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ORIGINAL ARTICLE

Corticosteroids and the risk of scleroderma renal crisis: a systematic review

Gerald Trang · Russell Steele · Murray Baron · Marie Hudson

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Abstract Scleroderma renal crisis (SRC) has been associated with the use of corticosteroids (CS) in retrospective studies. Using an evidence-based approach, we undertook a systematic review of the literature to identify prospective studies in which scleroderma patients were administered CS to ascertain the risk of SRC in those patients. A comprehensive search was conducted using Medline, EMBASE, the Cochrane Library, and Web of Science. All original prospective clinical studies were eligible if they enrolled SSc patients newly treated with CS. Selected studies were reviewed, and data extraction was systematically performed for the dose and duration of the CS intervention as well as the occurrence of SRC. Twenty-six studies with a total of 500 SSc patients commencing new CS therapy were included in the systematic review. Ten definite cases of SRC, equivalent to a rate of 2%, were identified. In the subset of early diffuse patients, the rate of SRC was 4%. All 10 definite cases of SRC occurred in patients who received medium- to high-dose CS therapy. Seven cases occurred in the setting of stem cell transplant. CS are associated with SRC, although this may be due to confounding by disease severity and/or co-intervention. Great caution must continue to be exerted when initiating such therapy, especially in high doses and in the early diffuse subset of SSc patients.

Keywords Systemic sclerosis · Scleroderma renal crisis · Corticosteroids · Systematic review

G. Trang
McGill University, Room A-216,
3755 Cote Ste Catherine Street, Montreal,
QC H3T 1E2, Canada

R. Steele
Jewish General Hospital and McGill University,
Room A-216, 3755 Cote Ste Catherine Street,
Montreal, QC H3T 1E2, Canada

M. Baron · M. Hudson (✉)
Division of Rheumatology, Jewish General Hospital and McGill University, Room A-216, 3755 Cote Ste Catherine Street,
Montreal, QC H3T 1E2, Canada
e-mail: marie.hudson@mcgill.ca

Introduction

Systemic sclerosis (SSc) is a connective tissue disease of uncertain aetiology characterized by the pathophysiologic triad of vascular damage, fibrosis of the skin and internal organs, and autoimmunity and inflammation [1]. Scleroderma renal crisis (SRC) is one of its most feared complications. It is characterized by acute renal failure usually accompanied by malignant hypertension [2]. Although the advent of ACE inhibitors has dramatically improved the outcome from SRC [3], mortality remains high, climbing up to 50% within a year in one study of early diffuse systemic sclerosis (dcSSc) patients [4]. A significant number of patients who survive require short- and/or long-term dialysis, and some eventually require renal transplant [2].

Dating back to 1951, there has been concern about corticosteroids (CS) and their potential role in precipitating SRC in SSc [5]. Multiple case reports [6–11] and retrospective studies subsequently supported a possible association [12–14]. In a case–control study of 110 SSc patients from the Pittsburg cohort who developed SRC between 1981 and 1993, new use of prednisone in dosages $\geq$15 mg/day was associated with a fourfold increase in the onset of SRC (odds ratio 4.37, 95% confidence interval 2.03–9.43) [12]. On the other hand, in a recent retrospective analysis of the 134 patients who participated in the D-penicillamine

trial [15], CS were not an independent risk factor for SRC in early dcSSc [4]. However, in subgroup analysis, low dosages of prednisone (mean 7.4 mg/day) were associated with the onset of SRC only in patients with severe skin involvement with large joint contractures.

The data thus remain conflicting and suboptimal, and studies based on prospective data are needed to clarify the role of CS in precipitating SRC [12, 16]. Our objective was therefore to perform a systematic review of the literature to identify prospective studies of SSc patients newly treated with CS to determine whether these patients were at an increased risk of SRC.

Methods

Search strategy and study selection criteria

In August 2009, a comprehensive search was performed on four databases including Medline, EMBASE, the Cochrane Library, and Web of Science (see "Appendix" for a template of the complete search) by one author (GT) assisted by a professional librarian. Using the Ovid search engine, Medline and EMBASE were searched using the following terms:

1. systemic sclerosis, scleroderma
2. prospective studies, clinical trial
3. steroid, corticosteroid, glucocorticoid, prednisone, prednisolone, methylprednisolone, dexamethasone
4. stem cell transplantation, antithymocyte globulin (these terms were added because we were aware that transplant protocols were including CS to prevent serum sickness from antithymocyte globulin therapy.)

