and exposure over time

For each patient, we calculated the prevalence of any glucocorticoids use at study entry and the respective dosages. In order to study temporal trends, a cross-sectional analysis evaluating the yearly prevalence of glucocorticoids users was performed between 2013, 1st January, (when glucocorticoids use and dose started to be documented), and 17th May 2019). The annual prevalence of glucocorticoids use was defined as the proportion of users per 100 individuals for the corresponding year.

For every patient, we identified episode(s) of glucocorticoids use over the entire follow-up. Several treatment episodes from a single patient could have been included. The duration of each episode was the time between two consecutive visits if glucocorticoids were prescribed at both visits. If prescribed at a given visit, but discontinued to the following one, the time spent on glucocorticoids for this treatment episode was considered as half of the time elapsed between the two observations, to account for potential between-visit tapering. Where information was lacking, we carried forward the glucocorticoids status (i.e. 'user' or 'nonuser') of the most recent available visit. In the case of patients on these drugs at the last observation, we added 6-month to the total time spent on glucocorticoids to account for potential tapering of the drug. Time spent on glucocorticoids was then calculated by summing each duration of treatment episode since study entry, and was expressed in months. For patients with no available information on corticosteroids use at baseline, the total follow-up time was calculated from the date of the first visit with available information on glucocorticoids onward, and adding 6-month to total follow-up time. Time spent on glucocorticoids was then normalised by the overall follow-up time, to obtain, for each patient, the percentage of time spent on glucocorticoids.

Subgroup analyses

Prevalence of glucocorticoid utilization at study entry, time-trends, time spent and proportion of time spent on glucocorticoids, were also evaluated in the subgroup of patients with an early (< 3 years) disease duration, and in patients with limited cutaneous and diffuse cutaneous subset. We also showed the proportion of users at baseline and the median proportion of time spent on glucocorticoids across main recruiting countries (those including more than 100 patients).

Statistical analysis

For categorical variables, data were presented as frequencies and percentages. Continuous variables were expressed as median [range, interquartile range]. The annual prevalence of glucocorticoids use was defined as the yearly proportion of glucocorticoids

users/100 patients. For glucocorticoids users, the association between the median proportion of time spent on glucocorticoids per country and the median proportion of time spent on immunosuppressants per country was estimated by Spearman correlation.

Factors associated with the proportion of time spent on glucocorticoids were determined based on expert knowledge, and the association was evaluated using multivariable linear regression model using age, sex, time from first non-Raynaud, SSc subset, current digital ulcers, puffy fingers, modified Rodnan skin score, worsening of skin, worsening of cardiopulmonary, worsening of vascular, joint synovitis, tendon friction rubs, pericardial effusion, anti-Scl70 positivity, forced vital capacity (FVC), diffusing lung capacity for carbon monoxide (DLCO), presence of interstitial lung disease, creatine kinase elevation, C-reactive protein.

Missing data were imputed with multiple imputation (MI) using the R package MICE and the predictive mean matching algorithm. For the imputation model, all the above variables, except age and gender, were used.

A P value < 0.05 was considered statistically significant. Analyses were performed using R 4.1 statistical software (R Development Core Team, Vienna, Austria).

Results

Baseline characteristics, prevalence and factors associated with glucocorticoids use at study entry

We studied 9819 of 9989 patients with available data on glucocorticoids over time, of whom 8109 (82%) had information on baseline glucocorticoids use.

The 9819 patients included were mostly females (85%), lcSSc (73%), with a median age of 58 years [IQR 48 - 67] and median disease duration from the first non-Raynaud's of 8 years [IQR 3.3 - 14.4]. Less than one tenth (n = 724; 7%), and about one-fifth (n = 1896; 19%) of patients had <1- and <3- year disease duration, respectively. The main characteristics of the disease at baseline are summarized in Table 1.

