

# Renal complications and scleroderma renal crisis

C. P. Denton<sup>1</sup>, G. Lapadula<sup>2</sup>, L. Mouthon<sup>3</sup> and U. Müller-Ladner<sup>4</sup>

Scleroderma renal crisis (SRC) occurs in 5–10% of SSc patients, who may present with an abrupt onset of hypertension, acute renal failure, headaches, fevers, malaise, hypertensive retinopathy, encephalopathy and pulmonary oedema. Patients at greatest risk of developing SRC are those with diffuse cutaneous or rapidly progressive forms of SSc, and treatment with a recently commenced high dose of corticosteroid. Laboratory tests may demonstrate hypercreatininaemia, microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and hyperreninaemia. Renal crisis is also linked to a positive ANA speckled pattern, antibodies to RNA polymerase I and II, and an absence of anti-centromere antibodies. Early, aggressive treatment with angiotensin-converting enzyme inhibitors has improved prognosis in SRC, although 40% of the patients may require dialysis, and mortality at 5 yrs is 30–40%. Median time to recovery is 1 yr, and typically occurs within 3 yrs. Prognosis is worse for males, but may not be related to corticosteroid use, presence of MAHA or severity of renal pathology. Modification of endothelin over-activity, which is implicated in the pathogenesis of SRC, may offer a future therapeutic approach.

**KEY WORDS:** Endothelin-1, Systemic sclerosis, Scleroderma renal crisis.

## Introduction

SSc is an autoimmune disease of uncertain aetiology that is characterized by inflammation and fibrosis in the skin and internal organs. Patients with SSc may experience severe and life-threatening renal complications of the disease, which are most common in females with dcSSc [1, 2]. The most important renal complication in SSc is scleroderma renal crisis (SRC), estimated to affect 5–10% of all SSc patients [3].

SRC typically causes an abrupt onset of a moderate-to-marked hypertension that is accelerated and often malignant, and acute renal failure [4]. Historically, mortality among patients with SRC at 1 yr was very high [5], although early treatment with angiotensin-converting enzyme (ACE) inhibitors has reduced this to an estimated 24% [6]. During the period 1972–2002, the proportion of deaths in SSc patients attributed to SRC decreased from 42 to 6% [7]. Despite this progress, long-term mortality in SRC remains high [1, 8]. SRC also constitutes one of the few medical emergencies in rheumatology, requiring early identification and aggressive treatment to preserve kidney function.

This article reviews the clinical presentation of SRC, exploring the factors influencing risk and outcome. A case history of an SRC patient is employed to highlight effective clinical management of SRC, and future developments in the treatment of SRC are discussed.

## Clinical presentation of SRC

The cardinal features of SRC comprise a new onset of significant systemic hypertension (>150/85 mmHg) and decreased renal function [ $\geq 30\%$  reduction in estimated glomerular filtration rate (eGFR)]. While a minority of patients may appear normotensive, their blood pressure will invariably be increased from baseline and accompanied by other manifestations characteristic of SRC [9]. For an estimated 20% of the patients,

diagnosis of SRC may precede diagnosis of SSc; therefore, early identification of SSc is highly important [8].

Patients with SRC may exhibit headaches, hypertensive retinopathy associated with visual disturbances and encephalopathy, seizures, fever and general malaise. Pulmonary oedema is also common, resulting from water and salt retention due to large overload and oliguria. Arrhythmia, myocarditis and pericarditis, if present, may indicate poorer prognoses [10].

Changes in clinical chemistry that may be observed in patients with SRC include increased plasma creatinine, microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and hyperreninaemia. Hypercreatininaemia may affect  $\geq 96\%$  of the patients, and the prevalences of MAHA and thrombocytopenia are estimated to be 60 and 50%, respectively [8]. High levels of renin may induce hypertension, which may be alleviated following nephrectomy [11]. Urinalysis commonly demonstrates mild proteinuria and haematuria, with granular casts evident on microscopy.

Early pathological changes comprise mucin accumulation in arcuate and interlobular arteries, mucoid intimal thickening and fibrinoid necrosis of arterioles with fibrin thrombi [12]. Subsequent manifestations include hypertensive vascular damage, glomerular ischaemia, thrombotic vascular occlusion and fibrosis, and proliferation of intimal cells.

