A pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis

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Abstract

Objective

This pilot study was aimed at evaluating the efficacy and safety of a protocol-based treatment strategy combining mycophenolate mofetil (MMF), intravenous (IV) methylprednisolone (MP) pulses and low-dose glucocorticoids (GC) in early systemic sclerosis (SSc) patients suffering from either active interstitial lung disease (ILD) or extensive skin disease.

Patients and methods

Sixteen SSc patients were recruited in the study, 9 based on the severity of their skin involvement (modified Rodnan total skin score [TSS] ≥ 15) and 7 based on the presence of active ILD. Patients received 3 consecutive daily IV MP pulses, followed by 5 additional monthly IV MP pulses. MMF (0.5 g bid for one week; then, 1 g bid) and low-dose (5-10 mg/day) oral prednisolone were prescribed for one year. Patients were assessed at baseline, month 6 and 12. Statistics were by ANOVA.

Results

TSS and Health Assessment Questionnaire significantly improved over time. In ILD patients, the vital capacity, forced expiratory volume in one second and carbon monoxide diffusing capacity significantly improved. Although the difference was not statistically significant, ground glass lesions decreased, based on semi-quantitative planimetry analyses performed on chest high-resolution computerized tomography. Toxicity was low and none of the patients suffered from renal crisis.

Conclusion

The results of this pilot study suggest that the combination of MMF, IV MP and low-dose GC might achieve good clinical, functional and radiological results in patients suffering from severe early SSc.

Key words

Systemic sclerosis, scleroderma, early, treatment, mycophenolate mofetil, Glucocorticoids, pulse therapy, methylprednisolone.

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Introduction

Systemic sclerosis (SSc) is a life-threatening disease whose treatment remains difficult (1). Besides other pathways, inflammatory changes and autoimmune responses play a critical pathogenic role, thereby explaining why several immunosuppressive regimens have been proposed, such as steroids, cyclophosphamide, anti-thymocyte globulin, methotrexate, *etc*. Interestingly, oral cyclophosphamide was recently shown to be modestly superior to *placebo* for scleroderma lung disease (2).

Mycophenolate mofetil (MMF), by inhibiting the *de novo* synthesis of purines, displays potent immunosuppressive properties on B and T lymphocytes and is now widely used in transplant medicine (3-5) and lupus nephritis (6-8). Moreover, MMF inhibits the proliferation of vascular smooth muscle cells (9) and fibroblasts (10), thereby suggesting that the drug might be effective in diseases such as scleroderma, in which fibrotic processes are prominent.

Glucocorticoids (GC) are sometimes prescribed as a potent antiinflammatory and immunosuppressive agent to treat specific disease manifestations of SSc, such as interstitial lung disease (ILD) or myositis, but their use is controversial, given the risk of precipitating a renal crisis (11). In a placebo-controlled study, Sharada *et al*. noted a significant improvement in the modified Rodnan total skin score (TSS) after treatment with intravenous (IV) dexamethasone pulse therapy in diffuse SSc (12).

This pilot study is aimed at evaluating the efficacy and safety of a one-year protocol-based treatment strategy combining MMF, IV methylprednisolone (MP) pulses and low-dose GC in early SSc patients suffering from either active ILD or extensive skin disease.

Patients and methods

Inclusion and exclusion criteria

Consecutive male or female patients, aged ≥ 18 years, suffering from SSc according to the ACR criteria (13), with a disease duration (first non-Raynaud manifestation) of less than 3 years, were included in this pilot study if their TSS (14) was ≥ 15 ("Skin patients") and/or if they suffered from active ILD ("ILD patients"). Patients with both severe skin disease and ILD (n = 3) were classified as "ILD patients" for the purpose of subset analyses.

Active ILD was defined as the combination of abnormal lung function tests (carbon monoxide diffusing capacity [DLCO] or vital capacity ≤75% of predicted value) and one of the two following: ground-glass appearance on high-resolution chest computerized tomography scan (HRCT) or abnormal bronchioloalveolar lavage analysis (lymphocytes ≥ 15%, neutrophils ≥ 3%, eosinophils ≥ 1%).

Patients with a history of scleroderma renal crisis, a serum creatinine value ≥ 2 mg/dl, a vital capacity (VC) ≤ 50% of predicted value, a left ventricular ejection fraction ≤ 40%, a DLCO ≤ 40%, previous treatment (within 6 months) with d-penicillamine or immunosuppressive drugs other than low-dose GC (< 15 mg equivalent prednisolone/day), a previous malignancy or diabetes mellitus were excluded from the study. The study was approved by the Ethics Committee of the participating hospitals and all patients signed an informed consent.

