Review

Glucocorticoids in systemic sclerosis: weighing up the benefits and risks – a systematic review

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ABSTRACT

Objectives. *To identify indications for which different dosages of glucocorticoids (GCs) have been prescribed in systemic sclerosis (SSc), and to assess the efficacy and safety of GCs in SSc.*

Methods. *A literature search focusing on experimental studies, observational studies, and case reports describing GC use in SSc was conducted using PubMed, EMBASE and Cochrane databases. Information about the study population, GC therapy and its effects was recorded. Available data have been summarised, and efficacy and safety of GCs have been assessed for different indications and dosages.*

Results. *Forty-four studies and 93 case reports were included in this review. GCs were applied in the treatment of interstitial lung disease (ILD), diffuse cutaneous disease, myopathy, painful hands and cardiac involvement, or accompanying anti-thymocyte globulin to prevent serum sickness in the context of stem cell transplantation. GCs were used in different dosages, predominantly in combination with other immunosuppressive treatments. Monotherapy with GCs led to inconsistent results.*

Most adverse events recorded were infections. Twenty-three cases of scleroderma renal crisis (SRC) have been reported, mainly in patients with early diffuse disease (n=10) or with anti-thymocyte treatment (n=10). These patients were treated with low to medium dose GCs (n=10), high-dose GCs (n=11) and pulse therapy (n=2).

Conclusions. *Evidence of a beneficial role of GCs in SSc is limited. GCs have been part of the therapeutic strategy in the management of ILD, diffuse cutaneous disease or myositis. Awareness for the risk of SRC should persist, especially in patients with diffuse disease who are also treated with possibly nephrotoxic drugs.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by increased production of collagen and other connective tissue components, resulting in skin hardening and scarring, and fibrosis of internal organs. SSc is categorised into diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) on the basis of the clinical presentation and the extent and distribution of skin involvement (1). Our understanding of the pathogenesis of SSc is limited and many processes still have to be unravelled (2). In early phases, a prevalent pathological finding is the presence of inflammatory infiltrates in target organs, which will be almost completely replaced by fibrosis in later stages of the disease. The presence of antinuclear antibodies, inflammatory lesions in the target organs and increased concentrations of profibrotic cytokines (*e.g.* transforming growth factor-beta, connective tissue growth factor, interleukin-4) locally and systemically are main features of the immune response in SSc (2). Damage to and apoptosis of endothelial cells, immune system dysregulation and fibroblasts hyperactivation represent three important mechanisms responsible for the development of the disease.

SSc can cause skin problems and severe dysfunction and failure of almost every internal organ (3), leading to physical disability and decrease of the quality of life (4-5). Moreover, severe organ involvement, often occurring early in the course of the disease, reduces the survival rate (6). The overall mortality rate of patients with dcSSc is approximately five- to eight-fold higher than that of the general population (7). Most deaths among dcSSc patients are nowadays due to pulmonary fibrosis and/or pulmonary hypertension rather than to scleroderma renal crisis (SRC), which

has been the most common cause of death in past decades (7-9).

Pharmacological therapy is based mainly on the use of immunosuppressive drugs, which were shown to have only limited efficacy (10). Nevertheless, it is believed that in an early stage, disease modification could be possible with the use of anti-inflammatory and immunosuppressive agents (10). Immunosuppressive medication such as cyclophosphamide is used in the treatment of active interstitial lung disease (ILD) and early diffuse disease. Other frequently used drugs are azathioprine, methotrexate and mycophenolate mofetil (10).

Glucocorticoids (GCs) are being widely used in the treatment of many autoimmune diseases, but their use in SSc is controversial (11). The efficacy in SSc is not well-established and the correct indications for GC therapy are unknown. In SSc, possible beneficial effects of GCs are on inflammation, on endothelial cells by decreasing vessel permeability and decreasing expression of adhesion molecules, and on modulation of fibroblasts (12). On the other hand, possible harmful effects of GCs are on inhibition of prostaglandins (13) and on strengthening the response to vasoconstrictive substances like catecholamines (12). These actions could potentially be perilous in SSc, in which vascular damage can result in Raynaud's phenomenon, digital ulcers, pulmonary hypertension and SRC (14). These factors together with the fear of generic adverse events (AEs) related to chronic GC use could explain the restraint to GC use in SSc (15-16). Despite the uncertainty about benefits and risks of GCs, extensive use of this medication in SSc patients has been described in several surveys (17-18). Although GCs are being used in the treatment of arthritis, myositis, puffy hands, cutaneous disease and ILD, no data nor recommendations addressing the indications and appropriate dosages for GC therapy in SSc have been published (3, 19-21).