## Pathogenesis of SRC

The pathogenic mechanisms underlying SRC are not completely understood, and may involve intimal thickening of the renal interlobular and arcuate arteries as a result of endothelial cell injury. Epithelial-to-mesenchymal transdifferentiation and fibrosis in the glomerular and tubulointerstitial compartments, and dysregulation of ET-1 receptor expression, may also encourage renal disease progression [12, 13].

Decreased renal perfusion results from narrowing of arterial vessels, leading to hyperplasia of the juxtaglomerular apparatus and increased renin release. Pathological changes can be found in the renal vasculature of SSc patients without renal crisis, and neither biopsy findings nor plasma renin activity can accurately predict the occurrence of SRC. Other events may be required to trigger the acute onset and rapid progression of renal failure, which is exacerbated by hyperreninaemia.

## Risk factors for SRC

The development of SRC has been observed to be associated with dcSSc [8]. In a single-centre study in the UK, Penn *et al.* [8]

<sup>1</sup>Centre for Rheumatology, Royal Free Hospital, London, UK, <sup>2</sup>Department of Internal Medicine and Public Medicine, Rheumatology Unit, University of Bari, Bari, Italy, <sup>3</sup>Hôpital Cochin, Assistance Publique des Hôpitaux de Paris (AP-HP), Paris, France and <sup>4</sup>Department for Internal Medicine and Rheumatology, Justus-Liebig University, Giessen, Germany.

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Correspondence to: C. P. Denton, Centre for Rheumatology, Royal Free Hospital, Pond Street, Rheumatology Unit, Lower Ground Floor, London NW3 2QG, UK. E-mail: c.denton@medsch.ucl.ac.uk

estimated the frequency of SRC in a population of 706 patients. A total of 12% of dcSSc patients and 2% of lcSSc patients were observed to have developed SRC, with an odds ratio  $>7$ ; data that are comparable with those from an earlier study [2, 8].

Rapid, progressive skin disease may represent another risk factor; the estimated median duration of SSc at SRC diagnosis is a mere 8 months [8, 14, 15]. An estimated 66% of the SSc patients develop SRC within 1 yr of diagnosis, rising to 86% at 4 yrs [8, 14]. Patients with lcSSc typically develop SRC later in SSc disease course, and gender appears not to influence risk [8].

SRC has been linked to corticosteroid therapy; 60% of the patients have received corticosteroids prior to presentation [8, 14, 16]. Steen and Medsger [17] observed that for many SRC patients, a recent history of high-dose corticosteroid use (e.g. prednisolone or equivalent at  $>15$  mg/day) preceded SRC diagnosis.

Whilst chronic corticosteroid use may not be associated with additional risks, greater numbers of patients who commenced new, low-dose corticosteroid treatments developed SRC vs controls [17]. Odds ratios for the development of SRC associated with corticosteroid exposure during 1- or 3-month periods have been estimated to be 17 and 24, respectively [14]. The SSc patients most likely to receive corticosteroids are those with early dcSSc, the same patients at greatest risk of SRC; however, there is no evidence of a causal effect. Physicians may therefore wish to consider alternative immunosuppressants or prophylactic use of D-penicillamine if corticosteroid administration is unavoidable [8, 14, 17]. There is, however, only limited evidence to support the clinical efficacy of D-penicillamine as a prophylactic [17].

Other risk factors for SRC include anaemia, HRT, pericardial effusion, cardiac insufficiency, high skin score and large joint contractures, the presence of antibodies to RNA polymerases (ARA; see below) and new cardiac events [1, 17, 18].

### Association of autoantibodies with SRC

ANAs are detectable in virtually all SSc patients, and a strong association exists between SRC and an ANA speckled pattern positive status, which occurs in 60% of the SRC patients [8]. The incidences of extensive skin and renal disease are also significantly higher in patients with SSc-specific ARA (I and III) [19], which are measurable in 59% of the SRC patients [8]. Anti-fibrillar or anti-U3-RNP antibodies (AFA) may also identify young patients at risk of developing internal organ manifestations of SSc, including SRC [20]. Conversely, SSc patients exhibiting anti-centromere antibody or anti-topoisomerase 1 antibody are less likely to develop renal disease [8, 19].