Treament protocol

Patients received IV MP pulse therapy (15 mg/kg) on three consecutive days and 5 additional monthly MP pulses (1 pulse; same dose). Low-dose GC (between 5 and 10 mg equivalent prednisolone/day) was prescribed for 1 year. The dose of MMF was 1 g bid during one year, except during the first week of treatment (500 mg bid) to avoid gastrointestinal intolerance. The total dose of MMF could be split up in 3 to 4 takes per day.

Blood pressure was carefully monitored and an angiotensin-converting enzyme inhibitor (ACEI) was prescribed *per* protocol in hypertensive (diastolic ≥ 90 mm Hg) patients. Prevention of GC-induced osteoporosis was applied. Other DMARDs or immunosuppressive drugs than those prescribed *per* protocol were not allowed.

Outcome measures

Each patient was assessed by the same

investigator throughout the study using the following outcome measures: clinical examination, TSS (14), routine biochemistry, lung function tests, chest high resolution computerized tomography (HRCT), 6-minute walking distance, disability index of the Health Assessment Questionnaire (HAQ-DI) (15), Scleroderma Health Assessment Questionnaire (SHAQ) visual analog scales (100-mm scales based on past week patient's perception of interference with their activities due to Raynaud's phenomenon [VAS 1], finger ulcers [VAS 2], gastrointestinal problems [VAS 3], lung problems [VAS 4], overall problems [VAS 5] and pain [VAS 6]) (16).

By protocol, patients were considered as "responders" to therapy if they experienced the following improvements: for the TSS, a decrease by 30% of more; for the VC, FEV_1 and the DLCO, an increase by 10% or more; for the HAQ-DI, a decrease of 0.5 (0-3 scale) or more; and for the 6-minute walking distance, an increase by 15% or more.

Semi-quantitative planimetry analyses were performed on chest HRCT at baseline, 6 and 12 months in patients with ILD to evaluate ground-glass opacity, consolidation areas, interlobular thickening and honeycombing on 5 predefined HRCT slices (aortic arch, azygos arch, distal portion of the bronchus intermedius, right inferior pulmonary vein and liver dome). Grading was from 0 to 4 (0 = normal; 1 = 1-25% surface involvement; 2 = 26-50% involvement; 3 = 51-75% involvement; 4 = 76-100% involvement). The radiological scores correspond to the mean (± SD) of the gradings made on the 5 HRCT slices. Side-by-side comparison of HRCT images were performed by one experienced thoracic radiologist blinded to the clinical data on a dedicated workstation (EBW workstation, Philips Medical Systems, Cleveland, OH).

Statistics

As this was a pilot study, power calculation was not performed. Statistics were by ANOVA or paired *t*-tests, as appropriate.

Results

Baseline data

Sixteen consecutive patient volunteers meeting the inclusion criteria were recruited in the study, 9 based on the severity of their skin involvement (modified Rodnan total skin score ≥ 15) ("Skin patients") and 7 based on the presence of active ILD ("ILD patients") (see *Patients and methods* for definitions). Patients' characteristics at baseline are described in Table I. Of note, mean disease duration was less than one year and only one patient had received immunosuppressive therapy before entry in the protocol, namely methotrexate that had been stopped 8 months before.

Clinical, biological and functional tests

As indicated in Table II, the total skin score and the HAQ-DI significantly improved over time, as well as the SHAQ

Table I. Baseline characteristics*.

Age (years)	47 ± 12
F/M (n)	12/4
Disease duration (years)	0.8 ± 0.8
SSc according to ACR criteria (%) (ref.13)	100
lSSc/lcSSc/dcSSc according to Leroy (n) (ref. 21)	1/2/13
Total skin score	20 ± 12
Abnormal capillaroscopy (%)	92
Positive ANA (Hep-2) (%)	81
Past oral GC therapy (%)	25
Past IV MP pulse therapy (%)	0
Past cyclophosphamide therapy (%)	0
Past azathioprine therapy (%)	0
Past d-penicillamine therapy (%)	0
Past methotrexate therapy (%)	7
Past ACEI therapy (%)	14

*Except stated otherwise, figures are mean ± SD. F: Female; M: Male; SSc: systemic sclerosis; lSSc: limited systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; GC: Glucocorticoids; IV: Intravenous; MP: Methylprednisolone; ACEI: Angiotensin-converting enzyme inhibitor.