This literature search has been undertaken to identify the indications for which GCs have been prescribed in SSc and the dosages in which they

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Appendix 1

("Scleroderma, Systemic"[Mesh] OR "Scleroderma, Diffuse"[Mesh] OR "Scleroderma, Limited" [Mesh] OR "Scleroderma" [tiab] OR "CREST" [tiab]) AND ("adrenal cortex hormone*"[tiab]OR"adrenalcorticalhormone*"[tiab]OR"adrenalcorticalsteroid*"[tiab] OR "adrenal steroid*"[tiab] OR "adrenal steroid hormone*"[tiab] OR "adrenocortical hormone*"[tiab] OR adrenocortical steroid*[tiab] OR adrenocorticosteroid*[tiab] OR corticoid[tiab] OR "corticosteroid hormone"[tiab] OR "Glucocorticoids"[Mesh] OR glucocort*[tiab] OR glucocorticoidsteroid*[tiab] OR glucocorticosteroid*[tiab] OR predniso*[tiab] OR *cortison*[tiab] OR hydrocortison*[tiab] OR triamcinolon*[tiab] OR dexamethason*[tiab] OR betamethason*[tiab] OR methylpredniso*[tiab] OR deflazacort*[tiab] OR corticosteroid*[tiab])

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have been used. Furthermore, the efficacy and safety of GCs in different conditions will be reported.

Methods

Literature search

PubMed, EMBASE and The Cochrane Library were searched for literature up to and including October 2012. Key terms 'systemic sclerosis' and 'glucocorticoids' were used to search through titles and abstracts in all databases. Synonyms and plurals of the search terms were combined using Boolean operators (AND, OR) (see Appendix 1). An additional search was performed comprising the terms 'systemic sclerosis' and 'stem cell transplantation' or 'anti-thymocyte globulin'. This was conducted in order to find articles in which the word 'glucocorticoids' (or synonym) was not mentioned in title nor abstract, but in fact GCs had been used to prevent serum sickness from anti-thymocyte globulin treatment.

Inclusion criteria and procedure

We included all studies satisfying the following criteria:
• Study design: all experimental and observational (prospective or retrospective) studies and case reports.
• Patients: adult patients (age ≥18 years) affected by systemic sclerosis fulfilling the American College of Rheumatology (22) and/or Leroy criteria (23) for the diagnosis of SSc.
• Intervention: local or systemic GCs used as monotherapy or as co-medication for a specified indication.

Articles in languages other than English, studies with animals or children, and studies in overlap syndromes were excluded.

Titles and abstracts of all identified citations were reviewed by two of the authors (MI, MG). Full text versions of potentially relevant articles matching our search criteria were screened and again checked for eligibility. Disagreements regarding the inclusion of articles were resolved by discussion with all authors.

Data extraction and quality assessment of included studies

Standardised data extraction forms were used. The following items have been recorded: number of patients included; indication for GC use; preparation, route of administration, dose, and concomitant medication of GC therapy used. GC doses ≤7.5 mg prednisone daily were defined as low dose therapy; doses >7.5 but ≤30 mg prednisone daily as medium dose, doses >30 to <250 mg prednisone daily as high dose therapy, and doses >250 mg prednisone daily as pulse therapy (24). Furthermore, the reported data on efficacy, occurrence of AEs, and SRC were recorded.

The quality of the methodology of the experimental studies has been rated by the criteria recommended by Jadad (25). The Newcastle-Ottawa quality assessment scale has been used to assess the quality of the observational studies included (26).