Of the 8109 patients with available data on glucocorticoids use at study entry, 2769 (34%) were considered 'users' at median daily dose of 7.5 mg [IQR 7.5 - 15], with higher figures for dc- compared to lcSSc patients (966/1991, 48% vs. 1645/5610, 29%; P < 0.001)(Table 1). A minority of patients had prescribed >15 mg/day (n = 146; 2%) prednisone equivalent. On average, patients receiving glucocorticoids at baseline were more frequently males, dcSSc, anti-Scl70 positive, reported more commonly a worsening of skin, cardiopulmonary, vascular conditions, had an overall more active disease, more joint synovitis, pericardial effusion, higher C-reactive protein, and worse FVC and DLCO values (Table 1). Patients treated with >15 mg/day vs those receiving ≤ 15 mg/day of prednisone equivalent were more frequently males,

dcSSc, had a shorter disease duration, and a higher prevalence of worsening of skin and respiratory symptoms, lower respiratory volumes, creatine kinase elevation, and an overall higher disease activity (Supplementary Table S1, available at *Rheumatology* online). In the whole sample, glucocorticoids were in most of cases (64%) associated with parallel use of an immunosuppressive drug, mainly methotrexate (29%), cyclophosphamide (21%), mycophenolate mofetil (21%), azathioprine (17%), rituximab (6%).

In the subgroup of patients with an early disease duration (< 3 years from first non-Raynaud's onset) (n = 1896), the prevalence of users was in line with that observed in the entire sample (51% for dcSSc vs. 30% for lcSSc, P < 0.001), but the proportion of diffuse patients receiving glucocorticoids in combination with immunosuppressors raised to 80%.

Exposure over time to glucocorticoids

During a median follow-up of 33.2 months [IQR 13.1 - 62.6], 3775 (38%) patients (52.3% dcSSc, n = 1308/2498; 33% lcSSc, n = 2240/6697; P < 0.0001) had received steroids at least once, with a median dose of 5 mg/day. Twenty-one percent of patients who had received glucocorticoids experienced at least one episode of arthritis during the follow-up, 12% at least one episode of myositis and/or increased creatine kinase values, and 30% either arthritis or myositis and/or increased creatine kinase values.

The median time spent on glucocorticoids was 6 months [IQR 6-9, range 1 - 96]. On average, they spent 25% [IQR 12 - 58] of their follow-up time on glucocorticoids. For patients who were followed-up for > 1 year (n = 2959), 971 (33%) and 647 (22%) had received glucocorticoids for more than 6 and 12 months, respectively (Figure 1). Exposure to glucocorticoids was significantly longer for males (median 28% [IQR 13 - 71] vs. 25% [IQR 12 - 53], P < 0.01), but comparable between limited and diffuse subsets. Accordingly, the number of patients on glucocorticoids for more than one-third (503/1308 [38%] dcSSc vs. 862/2240 [38%] lcSSc; P = 0.987) or more than half (365/1308 [28%] dcSSc vs. 577/2240 [26%] lcSSc; P = 0.162) of the follow-up time was also comparable between the subsets. The analysis of patients with an early disease (time from the first non-Raynaud's onset < 3 years), led to similar results, both in terms of proportion time spent on glucocorticoids (median 27% [IQR 14-49] of follow-up time), or for the rate of SSc patients receiving glucocorticoids for more than one-third (132/336 [39%] dcSSc vs. 147/418 [35%] lcSSc; P = 0.24), or more than half (94/336 [28%] dcSSc vs. 114/418 [27%] lcSSc; P = 0.83) of the follow-up time.

The longitudinal analysis of glucocorticoids prescription showed that they were used in combination with an immunosuppressive drug in 2462/4356 (57%) of the visits, mainly with methotrexate (24%), mycophenolate mofetil (18%), cyclophosphamide (16%), azathioprine (14%) and rituximab (6%).