### Monitoring patients for SRC

Careful monitoring of patients with newly diagnosed SSc, a history of corticosteroid therapy and presence of specific ANA may enable early detection of SRC. In patients at greatest risk, blood pressure should be monitored monthly, with daily self-monitoring introduced if signs of hypertension are exhibited. Quantification of serum creatinine concentrations and evaluation of protein content and protein-creatinine ratios in urine may also detect SRC onset [21].

Calculating eGFR is best done using the Modification of Diet in Renal Disease formula, which can accurately identify patients with renal impairment [21]. However, assessments of renal function are limited by the compromised renal function in SSc patients without overt renal disease. Decreased renal plasma flow, higher renal vascular resistance and a blunted response to an amino acid challenge are common observations [3].

### Factors affecting renal outcome and mortality

Whilst  $\sim 25\%$  of the SRC patients require dialysis at presentation, many recover sufficient renal function for this to be discontinued.

Yet, 40–66% of these patients may never recover renal function, requiring chronic dialysis or renal transplantation [8–10]. The median time to recovery is  $\sim 1$  yr and decreases in likelihood over time. Recovery is uncommon after 24 months and unlikely after 3 yrs. In patients who do not require dialysis, improvements in renal function are detectable for at least 3 yrs, a slow recovery process that likely includes vascular remodelling [8]. The assessment of prognosis may be facilitated by renal biopsy (Fig. 1) [8].

Predictors of poor outcome include dcSSc, skin scores  $\geq 20$  and evidence of cardiac involvement [1, 14]. Older patients who require dialysis are less likely to recover renal function. There appears to be no correlation between renal outcome and eGFR prior to onset of SRC, or between corticosteroid use and renal outcome or mortality [8]. Van den Born *et al.* [22] reported the presence of MAHA to be associated with more severe hypertension and a higher frequency of renal dysfunction [22], but other studies have not supported this conclusion [8, 23].

In patients who require dialysis, those with higher blood pressures and serum creatinine concentrations are most likely to recover renal function (Fig. 2) [8]. Patients who present in renal crisis with normal blood pressure are at greatest risk of mortality or of needing chronic renal replacement therapy [14]. The underlying basis for improved outcomes in patients with hypertension is poorly understood, but may relate to an absence of cardiac involvement, or a more favourable response to ACE inhibitors.

Long-term survival in SRC is poor, especially for patients who do not recover renal function (Fig. 3) [2, 8, 14]. Increased mortality has been observed in males, patients aged  $>53$  yrs and