Summarising and interpreting the available data

The results of the literature search were separated for clinical studies and case reports. Tables summarising the GC use for different indications were created. Efficacy of GCs has been assessed for different indications and for different dosages applied. Special attention
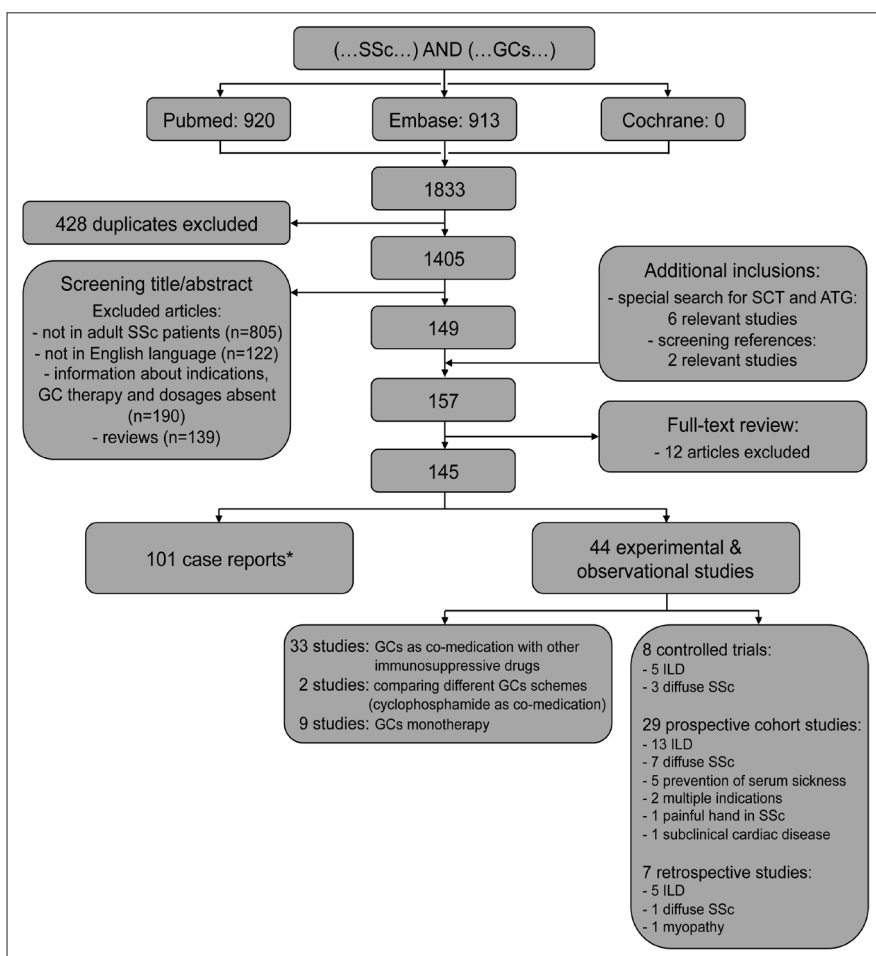
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Fig. 1. Flow chart of search strategy.
This flow chart shows the literature search performed with databases Pubmed, Embase and the Cochrane Library. The search was limited to titles and abstracts. After screening titles and abstracts and the full-text review, 145 articles were included in this exercise.
*Of the 101 case reports found, 8 were not available for full-text review.
SSc: systemic sclerosis; GCs: glucocorticoids; SCT: stem cells transplantation; ATG: anti-thymocyte globulin; ILD: interstitial lung disease

was paid to the reporting of GC-related AEs and SRC

Results
Literature search
The literature search resulted in 920, 913 and 0 hits in PubMed, EMBASE and the Cochrane Library, respectively (Fig. 1). After excluding duplicates and screening titles and abstracts with respect to selection criteria, 149 articles were deemed potentially relevant. Another 8 relevant studies were found in the additional search and by screening references of included articles. Forty-four experimental and observational studies, including 891 patients, were selected. Ninety-three available case reports were kept as a separate category.

GCs were used for the treatment of ILD (23 studies), dcSSc (10 studies), myopathy (1 study) and painful hands (1 study), or were used to prevent serum sickness (6 studies). One study assessed cardiac function in patients with and without GC treatment and in 2 studies the indications for GC therapy were not clearly mentioned. In 33 studies GCs were used as co-medication with other immunosuppressive drugs, while in 9 monotherapy with GCs was applied. Only 2 studies compared different GC schemes accompanying cyclophosphamide treatment.

Interstitial lung disease
– Description of studies
Twenty-three studies (5 controlled trials of which 1 high quality randomised

controlled trial, 13 prospective and 5 retrospective studies) reporting GC use in the treatment of ILD were found, including 478 patients in total with a mean follow-up period of 20 months (27-49). The characteristics of the studies are included in Table I. In the majority of these studies, GCs were used in low to medium doses (*i.e.* ≤30 mg prednisone equivalent) and combined with other immunosuppressive drugs (27-37). In some studies, GC pulses and/or high oral doses (*i.e.* >30 mg prednisone equivalent) were used as part of induction therapy (34, 36, 38-41, 47-48). Monotherapy with GCs was applied in 3 studies (42-44). Only 2 studies directly compared two different GC schemes applied together with cyclophosphamide pulses (36, 49).