Table II. Clinical, biological and functional evaluation*.

Patients	Parameter	Baseline	M6	M12	*p* value
ALL (n = 16)	Total skin score	20 ± 12	14 ± 12	13 ± 11	**< 0.0001**
	HAQ-DI	1.1 ± 0.7	0.7 ± 0.8	0.6 ± 0.7	**0.021**
	SHAQ VAS 1 (Raynaud's)	37 ± 28	36 ± 36	27 ± 29	0.674
	SHAQ VAS 2 (Finger ulcers)	32 ± 40	29 ± 38	26 ± 35	0.963
	SHAQ VAS 3 (Gastrointestinal)	26 ± 29	21 ± 32	20 ± 31	0.804
	SHAQ VAS 4 (Lung)	25 ± 32	34 ± 30	22 ± 26	0.926
	SHAQ VAS 5 (Overall)	41 ± 30	39 ± 32	25 ± 28	0.094
	SHAQ VAS 6 (Pain)	47 ± 31	25 ± 30	29 ± 32	**0.031**
	CRP (mg/dl)	2.0 ± 5.3	0.4 ± 0.5	0.5 ± 0.8	0.311
ILD (n = 7)	VC (ml)	2598 ±567	2834 ± 527	2943 ± 591	**0.012**
	VC (% of predicted)	76 ± 22	83 ± 15	86 ± 17	0.099
	FEV_1 (ml)	1971 ±383	2321 ± 393	2347 ± 452	**0.0009**
	FEV_1 (% of predicted)	76 ± 15	91 ± 11	90 ± 13	**0.003**
	DLCO (% of predicted)	63 ± 11	73 ± 12	76 ± 13	**0.0009**
	6-min walking distance (m)	506 ±117	582 ± 69	567 ± 36	0.110
SKIN (n = 9)	Total skin score	26 ± 9	21 ± 10	18 ± 10	**0.002**

*Values are mean ± SD. *P* values were measured by ANOVA. ILD: Interstitial Lung Disease; HAQ-DI: Health Assessment Questionnaire; SHAQ: Scleroderma Health Assessment Questionnaire; VAS: Visual Analog Scale (see *Patients and methods*); VC: Vital Capacity; FEV_1: Forced Expiratory Volume in one second; DLCO: carbon monoxide diffusing capacity.

Table III. Percentages of responders*.

Patients	Parameter	Responders (%)	
		M6	M12
ALL (n = 16)	Total skin score	50	69
	HAQ-DI	50	50
ILD (n = 7)	VC	50	83
	FEV_1	57	86
	DLCO	71	71
	6-min walking distance	29	14
SKIN (n = 9)	Total skin score	33	56

*Patients were considered as "responders" if they experienced the following improvements: for the modified Rodnan total skin score, a decrease by 30% of more; for the VC, FEV_1 and the DLCO, an increase by 10% or more; for the HAQ-DI, a decrease of 0.5 or more; and for the 6-minute walking distance, an increase by 15% or more. HAQ-DI: Health Assessment Questionnaire; ILD: Interstitial Lung Disease; VC: Vital Capacity; FEV_1: Forced Expiratory Volume in one second; DLCO: carbon monoxide diffusing capacity.

Table IV. Radiological scores over time in ILD patients*.

Pattern	Baseline	M6	M12
Ground-glass appearance	4.14 ± 2.73	2.43 ± 2.30 $p = 0.06$	2.71 ± 2.69 $p = 0.13$
Consolidation areas	0.57 ± 0.98	0.14 ± 0.38 $p = 0.36$	0.00 ± 0.00 $p = 0.17$
Interlobular thickening	2.43 ± 2.51	2.14 ± 2.54 $p = 0.46$	2.43 ± 2.64 $p = 0.99$
Honeycombing	1.29 ± 1.89	0.71 ± 1.50 $p = 0.23$	1.00 ± 1.73 $p = 0.17$

*Values are mean ± SD radiological scores obtained by semi-quantitative analyses performed at 5 different anatomic areas on high resolution computerized tomography (see *Patients and methods*). *P* values (*vs* baseline) were measured by paired *t*-tests. ILD: Interstitial Lung Disease.

visual analog scale dealing with patient's perception of pain (VAS 6). The drop of serum CRP titers was not statistically significant. For more specific outcome measures, the two subgroups of patients were further analyzed. In "ILD patients", the VC, the FEV_1 and the DLCO significantly improved over time. Although a 10% improvement in the 6-minute walking distance was observed, the difference did not reach the level of statistical significance. Of note, the TSS also improved over time in the "Skin patients" subgroup. The percentages of "responders" (as defined in *Patients and methods*) are given in Table III. Out of the 15 patients with a baseline TSS ≥ 4, all but 2 improved their score by at least 4 points (data not shown).