Multivariable linear regression showed that the proportion of time spent on corticosteroids was positively associated with age, male sex, worsening of cardiopulmonary manifestations, synovitis, tendon friction rubs, pericardial effusion, lower FVC or DLCO, lung fibrosis at high-resolution computed tomography, increased creatine kinase or C-reactive protein, and negatively associated with the limited subset and the mRSS (adjusted R^2 = 0.06, P >0.0001). The results of linear regression in the whole sample, and in the subgroup of patients with early disease are shown in Table 2.

Temporal trends of glucocorticoids use

The annual proportion of glucocorticoids users gradually decreased between 2013 and 2018 in the overall sample of patients (36% in 2013 vs. 23% in 2018), both in those with lcSSc (23% in 2013 to 14% in 2018), or dcSSc (36% in 2013 to 23% in 2018). To adjust for disease severity, the same analysis performed in patients with an early disease duration confirmed the observed trend, with the rate of dcSSc glucocorticoids users falling from about 60% in 2013 to less than 40% in 2018. Figure 2 shows the temporal trend of glucocorticoids use in the whole sample and in early SSc patients.

Prescribing practices according to countries

The baseline proportion of glucocorticoids users (in the whole sample and for each SSc subset) across the main recruiting countries was highly heterogeneous, with the highest figures recorded in Russia, Turkey, and Poland, the lowest in Denmark and Belgium (Figure 1). In most countries, glucocorticoids have been prescribed in more than 50% of dcSSc patients (Figure 1).

The median proportion of time spent on glucocorticoids also greatly varied across countries (Figure 3). We found a strong correlation between the median proportion of time spent on glucocorticoids and the median proportion of time spent on immunosuppressants per country among patients treated with glucocorticoids (rho 0.71 [95%CI 0.30 - 0.90], P = 0.001)(Supplementary Figure S1, available at *Rheumatology* online). The wide range of time spent on glucocorticoids within each country mirrors the high variability in prescribing patterns across countries.

Discussion

We have shown that glucocorticoids were commonly prescribed in SSc, mainly to patients with a more severe condition or presenting signs or symptoms of an active inflammatory disease. One-third of glucocorticoid-treated patients had an active musculoskeletal inflammatory condition over their disease course. Although more dcSSc patients received glucocorticoids,

the duration of treatment (on average a quarter of follow-up time) was similar in the two subsets. We observed a huge heterogeneity of glucocorticoids prescription across and within countries, and the mean time spent on these agents was poorly explained by patient's features. Interestingly, these drugs are being gradually less prescribed. Doses higher than 15 mg/day were rarely given, mainly to patients with a high disease activity and with lung and skin worsening disease.

Our cross-sectional analysis revealed that, at study entry, about one third of lcSSc and half of dcSSc patients were current corticosteroid users, with similar figures in both the whole sample and in the subgroup of incident patients. This finding, consistent with the results of a meta-analysis from national and international SSc registries and cohorts (10), confirms a large use of these drugs in SSc, irrespective from disease duration (our main analysis focused on patients with a median disease duration of about 8 years), and in spite of the absence of evidence about their efficacy (1, 13, 15). In daily practice, by analogy with other inflammatory autoimmune diseases, glucocorticoids are prescribed in SSc to obtain symptoms relief or to treat overt active inflammatory manifestations (1). They are also delivered in combination with immunosuppressive drugs for interstitial lung disease or diffuse skin fibrosis (1, 13, 15), even if their utility is not proven. The results of two randomized controlled trials investigating the efficacy of glucocorticoids in early diffuse disease (16, 17), will hopefully better drive their use in this subgroup of patients in next years. As far as interstitial lung disease, corticosteroids at a dose $\leq$ 10 mg per day are generally among the permitted concomitant medications in randomized controlled trials, but no study has specifically demonstrated any benefit of these agents for this indication. A recent European consensus statement, recommended against glucocorticoids monotherapy for the treatment of interstitial lung disease (18).