The Cochrane Library and Web of Science database were searched employing the terms from 1 to 4 above and adding the following limits:

5. NOT "multiple sclerosis", "tuberous sclerosis", "nodular sclerosis", "nuclear sclerosis", "biliary sclerosis", "localized scleroderma"

There was no language exclusion. The search was limited to published studies.

The abstracts of each reference identified by the search were reviewed to determine which studies would be selected for full-length review. In addition, relevant references from selected papers were also hand-searched by one author (GT) for potential inclusion in the review.

Studies were selected for inclusion in the systematic review according to the following criteria:

1. the study presented original data;
2. the study was prospective;
3. the study included SSc patients; overlap syndromes were acceptable as long as patients met criteria for SSc as well;
4. the study included patients newly treated with CS as part of the study protocol; route of administration was either oral or intravenous;
5. in the case of duplication with multiple articles publishing data on the same cohort, complementary articles and/or data sets were collapsed;
6. studies with a mixed patient population were included if, from the full text, a subset of patients with SSc could be separately characterized, and their outcome independently assessed.

Description of studies

Data from each selected study were extracted by one investigator (GT) and verified by a second investigator (MH) using a structured data extraction form. Differences were resolved by consensus. The following information was systematically extracted:

1. Author, journal, year of publication, country where study was done;
2. Study design (e.g., pilot, prospective, randomized trial);
3. Characteristics of the study population: sample size, age, percentage of female patients, disease duration, and percentage of patients with diffuse skin involvement;
4. The dose and duration of CS intervention as well as the main co-intervention(s). CS dose was defined as high, medium, and low dose as follows:
   (a) High dose: Initial administration in IV pulses, regardless of frequency, or in doses greater than 30 mg/day of prednisone equivalent;
   (b) Medium dose: Initial dosage between 16 and 30 mg/day, regardless of the tapering regimen; and
   (c) Low-dose: Dosage never exceeded 15 mg/day, regardless of duration;
5. Follow-up period; and
6. SRC outcome: definite occurrence, definite non-occurrence, or no specific mention of SRC in the paper.

Results

The search process identified 50 results from Medline, 230 from EMBASE, 125 from Web of Science, and 10 from the Cochrane Library (Fig. 1). After excluding duplicates,