Radiological data in " ILD patients "

Semi-quantitative planimetry analyses were performed on chest HRCT scans obtained from "ILD patients", as described in *Patients and methods*. While interlobular thickening and honeycombing did not improve over time, ground-glass appearance and consolidation areas were less prominent at month 6 and 12 compared to baseline, although the difference was not statistically significant (Table IV). Improvement of ground-glass appearance is illustrated in Figure 1.

Adverse events

One patient suffered from *Elastobacillus* enterocolitis at month 2 that required in-patient therapy. She recovered completely. Other side-effects included ophtalmic *Herpes zoster* (n = 1 episode), bronchitis (n = 4), diarrhea (n = 4), nausea (n = 1) and vertigo (n = 1). Out of these 12 adverse events, 10 were observed within the first 6 months of treatment. No episode of renal crisis was noted. Three patients were treated for hypertension (diastolic blood pressure > 90 mmHg) with an ACEI before entry in the protocol and their blood pressure remained under control throughout the study. A fourth patient developed hypertension at month 2 (170/100 mmHg). She was treated with a combination of an ACEI, a calcium-channel blocker and a β-blocker and her diastolic blood pressure values never exceeded 80 mmHg. None of these 4 patients suffered from renal impairment and none had biological signs of microangiopathy.

Discussion

The results of this prospective pilot study suggest that an immunosuppressive regimen combining MMF, IV MP and low-dose GC is safe in patients with early SSc. Since spontaneous improvement of the skin score may occur in early SSc, we are probably not allowed to claim efficacy on skin involvement without a control group. By contrast, as active ILD rarely improves in untreated SSc patients, our data suggest that the forementioned immunosuppressive regimen might be efficient for scleroderma lung disease.

So far, only two placebo-controlled trials have been completed in patients with scleroderma-associated ILD and both have provided evidence in favour of a potent immunosuppressive approach. Thus, Clemens *et al.* compared oral cyclophosphamide (CYC) and placebo for the treatment of pulmonary disease in a large cohort of US scleroderma patients (Scleroderma Lung Study). The CYC group experienced a significant beneficial effect on lung function tests, dyspnea, thickening of the skin and quality of life (2). In a British trial (Fibrosing Alveolitis in Scleroderma Trial; FAST), Hoyles *et al.* compared six monthly infusion of CYC followed by oral azathioprine with placebo. At 12 months, there was a 4.76 % difference in VC favouring CYC (17). While these trials open new