Even at low doses, long-term glucocorticoid use is associated with increased risk of infection, osteoporosis, cataract, cardiovascular events (19, 20), and tapering glucocorticoids as rapidly as clinically feasible is recommended in most systemic autoimmune diseases. Nevertheless, a glucocorticoid-free status was not reached in our sample for a considerable proportion of SSc patients. Indeed, we observed that nearly 1 of 3 treated patients followed for at least 1 year continued to receive $\geq$ 5 mg/day of corticosteroids for more than 6 months, and about 1 of 4 for more than 1 year. The reasons accounting for long-term glucocorticoids exposure in SSc are various and difficult to be completely understood. Physician's beliefs about the utility of long-term exposure to corticosteroids (21), failure to achieve discontinuation (22, 23), or the poor knowledge about the detrimental effects of long-term low dose corticosteroids use (24), could at least in part explain such observation.

Glucocorticoids prescription hugely varied across and within countries in our study, and the variability of glucocorticoids exposure was poorly explained by patient's related information. The strong correlation found between the extent of glucocorticoids use and that of immunosuppressive drugs weakens the hypothesis that the larger use of glucocorticoids in some countries could be justified by the unavailability of drugs with steroid-sparing effect. Conversely, it could reflect regional differences in management practices (i.e. physicians more prone to prescribe glucocorticoids and immunosuppressive drugs in some countries). A comprehensive analysis of the relationship between the prescription of glucocorticoids, immunosuppressive agents, and disease severity, would help to better understand differences in SSc management. This deserves a dedicated study and is beyond the aim of this paper. The high variability in glucocorticoids prescribing practices within countries also suggests that the lack of agreement among physicians (25) might be the main driver. Even if we cannot demonstrate this aspect by the analysis of our data, various studies have clearly shown that there is no consensus on how, to whom, and for how long glucocorticoids should be prescribed in SSc (12, 25-27). In the European Scleroderma Observational Study (ESOS) just about half of early diffuse patients received or had received glucocorticoids (12). Discrepancy in glucocorticoids use was highlighted in a survey conducted among experts from the Scleroderma Clinical Trials Consortium and from the Canadian Scleroderma Research (25). The observation that patient's characteristics explained only about 6% of the variability of glucocorticoids exposure in our multivariable model, further support this hypothesis. That said, we should acknowledge that in spite of a huge variability in prescribing practices, we found high consistency about the doses used, given that only a very small proportion of patients with a very active and severe disease had received more than 15 mg per day of prednisone equivalent. We remind that the risk of scleroderma renal crisis should always be kept in mind when prescribing prednisone equivalent higher than 15 mg per day to SSc patients.

Interestingly, glucocorticoids were less prescribed over time. This seems to be unrelated to the inclusion of patients with a milder disease these last years, since the same trends was also shown for those with a severe disease (early dcSSc). Reasons for this finding can include a better knowledge about the lack of proofs demonstrating the utility of these agents for preventing lung or skin fibrosis worsening (1, 2, 15, 28). We can also hypothesize that the growing awareness about the harms related to glucocorticoids chronic use, could represent a contributing factor. Actually, more attention is being paid over the last few years to the side effects associated with long-term glucocorticoids exposure, even if used at low dosages (29-

36), and steroid-free strategies are increasingly tested for systemic autoimmune diseases (37-39).

This study has some limitations. Due to the lack of available information, we were not able to explore the main indications for glucocorticoids prescription or discontinuation. This could have enabled us to better understand if long-term use is driven more by the need to control symptoms, by physician's beliefs about their potential effectiveness to slow down fibrosis accumulation, or by other reasons. Moreover, we could not appraise the potential SSc-(un)related consequences of the long-term intake of corticosteroids since many of these complications need to be investigated in a longer time span. Information bias is an issue, for two reasons. First, misclassification of glucocorticoids use is possible, since some patients could have filled a prescription only for short-term use in case of flares, or may have received these compounds for other reasons. Second, time on glucocorticoids was extrapolated between visits, and after last visit (by adding 6 months). However, this measurement error should not lead to systematic bias because it is not likely associated with clinical characteristics. Finally, our data mirrors the practice observed in the EUSTAR centers, that could not be representative of the whole picture of glucocorticoids management in a given country.