– Efficacy
GCs have been used as monotherapy in only 3 studies, of which the results are conflicting (42-44). Two uncontrolled prospective studies showed stabilisation or improvement of the lung function in 63% of patients treated with high oral doses, and in all 4 patients after dexamethasone pulses (43-44). In contrast, the retrospective study showed a decline in lung function in patients treated with high dose GCs (42).
In the only high quality randomised placebo-controlled trial included, a trend towards stabilisation of lung function in patients treated with cyclophosphamide pulses followed by azathioprine and alternate day low-medium dose GCs was found (27). The difference between this treatment and placebo treatment was not significant (27). The effect of adding high dose oral prednisone treatment to pulse treatment with cyclophosphamide is unsure, since studies are reporting conflicting results (36, 38). However, when GC pulses are combined with cyclophosphamide pulses, stabilisation of the lung function has been described repeatedly, but only in uncontrolled studies (41, 47).

– Safety
Many AEs were reported. Some AEs, such as leukopenia, haemorrhagic cystitis, alopecia and vesical leukoplakia,

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Table I. Characteristics of studies on interstitial lung disease.

First author	Design	Intervention	Patients (n)	GC dose	Outcome	Pre-treatment	Post-treatment	P-value*	Follow-up (months)	SRC	Quality
Hoyles 2006 (27)	RCT	Cyc+Pred+AZA vs. placebo only	22 vs. 23	Medium	FVC DLCO	80.1 ±10.3 / 81.0 ±18.8 52.9 ± 11.5 / 55.0 ± 12.9	82.5 ± 11.3 / 78.0 ± 21.6 49.6 ± 10.7 / 51.8 ± 14.9	ns ¥ ns ¥	12	0	4†
Domiciano 2011 (38)	RCT	Cyc+Pred vs Cyc	9 vs. 9	High	FVC DLCO	64.7 ± 7.7 /67.3 ± 6.4 69.8 ± 22.5 / 61.8 ± 16.8	65.4 ± 8.7 / 62.8 ± 18.9 65.3 ± 10.8 /42.80 ± 15.61	ns ¥ ns ¥	36	0	1†
Perez-Campos 2012 (49)	RCT	Cyc+Pred 10 mg vs. Cyc+Pred 1 mg/kg/day	13 vs. 10	Medium vs high	FVC	67.7 / 51.8	71.7 ± 17.5 / 57.8 ± 15.3	?	12	0	1†
Pakas 2002 (36)	CT	Cyc+Pred<10 mg vs. Cyc+Pred 1 mg/kg/day	12 vs. 16	Low-medium vs high	Δ FVC Δ DLCO		-0.7 / +12.4 +0.9 / +7.3	ns / <0.001 ns / 0.03	12	0	4/0/3‡
Davas 1999 (28)	CT	Cyc IV+Pred vs Cyc oral+Pred	8 vs. 8	Medium	FVC DLCO	86.1 / 73.2 60 / 59.9	93.6 / 74.2 81.5 / 71.7	0.02 / ns 0.01/ 0.03	12	?	3/1/3‡
Silver 1993 (35)	Pr	Cyc+Pred	10	5-40 mg/day	FVC - DLCO	51.4 ± 2.5 - 54.5 ± 7.4	63.6 ± 4.3 - 47.9 ± 4.7	≤0.001 / ns	18-24	?	4/NA/3‡
Beretta 2007 (29)	Pr	Cyc+Pred	33	Medium	FVC - DLCO	77.0 ± 16.2 - 48.8 ± 13.5	81.2 ± 19.3 - 55.8±14.6	ns / 0.01	12	?	4/NA/3‡
Giacomelli 2002 (30)	Pr	Cyc+Pred	23	Medium	FVC - DLCO	91 (36-123) - 50.5 (19-88)	91 (39-123) - 64.5 (47-87)	ns / ns	6	?	3/NA/3‡
Akesson 1994 (31)	Pr	Cyc+Pred	18	Medium	FVC - DLCO	74 (46-102) - 52 (42-86)	80 (50-110) - 52 (33-80)	0.01 / ns	12	?	4/NA/3‡
Wanchu 2009 (39)	Pr	Cyc+Pred	36	High	FVC - DLCO	63.26 ± 14.2 - 39.08 ± 21.06	65.89 ± 12.8 - 41.29 ± 17.04	ns / ns	6	0	4/NA/3‡
Behr 1996 (43)	Pr	Pred	38	High	decrease of FVC or TLCO>10%	-	36.8% of pts	?	12	?	3/NA/3‡
Tochimoto 2011 (40)	Pr	Cyc+Pred	13	High	FVC	82 ± 15	87 ± 11	ns	48	0	3/NA/3‡
Airò 2007 (45)	Pr	Cyc+MPred	13	High	FVC - DLCO	74 (61-84) - 41 (39- 51)	76 (64-101) - 44 (35-46)	0.05 / ns	18	1**	3/NA/3‡
Griffiths 2002 (41)	Pr	Cyc+MPred	14	Pulse	FVC - DLCO	93 (70-102) 65 (54-85)	91 (74-111) 60 (45-77)	ns ns	12	0	3/NA/3‡
Pai 1995 (44)	Pr	Dexamethasone	5	Pulse	Dyspnoea	-	Improved in 3 pts; stable in 1 patient	?	?	?	0/NA/1‡
Yiannopoulos 2007 (47)	Pr	Cyc+MPred	13	Pulse	FVC - DLCO	83.8 ± 25.5 - 59.2 ± 20.7	90.0 ± 32.3 - 61.3 ± 28.5	ns / ns	48	0	2/NA/3‡
Liossis 2006 (37)	Pr	MMF+Pred	6	Medium	FVC - DLCO	65.6 - 64.2	76.2 - 75.4	ns / 0.03	6	0	3/NA/3‡
Simeon-Aznar 2008 (48)	Pr	Cyc+Pred	10	High	FVC - DLCO	55.5 - 71.7	58.5 - 68	ns / ns	24	0	2/NA/3‡
Tzelepis 2007 (34)	Re	Cyc+Pred	59	Low-medium and high	↑ ≥10% FVC Δ FVC ± 10% ↓ ≥10% FVC		17% of pts 62.7% of pts 20.3% of pts	?	36	0	2/NA/3‡
↓Dheda 2004 (33)	Re	AZA+Pred	11	Low	FVC	54.25 ± 3.53	60.00±6.21	ns	18	?	3/NA/3‡
Swigris 2006 (32)	Re	MMF+Pred	9	Medium	Δ FVC - Δ DLCO		+ 2.3% - + 2.6%	ns / ns	12	?	2/NA/1‡
Airò 2004 (46)	Re	Cyc+MPred	16	High	FVC - DLCO	83 (71, 98.75)-46 (39.5, 51.25) ?	?	ns / ns	11	0	3/NA/0‡
Steen 1994 (42)	Re	Pred	21	High	FVC - DLCO	47 - 65	45 - 49	ns / ?	48-72	?	4/1/3‡