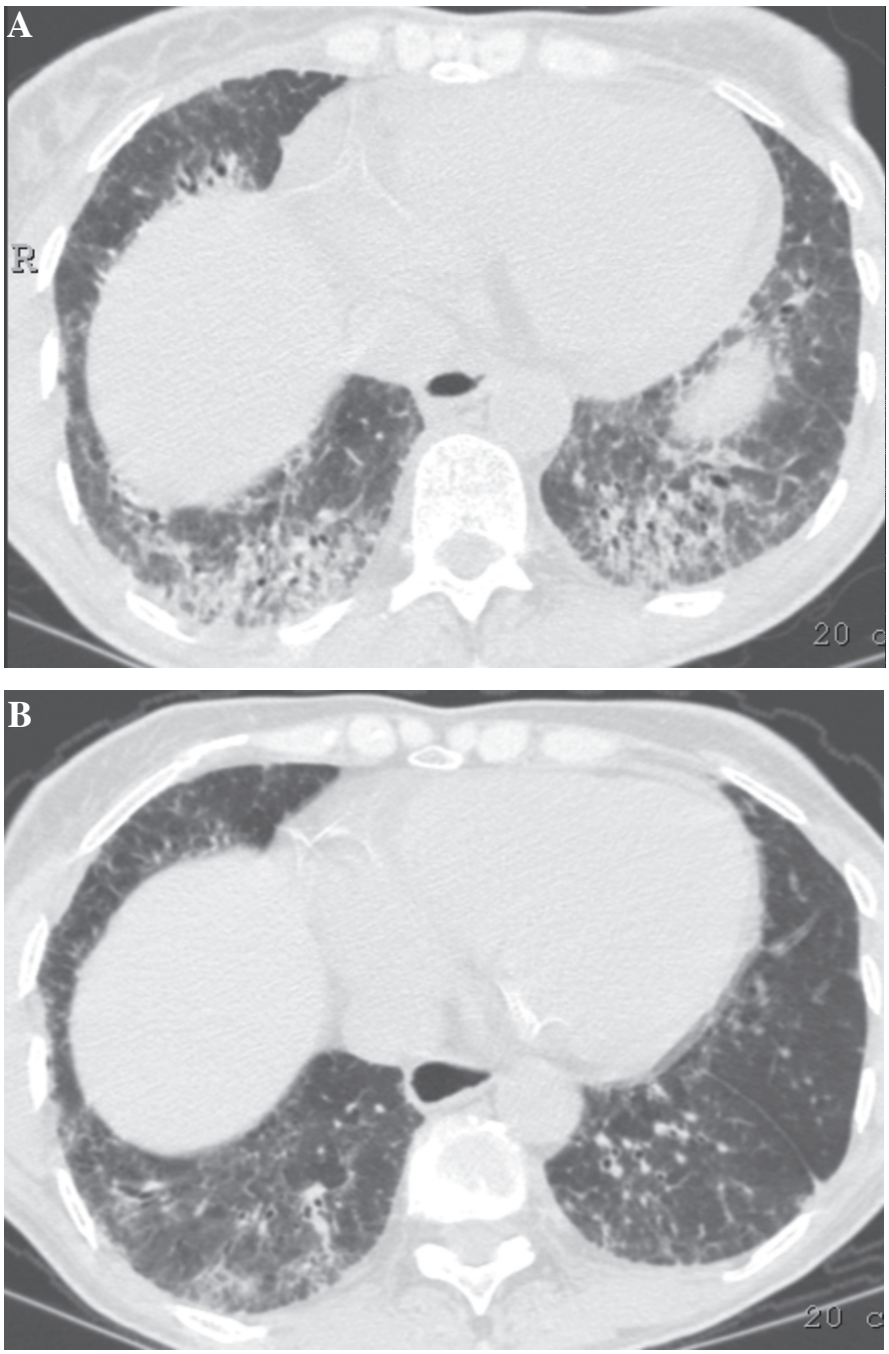

Fig. 1. Chest HRCT performed at baseline (A) and 12 months after therapy (B) at the level of the liver dome in a 55-year old woman suffering from SSc-associated active interstitial lung disease. Ground-glass opacities were graded 4 (between 76 and 100% of the surface) and 3 (between 51 and 75%) at baseline and after treatment, respectively. Note the presence of mild interlobular thickening on the two HRCT examinations.

hopes for the treatment of lung involvement in scleroderma patients, the toxicity of CYC should be underlined, in particular when the drug is prescribed orally on a daily basis for a prolonged period of time. Therefore, alternative immunosuppressive strategies, with fewer toxic drugs, should be tested, following the example of lupus nephritis where MMF is on the verge of replacing IV CYC as first-line therapy (6, 8). Few data are available on the safety and efficacy of MMF in scleroderma patients. Thus, Stratton *et al*. reported on 13 early SSc patients treated with MMF after induction therapy with anti-thymocyte globulin. Toxicity related to MMF was low, the skin score significantly improved over time but not the lung function tests (18). More recently, Liossis *et al*. treated five diffuse SSc patients suffering from active ILD with MMF and low-dose prednisolone, with a significant improvement of DLCO but not of lung volumes (19). Interestingly, our study confirms these results by demonstrating a significant effect over time on VC and DLCO, as well as a trend towards radiological improvement of ground-glass lesions. Whether this effect is due to MMF, IV MP, low-dose steroids or their combination can obviously not be addressed by our study. Of note, the percentages of responders for several outcome measures increased from month 6 to month 12, when IV MP therapy was stopped, thereby suggesting a role for MMF, alone or in combination with low-dose GC, in the improvement observed at 1 year. Finally, in a retrospective study dealing with a large cohort of diffuse SSc patients, Nihtyanova *et al*. compared the clinical course of 109 patients treated with MMF and 63 control patients receiving other immunosuppressive drugs. Survival was significantly better at 5 year in the MMF group and there was a significantly lower frequency of clinically significant pulmonary fibrosis (20). All together, these studies lend credence to the efficacy of MMF in SSc and support a controlled trial, in particular in patients suffering from lung involvement.