The strengths of this study are the availability of a large sample of patients, coming from different continents, and reflecting the daily clinical practices across the centres contributing to the EUSTAR database. Furthermore, we have for the first time prospectively explored the burden of glucocorticoids intake over time in SSc, topic that is (and has been) neglected in this disease so far.

In conclusion, low-dose oral corticosteroids are widely and long-term prescribed to SSc patients, mainly to those with a diffuse cutaneous subset. Glucocorticoids prescription is greatly heterogeneous across centers and countries, and is steadily declining in last years. Even if relatively few patients received more than 15 mg per day of prednisone, the risk of scleroderma renal crisis should always be considered for patients receiving this dosage. Identifying areas of high variability in practice underscores the need for better evidence to drive corticosteroids prescription and might also be instrumental to suggest potential targets for quality improvement.

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Conflict of interests

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Data availability statement. The data that support the findings of this study are available upon reasonable request.

Tables

Table 1. Characteristics of SSc patients included in the study.

Characteristics	Overall sample	Not on GC	on GC	P	Missing data (%)*
	N=9819	N=5340	N=2769		
Age, median (IQR)	58 (48-67)	58 (48-67)	57 (47-67)	0.253	0
Male sex, n, %	1476 (15)	734 (14)	490 (18)	<0.001	0
Body weight, Kg, median (IQR)	65 (57-75)	65 (57-74)	65 (56-75)	0.983	11
Disease characteristics					
lcSSc subset, n, %	6697 (73)	3965 (80)	1645 (63)	<0.001	6
Disease duration since first non-Raynaud symptom, median (IQR), years	8 (3.3-14.4)	7.5 (3-14)	7.5 (3-14)	0.124	15
mRSS, median (IQR)	5 (2-11)	5 (2-9)	7 (2-14)	<0.001	15
Raynaud’s phenomenon, n, %	9086 (95)	5043 (96)	2602 (96)	0.664	3

Intestinal symptoms, n, %	2325 (24)	1218 (23)	703 (26)	0.013	3
Puffy fingers, current, n, %	3411 (42)	1966 (43)	966 (41)	0.025	17
Current digital ulcers, n, %	1113 (14)	620 (12)	436 (17)	<0.001	18
Joint synovitis, n, %	1084 (11.6)	392 (8)	538 (21)	<0.001	4
Worsening of finger vascularization within the last month, n, %	1773 (20)	971 (20)	603 (24)	<0.001	9
Worsening of skin within the last month, n, %	1208 (14)	629 (13)	456 (18)	<0.001	9
Worsening of cardiopulmonary manifestation within the las month, n, %	1204 (11)	449 (9)	445 (17)	<0.001	8
Pericardial effusion, n, %	432 (6)	192 (5)	187 (9)	<0.001	28
Renal crisis, ever, n, %	142 (2)	63 (1)	55 (2)	0.006	2
Disease activity score 2001, score, median (IQR)	3 (2-5)	2 (1-5)	4 (2-6)	<0.001	0.5
DLCO/SB, median (IQR), % of predicted	69 (56-81)	71 (59-83)	64 (50-77)	<0.001	26
FVC, median (IQR), % of predicted	97 (81-110)	100 (85-113)	90 (74-105)	<0.001	21
Fibrosis at lung HRCT, n, %	2519 (45)	1048 (36)	1123 (60)	<0.001	43
Laboratory parameters					
Creatine kinase elevation (>3 ULN), n, %	667 (8)	330 (8)	274 (12)	<0.001	19
CRP elevation, n, %	1991 (23)	924 (19)	822 (33)	<0.001	28
Anti-centromere positive, n %	3543 (42)	2366 (50)	646 (27)	<0.001	14
Anti-topoisomerase I positive, n %	2799 (33)	1264 (27)	1067 (42)	<0.001	13
Anti-RNA polymerase III, n, %	374 (7)	226 (7)	105 (7)	0.854	43
Treatment					
Cyclophosphamide, n, %	843 (10)	256 (5)	566 (21)	<0.001	15
Methotrexate, n, %	1479 (18)	670 (13)	780 (29)	<0.001	16
Mycophenolate mofetil, n, %	990 (12)	406 (8)	563 (21)	<0.001	15
Azathioprine, n, %	763 (9)	282 (5)	462 (17)	<0.001	16
Rituximab, n, %	252 (3)	80 (1.5)	161 (6)	<0.001	0