The studies include 478 patients in total, of which at least 167 were affected with dcSSc. One SRC was reported. * p-value of testing for statistical difference between pre- and post-treatment values.** The patient with SRC suffered from dcSSc.¥Significance of the degree of change in the active treatment group versus the placebo group;†Jadad scale assessing randomisation, blinding, and description of withdrawals/dropouts (score 0-5)(25); ‡Newcastle-Ottawa scale assessing selection (0-4), comparability (0-2), and outcome (0-3)(26). GC: glucocorticoid; SRC: scleroderma renal crisis; RCT: randomised controlled trial; CT: controlled trial; Pr: prospective; Re: retrospective; Cyc: cyclophosphamide; Pred: predniso(lo)ne; MPred: methylprednisolone; AZA: azathioprine; MMF: mycophenolate mofetil; ?: unknown, not reported; dcSSc: diffuse cutaneous scleroderma patients; DLCO: carbon monoxide diffusing capacity; TLC: total lung capacity; FVC: forced vital capacity; FVC, TLC and DLCO are expressed as % of predicted; pts: patients.

Table II. Characteristics of studies on diffuse cutaneous disease.

First author	Design	Intervention	Patients (n)	GC dose	Outcome	Pre-treatment	Post-treatment	*p*-value*	Follow-up (months)	SRC	Quality
Sharada 1994 (57)	RCT	Dexamethasone vs placebo (no therapy)	17 *vs.* 18	Pulse	Total skin score	32.9 ± 8.9 / 30.6 ± 13.2	28.4 ± 12 / 34.7 ± 10	0.049/ 0.003	6	0	0†
Nadashkevich 2006 (55)	RCT	Cyc+Pred vs AZA+Pred	30 *vs.* 30	Medium	mRss	14.7 ± 1.06 / 14.3 ± 1.04	5.23 ± 0.5 / 14.5 ± 1.15	<0.01 / Ns	18	?	1†
Calguneri 2003 (50)	Pr	Cyc+Pred	24	Medium	sRss	42	20	<0.05	24	0	2/NA/3‡
Apras 2003 (51)	Pr	Cyc+MPred	11	Medium	sRss	48 (27-75)	32 (24-67)	0.007	12	0	3/NA/3‡
Vanthuyne 2007 (54)	Pr	MMF+MPred	13	Pulse	Total skin	20 ± 12	13 ± 11	<0.0001	12	0	2/NA/3‡
Valentini 2006 (53)	Pr	Cyc+Pred	12	Medium	mRss	23	10	0.002	12	?	3/NA/3‡
Takehara 2004 (56)	Pr	Pred	23	Medium	mRss	20.3 ± 9.3	8.7 ± 6.1	<0.001	12	0	2/NA/3‡
Ottewell 2009 (58)	Pr	Cyc+MPred	12	Pulse	mRss	26 (15-34)	16 (17-34)	0.13	18	?	2/NA/2‡
Smith 2010 (59)	Pr	Rituximab+ MPred	8	High	mRss	24.8 ± 3.4	14.3 ± 3.5	<0.05	6	0	2/NA/3‡
DeMarco 2002 (52)	Re	D-penicillamine +Pred	40	Low-medium	–	–	–	–	48	10**	3/NA/2‡