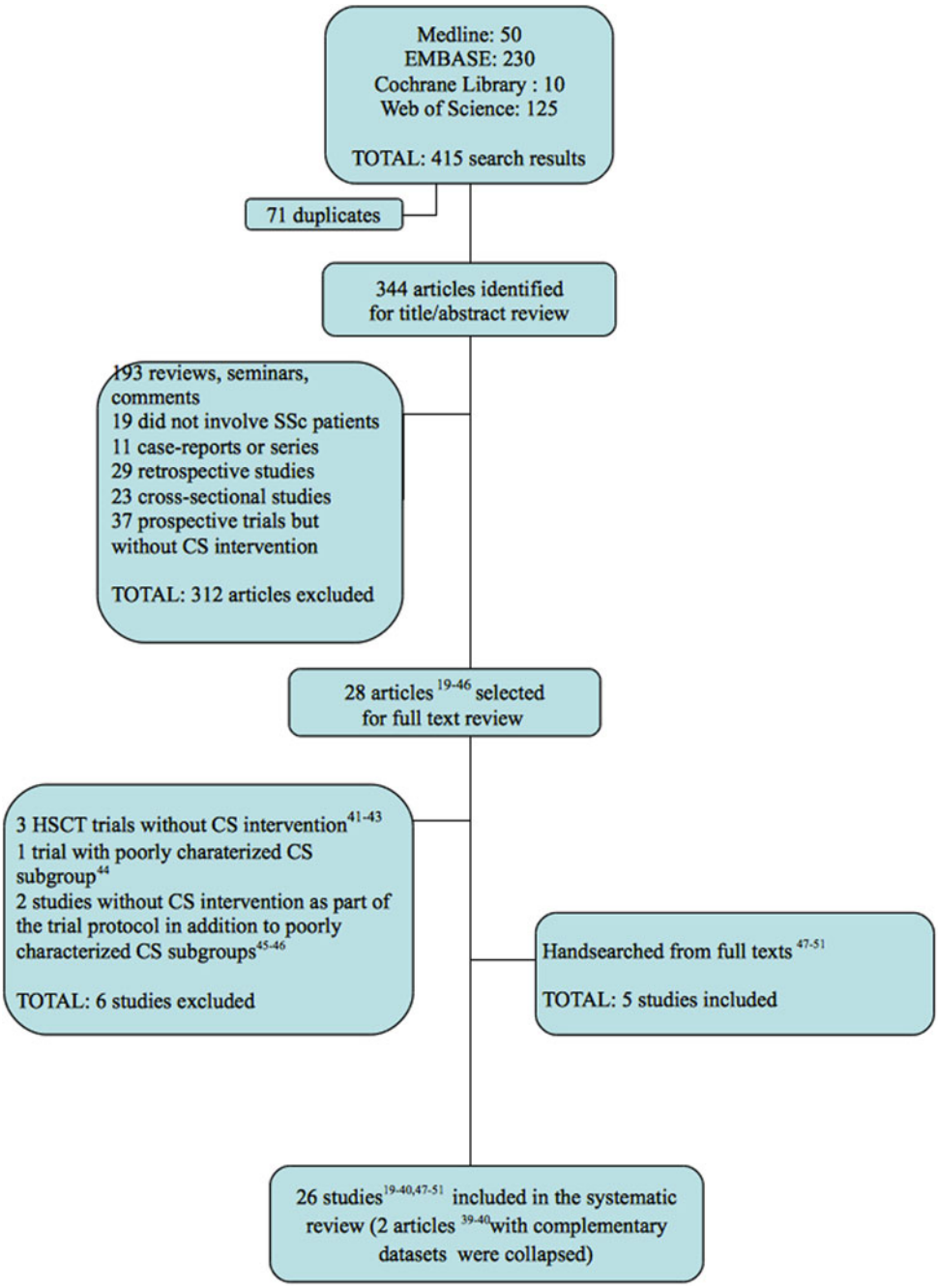

Fig. 1 Flowchart providing numbers of studies identified, excluded for various reasons and included in the systematic review

there was a total of 344 results. Title and abstract review led to the exclusion of 316 articles: 197 were reviews, seminars, or comments; 19 did not involve SSc patients, (e.g., graft-versus-host disease, localized scleroderma, other rheumatic diseases); 11 were case reports or case series; 29 were retrospective studies; 23 were cross-sectional studies; and 37 were prospective trials but without CS intervention. Thus, 28 articles were selected for full-text review [2, 17–44]. Of these, 6 were excluded: 3 did not have a CS intervention despite employing high-dose immunosuppression therapy; [39–41] one did not have an adequately characterized CS subgroup [42]; and two did not have CS as part of their study protocol, in addition to having a poorly characterized CS subgroup [43, 44]. In addition, 2 articles [37, 38] had complementary data sets and were collapsed. On the other hand, hand searching of the references of the 28 articles selected for full-text review yielded an additional 5 studies [45–49]. Thus, we included a total of 26 data sets in the systematic review [19–40, 47–51].

The characteristics of the studies included in the systematic review are presented in Table 1. The 26 data sets