GC, glucocorticoids; **IQR,** interquartile range; **mRSS,** modified Rodnan skin score; **SD,** standard deviation; **DLCO/SB.** Single breath diffusing capacity for carbon monoxide; **FVC.** Forced vital capacity; **HRCT,** High-resolution computed tomography; **ULN**, upper limit of normal. * Rate of missing data for patients with available data on glucocorticoids.

Table 2. Association of demographic and disease-related factors with the proportion time spent on glucocorticoids.

	Whole series N = 8109		Early SSc patients N =	
	Coef (95%CI)	**P value**	**Coef (95%CI)**	**P value**
Demographics				
Age	0.05 (0.01; 009)	<0.001	0.05 (-0.01; 0.13)	0.13
Male	2.3 (0.7; 3.9)	0.003	1.5 (-1.1; 4.1)	0.24
Characteristics of disease				
Time from first non-Raynaud	-0.02 (-0.09; 0.05)	0.55	-	-
lcSSc	-3.9 (-6.1; -1.6)	<0.001	-3.5 (-7.0; -0.06)	0.006
Current digital ulcers	-0.2 (-2.8; 2.3)	0.77	0.6 (-3.0; 4.3)	0.71
Puffy fingers	-0.031 (-1.8; 1.2)	0.58	1.3 (-1.0; 3.5)	0.22
mRSS	-0.09 (-0.3; 0.1)	<0.001	-0.07 (-0.3; 0.2)	0.17
Worsening of skin	1.6 (-1.5; 4.7)	0.07	1.8 (-1.4; 5.1)	0.21
Worsening of cardiopulmonary manifestation	5.6 (2.0; 9.3)	<0.001	8.5 (4.2; 12.8)	<0.001
Worsening of vascular manifestations	0.5 (-1.8; 2.9)	0.42	-1.3 (-4.2; 1.6)	0.29
Joint synovitis	8.5 (6.4; 10.5)	<0.001	6.5 (3.3; 9.7)	<0.001
Tendon friction rubs	4.4 (1.4; 7.4)	<0.001	2.7 (-1.7; 7.0)	0.21
Pericardial effusion	2.3 (-0.9; 5.4)	0.03	3.4 (-2.1; 8.8)	0.11
Anti-Scl70 positive	1.1 (-0.6; 2.7)	0.11	0.20 (-0.2; 4.8)	0.62
FVC	-0.01 (-0.1; -0.02)	<0.001	-0.01 (-0.08; 0.05)	0.57
DLCO	-0.04 (-0.1; 0.01)	<0.001	-0.05 (-0.12; 0.02)	0.04
Fibrosis at lung HRCT	4.4 (2.3; 7.0)	<0.001	5.2 (2.2 - 8.2)	<0.001
Laboratory				
Creatine kinase elevation	4.0 (0.9; 7.0)	<0.001	3.6 (-0.4; 7.6)	0.03
C-reactive protein	5.0 (3.0; 7.0)	<0.001	5.1 (2.2; 8.0)	<0.001

SE. Standard error; **lcSSc.** Limited cutaneous SSc; **mRSS.** Modified Rodnan skin score; **FVC.** Forced vital capacity; **DLCO.** Diffusing lung capacity for carbon monoxide; **HRCT,** High-resolution computed tomography.