The studies include 238 patients in total, of which 220 are on GC treatment. Ten cases of SRC were reported. *p-value of testing for statistical difference between pre- and post-treatment values. **The patients with SRC suffered from dcSSc. †Jadad scale assessing randomisation, blinding, and description of withdrawals/dropouts (score 0-5) (25). ‡Newcastle-Ottawa scale assessing selection (0-4), comparability (0-2), and outcome (0-3) (26).
GC: glucocorticoid; SRC: scleroderma renal crisis; RCT: randomised controlled trial; Pr: prospective study; Re: retrospective study; Cyc: cyclophosphamide; Pred: predniso(lo) ne; AZA: azathioprine; MPred: methylprednisolone; MMF: mycophenolate mofetil; mRss: modified Rodnan skin score; sRss: semiquantitative Rodnan scoring system; ns: not statistically significant; ?: unknown, not reported; NA: not applicable; dcSSc: diffuse cutaneous scleroderma.

could be specifically attributed to concomitant immunosuppressive treatment. Those which could be (partly) related to GCs were infections (19 patients), mood disturbances (4 patients), dyspepsia (1 patient), cushingoid appearance (1 patient), transient shortness of breath (1 patient), and cataract (1 patient). One case of SRC in a patient treated with high dose GCs was reported. Other GC-related serious AEs such as bone fracture, osteonecrosis, hypertension or diabetes mellitus have not been reported.

Diffuse cutaneous disease
– Description of studies
GCs have been used in the treatment of dcSSc disease in 10 studies (2 randomised controlled trials, 7 prospective and 1 retrospective study) (50-59). These studies include 238 patients in total with a mean follow-up period of 17 months (see Table II). Only in 2 studies GCs have been administered as monotherapy (56-57), while in other studies low to medium dose GCs (50-53, 55) or GC pulses (54, 58) were combined with other immunosuppressive drugs.

– Efficacy
We found only one low quality randomised controlled trial assessing the effect of dexamethasone pulse therapy on cutaneous disease. It included a GC naïve control group and showed little but significant benefit (decrease of skin score of 13% from baseline) in the treatment group, compared to a significant increase in the placebo group (57). Treatment with medium dose GCs as monotherapy in an uncontrolled prospective cohort study led to a significant improvement of skin disease (56). A beneficial effect of combination therapy including GCs has been shown in prospective studies in which IV pulse or low to high dose oral GC treatment has been used in combination with cyclophosphamide (50-51, 53, 55, 58), mycophenolate mofetil (54) or rituximab (59).

– Safety
Most of recorded AEs are generally known to be caused by concomitant im-

Table III. Characteristics of studies in which GCs were given to prevent serum sickness.

First author	Design	Intervention	Patients (n)	GC dose	Follow-up (months)	SRC	Quality
Burt 2011 (61)	RCT	SCT+ATG+Cyc+ MPred *vs.* Cyc IV	10 vs 9	Pulse	12	1*	4†
Oyama 2007 (64)	Pr	SCT+ATG+Cyc+MPred	10	Pulse	25	1*	3/NA/3‡
Matteson 1996 (62)	Pr	ATG+Pred	10	High	24	?	3/NA/3‡
Tarkowski 1993 (65)	Pr	ATG+MPred	3	High	15	?	3/NA/3‡
Nash 2007 (63)	Pr	SCT+ATG+Cyc+TBI +MPred	34	High	48	6*	3/NA/3‡
Stratton 2001 (66)	Pr	ATG+MMF+Pred	13	High	12	2*	3/NA/3‡

The studies include 80 patients on GCs in total, of which at least 77 were affected with dcSSc. Ten cases of SRC were reported.
*The patients with SRC suffered from dcSSc. †Jadad scale assessing randomisation, blinding, and description of withdrawals/dropouts (score 0-5) (25). ‡Newcastle-Ottawa scale assessing selection (0-4), comparability (0-2), and outcome (0-3)(26).
RCT: randomised controlled trial; Pr: prospective; Re: retrospective; GC: glucocorticoid; dcSSc: diffuse cutaneous systemic sclerosis; Cyc: cyclophosphamide; SRC: scleroderma renal crisis; Pred: predniso(lo)ne; MPred: methylprednisolone; MMF: mycophenolate mofetil; SCT: hematopoietic stem cell transplantation; ATG: anti-thymocyte globulin; TBI: total body irradiation; ?: unknown, not areported; NA: not applicable.