We were concerned that IV MP therapy could precipitate a scleroderma-related renal crisis, as indeed reported in the litterature (11). Blood pressure control as well as kidney function were therefore tightly controlled and no episode of renal impairment was observed after more than 120 MP pulses given to 16 patients. In this respect, it should be stressed that our patients, even those with active ILD, did not receive high-dose oral GC, which might be another contributing factor to renal crisis.

While our study obviously requires confirmation by a controlled trial, our results suggest that the combination of GC and MMF might achieve good clinical, functional and radiological results in patients suffering from early severe SSc, with GC providing a potent fast-

acting immunosuppression and MMF a long-term safe maintenance therapy, with potential antifibrotic properties.

References

1. CHARLES C, CLEMENTS P, FURST DE: Systemic sclerosis: hypothesis-driven treatment strategies. *Lancet* 2006; 367: 1683-91.
2. TASHKIN DP, ELASHOFF R, CLEMENTS PJ *et al*.: Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; 354: 2707-9.
3. CIANCIO G, MILLER J, GONWA TA: Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation* 2005; 80 (2 Suppl.): S191-200.
4. MANZIA TM, DE LIGUORI CARINO N, ORLANDO G *et al*.: Use of mycophenolate mofetil in liver transplantation: a literature review. *Transplant Proc* 2005; 37: 2616-7.
5. KOBASHIGAWA JA, MEISER BM: Review of major clinical trials with mycophenolate mofetil in cardiac transplantation. *Transplantation* 2005; 80 (2 Suppl.): S235-43.
6. CHAN TM, LI FK, TANG CS *et al*.: Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. HONG KONG-GUANGZHOU NEPHROLOGY STUDY GROUP. *N Engl J Med* 2000; 343: 1156-62.
7. CONTRERAS G, PARDO V, LECLERCQ B *et al*.: Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004; 350: 971-80.
8. GINZLER EM, DOOLEY MA, ARANOW C *et al*.: Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; 353: 2219-28.
9. SHIMIZU H, TAKAHASHI M, TAKEDA S *et al*.: Mycophenolate mofetil prevents transplant arteriosclerosis by direct inhibition of vascular smooth muscle cell proliferation. *Transplantation* 2004; 77: 1661-7.
10. MILJKOVIC DJ, CVETKOVIC I, STOSIC-GRUJICIC S, TRAJKOVIC V: Mycophenolic acid inhibits activation of inducible nitric oxide synthase in rodent fibroblasts. *Clin Exp Immunol* 2003; 132: 239-46.
11. STEEN VD, MEDSGER TA JR.: Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum* 1998; 41: 1613-9.
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: 91-4.
13. SUBCOMMITTEE FOR SCLERODERMA CRITERIA OF THE AMERICAN RHEUMATISM ASSOCIATION DIAGNOSTIC AND THERAPEUTIC CRITERIA COMMITTEE: Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581-90.
14. CLEMENTS PJ, LACHENBRUCH PA, SEIBOLD JR *et al*.: Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. *J Rheumatol* 1993; 20: 1892-6.
15. FRIES JF, SPITZ P, KRAINES RG, HOLMAN HR: Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137-45.
16. STEEN VD, MEDSGER TA JR: The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum* 1997; 40: 1984-91.
17. HOYLES RK, ELLIS RW, HERRICK AL *et al*.: Fibrosing alveolitis in scleroderma trial (FAST) – a Multi-Centre Prospective Randomised Double-Blind Placebo-Controlled Trial. AMERICAN COLLEGE OF RHEUMATOLOGY NATIONAL SCIENTIFIC MEETING 2005: Abstract L29.
18. STRATTON RJ, WILSON H, BLACK CM: Pilot study of anti-thymocyte globulin plus mycophenolate mofetil in recent-onset diffuse scleroderma. *Rheumatology* 2001; 40: 84-8.
19. LIOSSIS SN, BOUNAS A, ANDONOPOULOS AP: Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. *Rheumatology* 2006; 45: 1005-8.
20. NIHTYANOVA SI, BROUGH GM, BLACK CM, DENTON CP: Mycophenolate mofetil in diffuse cutaneous systemic sclerosis – a retrospective analysis. Rheumatology 2006; August 9 [Epub ahead of print].
21. LEROY EC, MEDSGER TA JR: Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; 28: 1573-6.