Table 1 Characteristics of the studies included in the systematic review

Author(s)	Country of study	Design	Sample characteristic	Percent Diffuse	Disease duration	Co-intervention	Steroid intervention	Dose	F/U	SRC outcome
Nash et al. [38]	USA	Pilot	34 early diffuse	100%	*M* 21 months (r4–51)	TBI/ATG/ CyPAHSCT	MP 1 mg/kg/day × 6 days, then Pred 0.5 mg/kg/day × 1 month, then tapered over 1 month	High	4 years	6 SRC (all within 2 months)
Vanthuyne et al. [36]	Belgium	Prospective	16 severe skin or ILD	81%	*m*0.8 ± 0.8 year	MMF	MP 15 mg/kg/day × 3 days, then monthly × 5 months, then Pred 5–10 mg/day × 1 year	High	12	None
Beretta et al. [35]	Italy	Open	33 active alveolitis	64%	*m*5.6 ± 5.3 year	CyP	Pred 25 mg/day × 3 months, then tapered to 5 mg/day	Med	12	No mention
Yiannopoulos et al. [34]	Greece	Prospective	13 early ILD	NR	*m*14.2 ± 8.3 months (and one >20 years)	CyP	MP 1 gm monthly pulse × 12 + MP 6–8 mg/day in between	High	48	None
Oyama et al. [33]	USA	Pilot	10 severe SSc	90%	*m*36.4 ± 15.4 months	CyP/ATG AHSCT	MP 1 gm/day × 5 days	High	25	1 SRC (within 1 month)
Airo et al. [32]	Italy	Prospective	15 active alveolitis	62%	*m*7.5(4.5–9.5 year)	CyP	MP 125 mg/day every 3 weeks × 17 pulses, then pred 5–20 mg/day	High	18	1 SRC
Liossis et al. [31]	Greece	Open	6 with active ILD	100%	*m*3.4 ± 3.2 year	MMF	Pred ≤10 mg/day	Low	12	No mention
Valentini et al. [30]	Italy	Prospective	13 diffuse	100%	*M*16(r5–21 months)	CyP; AZA	Pred 10 mg/day	Low	12	No mention
Hoyles et al. [29]	UK	RCT	45 early lung fibrosis (22 active treatment and 23 PBO)	36%	*M*33(r1–204 months) in active and *M*66(r3–322) in PBO group	CyP; AZA	Pred 20 mg every second day × 6 months	Low	12	None
Nadashkevich et al. [28]	Ukraine	Open comparative	60 early diffuse	100%	*M*6.6 (r3–12 months)	CyP/AZA	PSL 15 mg/day tapered to 0 over 6 months	Low	18	None
Takehara (2004)	Japan	Prospective	23 early diffuse	100%	"Early"	None reported	PSL 20 mg/day × 2–8 weeks, then tapered to 2.5–10 mg/day	Med	24	None
Apras (2003)	Turkey	Open	11 early diffuse	100%	*m*11.8 ± 7.1 months	CyP	MP 30 mg every second day, tapered every 6 weeks to 2.5 mg every second day	Low	12	No mention
Griffiths et al. [26]	UK	Prospective	14 lung involvement	NR	*m*3.14 ± 3.05 years	CyP	MP 10 mg/kg every 3 weeks × 3, then every 4 weeks × 3	High	26	None
Calguneri et al. [25]	Turkey	Open	24 early diffuse	100%	*M*12.5 (r6–18 months)	CyP	Pred 40 mg/day every second day, tapered every 6 weeks	Med	24	None
Giacomelli et al. [24]	Italy	Prospective	23 active alveolitis	74%	NR	CyP	Pred 25 mg/day × 1 month, then 5 mg/day	Med	6	No mention

Table 1 continued

Author(s)	Country of study	Design	Sample characteristic	Percent Diffuse	Disease duration	Co-intervention	Steroid intervention	Dose	F/U	SRC outcome
Pakas et al. [24]	Greece	Open	16 ILD	69%	*m*36.0 ± 28.6 months	CyP	Pred 1 mg/kg/day × 4 weeks, then tapered	High	12	None
			12 ILD	67%	*m*58.5 ± 52.1 months	CyP	Pred <10 mg/day	Low	12	None
Stratton et al. [22]	UK	Pilot	13 early diffuse	100%	*M*9(1–24 months)	ATG; MMF	PSL 20 mg/day × 1 week, tapered by 5 mg every week	Med	12	2 SRC (months 1 and 4)
Antoniades et al. [48]	Greece	Open	32 patients	47%	*m*6 ± 4.9 years	None reported	PSL 20 mg/day × 20 days	Med	20 days	None
Davas et al. [21]	Greece	Prospective	16 active alveolitis	100%	*M*5 years	CyP	Pred 10 mg/day	Low	12	No mention
Behr et al. [47]	Germany	Prospective	38 fibrosing alveolitis	NR	NR	CyP	PSL 1 mg/kg/day × 8–12 weeks, then tapered	High	56.8 weeks	No mention
Matteson et al. [20]	USA	Pilot	10 early with progressive skin and pulmonary disease cardiopulmonary and renal failure (months 7 and 24)	NR	≤3 years	ATG	PSL 100 mg/day × 5 days	High	24	No specific mention but 2 patients died of progressive
Pai et al. [19]	India	Prospective	5 patients	NR	NR	None reported	Dexa 100 mg/day × 3 days monthly × 6–20 months	High	6	No mention
Akesson et al. [46]	Sweden	Prospective	18 active ILD	44%	*M*2.5(r0.5–17 year)	CyP	Pred 30 mg/day tapered over 10 weeks to 2.5–10 mg/day	Med	12	No mention
Sharada et al. [18]	India	RCT	35 diffuse (17 active and 18 PBO)	100%	*m*3.9 ± 2.4 years active and *m*4.8 ± 5.6 PBO groups	None reported	Dexa 100 mg every month × 6 months	High	6	None
Tarkowski et al. [17]	Sweden	Pilot	3 severe	NR	*m*13 ± 9.64 years	ATG	MP 125 mg × 1	High	15	No mention
Becker et al. [45]	Germany	Prospective	5 patients (but only 3 received steroids)	NR	r1–7 years	Inosiplex	MP 1 gm × 1	High		No mention
Total			543 SSc patients; 500 on CS							10 definite SRC