Figure 1. Proportion of patients followed-up > 1 year who had been treated with glucocorticoids.

Legend. Proportion of patients followed-up > 1 year who had been treated with glucocorticoids (GC) for less or equal (blue bars) or more (red bars) than 6 months. Data are shown for the whole dataset and by countries, for diffuse cutaneous (left panel) or limited cutaneous (right panel) systemic sclerosis patients.

Figure 2. Yearly prevalence of glucocorticoids users.

Legend. Yearly prevalence of glucocorticoids (GC) users in the whole sample of patients (circles and solid lines), or in patients with a disease duration < 3 year (squares and dashed lines), according to disease subset.

Figure 3. Proportion time under glucocorticoids, and time under glucocorticoids for glucocorticoids users, in main recruiting countries.

Legend. GC, glucocorticoids.

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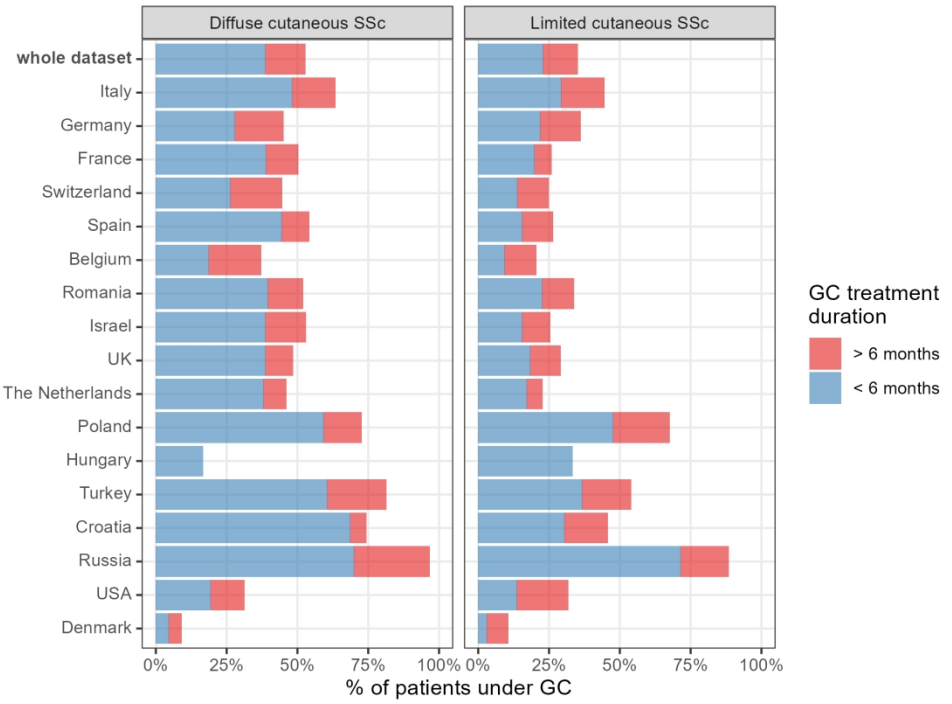