munosuppressive treatment (*i.e.* hyper-transaminasaemia, microhaematuria). Described AEs possibly related to GC use were infections (25 patients), gastrointestinal complaints (8 patients), vertigo (1 patient) and hypertension (2 patients). Ten cases of SRC in early dc-SSc patients taking low to medium dose GCs and D-penicillamine were reported after a mean duration of 0.9 year since start of the study (52). Baseline characteristics that predicted SRC included a modified Rodnan skin score of >20 (*p*<0.01), enlarged cardiac silhouette on radiograph (*p*=0.04), joint contractures (*p*=0.008), and prednisone use at entry (*p*=0.01) (52). Other serious AEs have not been reported.

Myopathy
Only one retrospective study has been found for this indication (60). Overall, high dose GCs were effective in 18 out of the 24 patients treated. The presence of inflammatory infiltrates in muscle biopsies appeared to be predictive of the therapeutic effect of GCs. Ninety percent of the patients with infiltrates in the muscle biopsy responded to GCs compared to only 38 percent in the group without infiltrates. Two cases of scleroderma renal crisis were recorded.

Prevention of serum sickness
– Description of studies
Six studies (1 controlled trial, 5 prospective cohort studies) reporting use of high dose or pulse GC treatment to prevent serum sickness in patients treated with anti-thymocyte globulin as monotherapy or as induction therapy for autologous haematopoietic stem cell transplantation were identified (61-66). These studies include 80 patients in total with a mean follow-up period 23 months. The characteristics of the studies are included in Table III.

– Efficacy
Serum sickness is a systemic immune-complex mediated condition, which is clinically characterised by fever, skin lesions, articular complaints, lymphadenopathy, leukopenia, and renal impairment, generally occuring 7 to 14 days after the exposure to a foreign substance (67). It has been described

Table IV. GC use in SSc case reports.

Indications	Number of case reports	Number of serious AEs
Respiratory disease	20	8 infections (4 pneumonitis, 1 active tuberculosis,
Renal disease	16	1 sepsis, 1 cytomegalovirus esophagitis, 1 disseminated
Diffuse SSc disease	12	candidosis)
Neurological disease	11	7 scleroderma renal crisis
Haematological disease	10	2 gastrointestinal bleeding
Cardiac disease	7	2 renal insufficiency
Muscular disease	7	1 ischaemic colitis
Gastrointestinal disease	2	1 deep venous thrombosis
Others	8	1 respiratory insufficiency

in 1.5 to 15.9% of patients exposed to anti-thymocyte globulin, which is commonly used to prevent rejection in patients with an organ transplantation (67) or to treat therapy-resistant vasculitis and dcSSc (66, 68).
High dose GCs or pulse therapy are routinely used to prevent serum sickness in these patients (67). It is not possible to extract the specific effects of GCs on disease progression in these studies, because of the different therapeutic schemes which have been used.

– Safety
Ten cases of scleroderma renal crisis were reported. Eight of these patients were treated with high dose GCs.

Other indications
One prospective study enrolling 12 consecutive SSc patients assessed the usefulness of lidocaine and triamcinolone injection in the carpal tunnel of patients with a painful hand. A good response (*i.e.* reduced pain score) was recorded in 83% of patients. Furthermore, a reduction in the frequency of Raynaud's attacks and healing of digital ulcers occurred in 83% of patients (69).
In 2 low quality prospective studies conducted in India, dexamethasone pulses were administered to 68 SSc patients, but the indications have not been clearly mentioned. Authors reported an improvement in skin score, dyspnoea, and gastrointestinal symptoms (70-71). However, they described the occurrence of some serious AEs: active tuberculosis (12 patients), onset of renal insufficiency (2 patients), psychosis (1 patient), and femoral osteonecrosis (1 case).
In one prospective study, the administration of medium dose of GCs for 20

days was associated with an improvement of cardiac performance evaluated by radionuclide ventriculography (72).

Case reports
In case reports, GCs have not only been prescribed for the indications mentioned above, but also for a.o. cardiac, haematological, renal and neurological manifestations of SSc. The indications and serious AEs encountered are described in Table IV.