NR not recorded; disease duration given as m (mean) ±SD or M (median) with IQR except if only "*r*" (full range, not IQR) is available; F/U in months except when otherwise specified; doses in mg/day unless otherwise specified; duration of CS is for F/U period unless otherwise specified; *MP* methylprednisolone, *Dexa* dexamethasone, *Pred* prednisone, *PSL* prednisolone, *AZA* azathioprine, *CyP* cyclophosphamide, *CyS* cyclosporine, *ATG* antithymocyte globulin, *MMF* mycophenolate mofetil, *AHSCT* autologous hematopoietic stem cell transplantation, *TBI* total body irradiation, *PBO* placebo

included a total of 500 patients. Overall, 81% of the patients were women, which is consistent with the gender distribution usually seen in SSc. Eighty percent (80%) of the patients had dcSSc. This is likely due to the fact that 11 of the 26 studies included only early dcSSc patients. The mean disease duration was 30 months (or 2.5 years), and the mean follow-up period was 17 months.

Ten definite SRC cases were reported among the 500 patients, equivalent to a rate of 2%. One other study also reported two patients who died because of progressive cardiopulmonary and renal disease, but these patients were not explicitly labeled as having had SRC. Of the 10 definite cases, 8 had received pulse CS therapy, 2 medium doses of CS, and none low-dose CS. Seven definite cases occurred in the context of autologous hematopoietic stem cell transplantation protocols. The two possible cases had both received antithymocyte globulin. Considering only the 11 studies limited to early dcSSc patients [18, 21, 22, 25, 27, 28, 30, 31, 33, 38, 49], we identified 9 definite SRC cases in 226 patients, which is equivalent to a rate of 4%.

Discussion

In this systematic review, we found that 2% of all SSc patients and 4% of early diffuse patients treated with CS developed SRC. In the literature, SRC has been reported to occur in 5–18% of SSc patients [13, 14, 50, 51]. Of these, 75–86% have been reported to occur within the first 4 years of disease [13, 50]. Taking the most conservative numbers, we thus estimate that the incidence of SRC within the first 4 years of disease is approximately 3.75% ($5 \times 75\%$). This is equivalent to an annual incidence rate of 0.94%. Using similar estimates for diffuse patients only, the annual incidence of SRC in the first 4 years would be approximately 2.34% [14]. Thus, the rates found in this systematic review are approximately twice those expected, both for SSc in general (2 vs. 0.94%) and in the early diffuse subset (4 vs. 2.34%). However, there is tremendous uncertainty present, on the one hand from the heterogeneity of the studies reviewed and on the other around the expected estimates calculated from the literature. Thus, it is difficult to conclude whether the doubling of rates found in this study is real or whether it would fall within the confidence intervals of the expected rates, if those were known. Also, the patients included in this review consisted largely of early, diffuse SSc patients with severe internal organ involvement, poor prognostic features and who were also treated with other potentially nephrotoxic therapies, such as total body irradiation, antithymocyte globulin, and cyclophosphamide. Thus, we cannot exclude the fact that our findings may also reflect, in part, some underlying confounding, with early SSc patients with severe organ involvement being most likely to receive CS and other co-interventions but also at greatest risk of developing SRC. On the other hand, patients included in this systematic review were possibly at lower risk of SRC, with several study protocols excluding patients with a history of prior SRC or renal abnormalities and others using "prophylactic" ACE inhibitors. Moreover, follow-up of some patients was as short as 20 days [48]. Finally, since there is no universally agreed definition, it is possible that mild or normotensive episodes of SRC may have been overlooked. These considerations would tend to have resulted in selecting low-risk patients and under-reporting of cases and, in turn, an *under-estimation* of the true rate of SRC in patients treated with CS. Thus, our results can be viewed as conservative estimates of the association between CS and SRC.