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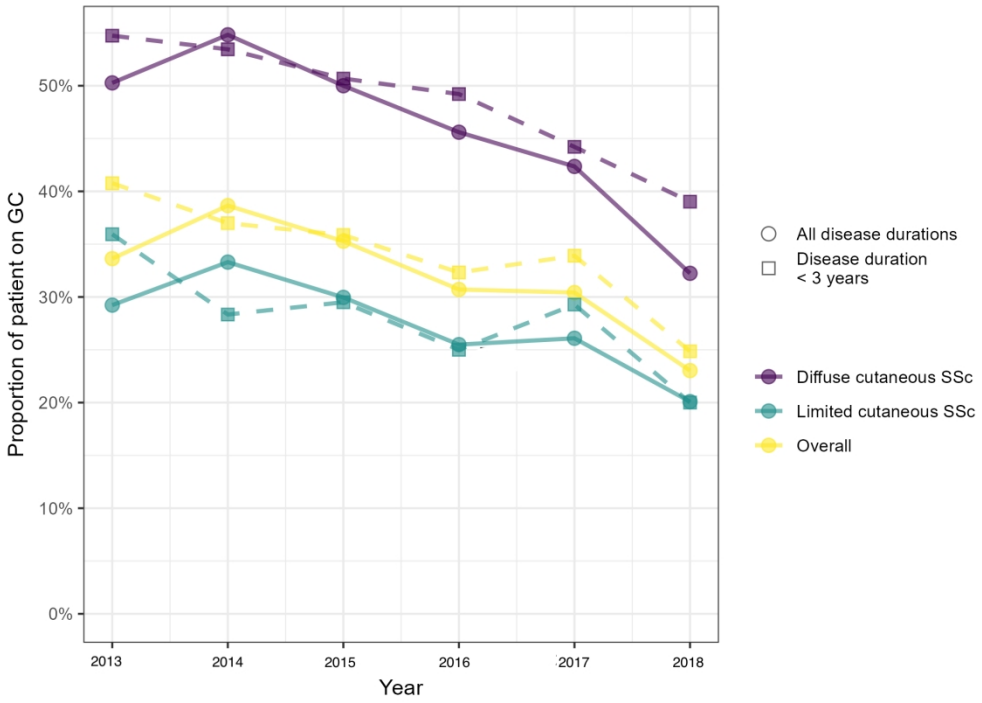

Figure 2. Yearly prevalence of GC users in the whole sample of patients (circles and solid lines), or in patients with a disease duration < 3 year (squares and dashed lines), according to disease subset.

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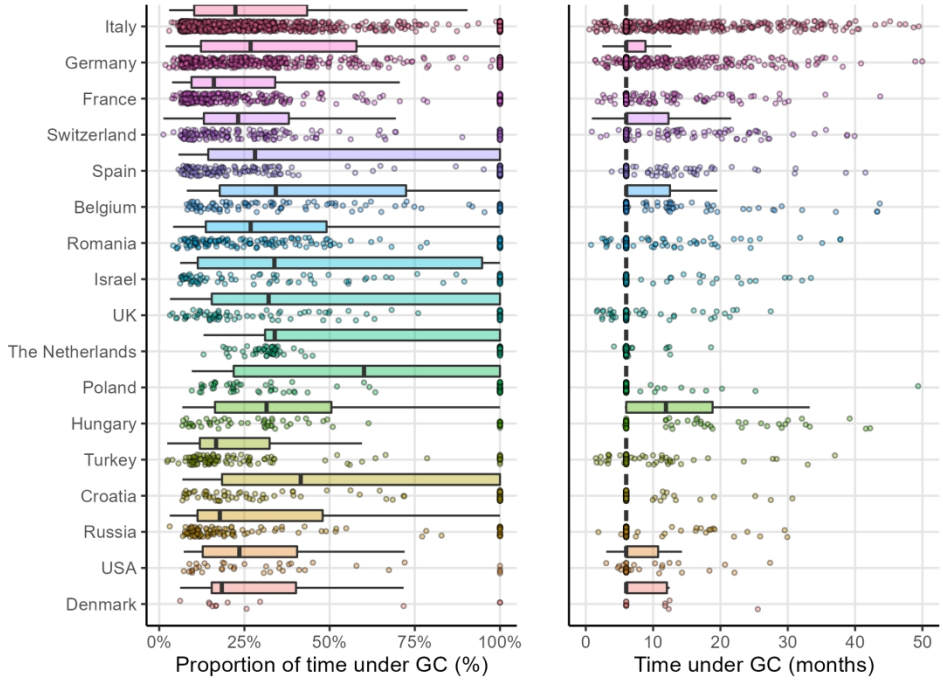

Figure 3. Distribution of the proportion of time under GC, and of the time under GC for GC users, in main recruiting countries.

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