Discussion
In this systematic literature review, we found 44 studies reporting on GC use in SSc. In the majority, GCs were used in combination with other immunosuppressive drugs. Monotherapy with GCs was applied in 9 studies. The indications for GC therapy were diverse, among which ILD (23 studies) and diffuse cutaneous disease (10 studies) were the most frequent ones.
The effectiveness of monotherapy is uncertain. In ILD, it led to contrasting results and had not been compared with a GC naïve group (42-44). For dcSSc, dexamethasone pulse treatment and not placebo showed a statistically significant but clinically not relevant decrease of skin thickening in a small and low quality trial (57); moreover also an increased risk of infections was recorded. In a retrospective study dealing with treatment of myopathy, beneficial effects of high dose GCs were found in patients with inflammatory infiltrates in muscle biopsies (60). These findings suggest usefulness of performing muscle biopsies before making treatment decisions. Unfortunately, the different inclusion criteria, different outcome measures, different follow-up periods,

and different study designs did not allow us to perform a meta-analysis with this data, because the results would have been not feasible for interpretation.

All combination therapy studies including GCs in ILD reported improvement or stabilisation of lung function, regardless of the GC dose administered or specific immunosuppressive comedication chosen (27-35, 37, 39-41, 45-49). These results would eventually suggest more effectiveness of combination therapy than monotherapy with GCs in ILD. All studies that used GCs in dcSSc showed improvement or stabilisation of skin scores, but control groups were lacking, so these data are not sufficient for firm conclusions. In only two studies, different dosages of GCs were compared (36, 49). One of them showed that high dose GC therapy was superior to low and medium dose treatment for pulmonary and cutaneous outcome, and did not lead to more AEs (36). However, caution is needed for interpreting these data on pulmonary outcome, since this could be biased by higher fibrosis scores at baseline in patients in the low and medium dose group (30).

The most frequently reported AEs were infections and gastrointestinal complaints, but SRC is the most worrisome: 23 cases were reported among 891 patients studied. Ten cases have been reported in a study with early dcSSc patients treated with D-penicillamine and low to medium dose GCs (52). Another ten cases were dcSSc patients treated with pulse or high dose GC therapy accompanying anti-thymocyte globulin treatment (61, 63-64, 66). The remaining 3 patients were treated with high dose prednisone for myositis or alveolitis. These data are in line with other observations (73-75), and show that SRC often occurred in early dcSSc patients with severe organ involvement and poor prognostic factors, who frequently also receive other potentially nephrotoxic therapies like total body irradiation, D-penicillamine and anti-thymocyte globulin. The causal relation between GC therapy and SRC is therefore hard to assess. Theoretically, an impaired production of prostaglandins by endothelium (13) and a stronger

vasoconstrictive response to substances like catecholamines could result in an increased risk of SRC with GC therapy. However, in clinical practice the individual influence of GCs can not be distinguished from confounding factors, such as disease severity and comedication.

It is difficult to determine the conditions in which GC therapy in SSc is effective and relatively safe. The data described to not allow us to draw firm conclusions on specific dosages, routes of administration, or treatment durations for which GC use is safe in SSc. Recent EUSTAR recommendations mention GCs only as possible therapy for arthritis (based on expert-opinion) (19). In an often referred to case-control study, chronic prednisone use in a dosages >15 mg/day was associated with a fourfold increase in the development of SRC (76). In contrast, a retrospective analysis conducted in early dcSSc patients from the D-penicillamine trial showed that low to medium dose GCs are also associated with the development of SRC, but predominantly in patients with severe skin involvement (modified Rodnan skin score ≥20) and joint contractures (52). So, although weighing risks and benefits of GC therapy is difficult, use of GCs in the minimal effective dose may be worthwhile. This exercise has some limitations. Our literature search was limited to the keywords 'glucocorticoids' and 'systemic sclerosis' in titles and abstracts, and therefore we might have missed studies with GCs as background therapy, if not mentioned in the abstract. The incomplete understanding of the pathogenic processes in SSc, the lack of randomised controlled trials, the presence of few small and often low quality studies, and the widespread use of GCs as co-medication did not allow us to draw firm conclusions about efficacy and risks of GC therapy. Unfortunately, no studies have addressed the use of GCs in arthritis, serositis or myocarditis. Future research could definitely be helpful in unravelling these consequences of GC therapy in SSc.

In conclusion, available data suggest that a beneficial role of low to medium dosages of GCs in SSc is limited. GC

therapy could be part of the therapeutic strategy in the management of ILD, diffuse cutaneous SSc disease or myositis, but further studies are needed. Additional value of high dosages of GCs has not been proven in this context. There should be awareness for the risk of SRC, especially in the treatment of SSc patients with diffuse disease and poor prognostic factors.

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