A limitation of this study is underscored by our relatively small sample size and number of outcomes. CS are infrequently used in SSc, and SRC is indeed rare. Moreover, the studies included in this review are highly heterogeneous, in terms of country of origin, spectrum of disease (including patients with limited and diffuse disease and different disease duration and severity), steroid regimen, and co-interventions. Thus, the association between CS and SRC remains one that is particularly difficult to evaluate [16].

On the other hand, the strength of our data is based on an exhaustive review of the literature and on data collected prospectively. EUSTAR recently published 14 recommendations for the treatment of systemic sclerosis. One of the recommendations suggested that steroids were associated with a higher risk of SRC, and thus, patients on steroids should be carefully monitored for blood pressure and renal function. However, given that this recommendation was based on retrospective studies (level 2 and 3), the strength of the recommendation was only C. Our systematic review of prospective studies now provides level 1 evidence on the subject. Thus, for now, our estimates remain the best, albeit conservative, estimates of the risk of SRC associated with CS in SSc.

Our study provides additional support for the association between CS and SRC previously reported in retrospective studies but does not eliminate the possibility that the association may be due to confounding by disease severity or by co-intervention. Thus, great caution must continue when initiating CS therapy in SSc, especially at higher doses and for the early diffuse subset of patients.

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Appendix: search strategy

Medline

Database: Ovid MEDLINE(R) <1950 to August Week 1 2009>

Search Strategy:

1. Systemic sclerosis.mp. or Scleroderma, Systemic/ (14470)
2. Clinical Trial/(456645)
3. Prospective Studies/(266598)
4. (steroid* or corticosteroid* or glucocorticoid* or prednisone or prednisolone or methylprednisolone or dexamethasone).mp. [mp = title, original title, abstract, name of substance word, subject heading word] (382704)
5. stem cell transplantation/or antithymocyte globulin/ (20222)
6. 3 or 2 (662329)
7. 4 or 5 (400729)
8. 6 and 1 and 7 (50)

EMBASE

Database: EMBASE <1980 to 2009 Week 32>

Search Strategy:

1. Systemic sclerosis.mp. or Scleroderma, Systemic/ (7829)
2. Clinical Trial/(551097)
3. Prospective Studies/(84348)
4. (steroid* or corticosteroid* or glucocorticoid* or prednisone or prednisolone or methylprednisolone or dexamethasone).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (457911)
5. stem cell transplantation/or antithymocyte globulin/ (24097)
6. 3 or 2 (609254)
7. 4 or 5 (471731)
8. 6 and 1 and 7 (230)

Web of science (August 2009—125 results)

Topic = (scleroderma OR systemic sclerosis).
AND Topic = (prospective OR trial)
AND Topic = (steroid* OR corticosteroid* OR glucocorticoid* OR prednisone OR prednisolone OR methylprednisolone OR dexamethasone OR stem cell transplantation OR antithymocyte globulin)
NOT Topic = ("multiple sclerosis" OR "tuberous sclerosis" OR "nodular sclerosis" OR "nuclear sclerosis" OR "biliary sclerosis" OR "localized scleroderma")
Timespan = All Years. Databases = SCI-EXPANDED, SSCI, A&HCI

The Cochrane Library (August 2009—10 results)

(Advanced Search)
"scleroderma" OR systemic sclerosis in Title, Abstract or Keywords
and prospective OR trial in Title, Abstract or Keywords
and steroid* OR corticosteroid* OR glucocorticoid* OR prednisone OR prednisolone OR methylprednisolone OR dexamethasone OR stem cell transplantation OR antithymocyte globulin in Title, Abstract or Keywords
not "multiple sclerosis" OR "tuberous sclerosis" OR "nodular sclerosis" OR "nuclear sclerosis" OR "biliary sclerosis" OR "localized scleroderma" in Title, Abstract or Keywords

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