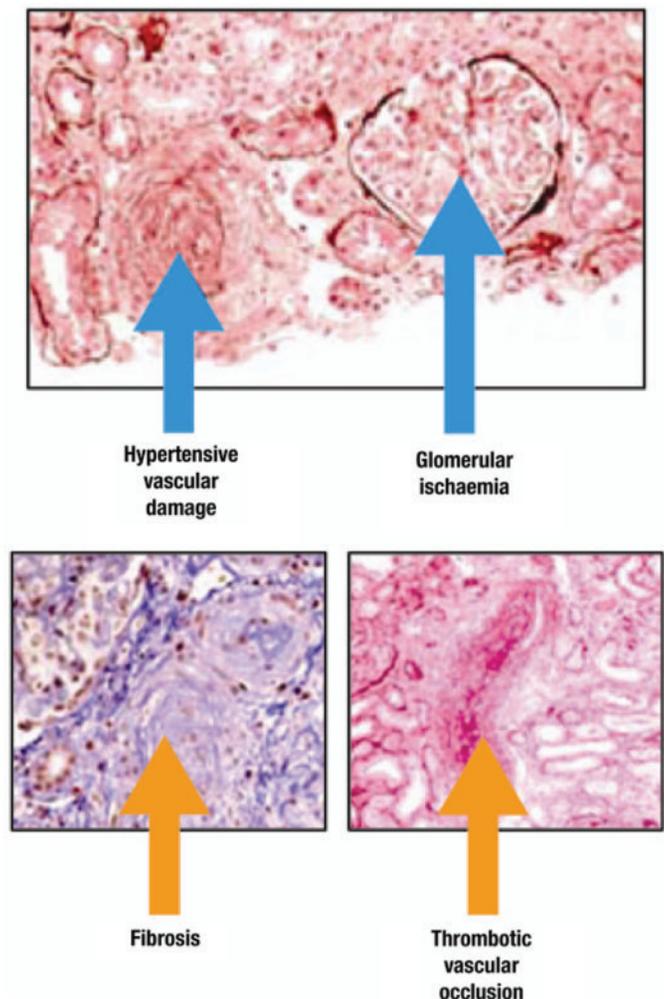


Fig. 1. Important features of renal biopsy in SRC patients.

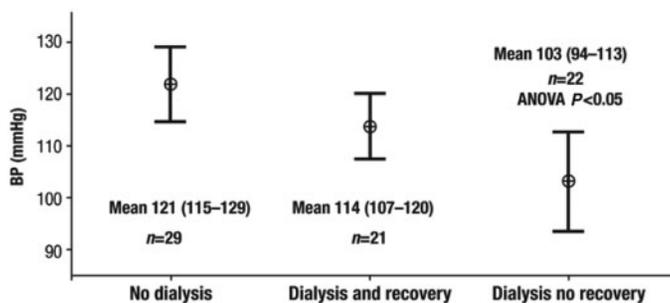


FIG. 2. The influence of diastolic blood pressure at presentation on outcome. Image reproduced with permission from [8]. Copyright 2000 Association of Physicians.

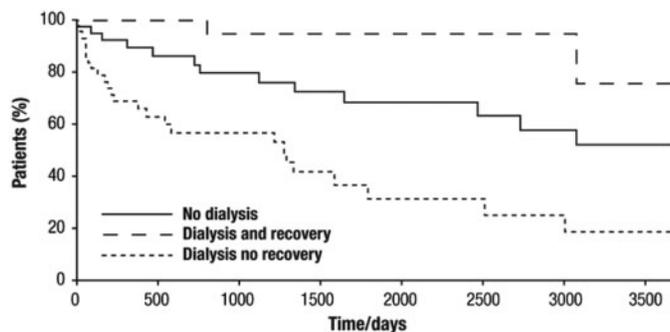


FIG. 3. Survival after SRC, by renal outcome. Image reproduced with permission from [8]. Copyright 2000 Association of Physicians.

patients with normal blood pressure at presentation [8, 14, 24]. Renal transplantation may improve survival, although decisions regarding surgery should be postponed to allow for possible recovery.

### Treatment of SRC

Aggressive treatment of hypertension in SRC patients is essential to prevent the occurrence of irreversible vascular injury [25]. ACE inhibitors significantly improve blood pressure for many patients and, in some cases, may also lead to regression of skin manifestations [18]. A gradual reduction in blood pressure should be sought, as sudden, excessive pressure decreases can further diminish renal perfusion and increase the risk of acute tubular necrosis.

The addition of calcium channel blockers may be beneficial for patients with inadequate blood pressure reduction on ACE inhibitor therapy alone. Intravenous iloprost may also help to reverse microvascular changes. Additional oral hypotensive agents (e.g. labetalol), together with nitrate infusion if there is pulmonary oedema, can be used as required. Plasma exchange is considered if there is substantial thrombotic microangiopathy. Renal function is supported by intermittent haemodialysis or continuous venous-venous haemofiltration.

### Case report

The difficulties inherent in diagnosing and treating SSc-related renal complications are best illustrated by the following case study.

A female, aged 51 yrs, presented in November 2001 with carpal tunnel syndrome and an unremarkable medical history. This patient was menopausal and taking HRT. During the subsequent 6 months, the patient developed lower limb oedema, which

progressed to the hands and face, coupled with generalized pain and hyperpigmentation of skin.

By June 2002, the patient had begun to exhibit manifestations of SSc localized to the face and hands, accompanied by weight loss, pain in multiple muscles and joints, and Raynaud's syndrome. HRT was discontinued and prednisolone commenced at 1 mg/kg/day for 1 month, the dose of which was subsequently reduced. Pulse cyclophosphamide was administered following withdrawal of prednisolone, although 4 weeks later the patient was hospitalized with Grade IV dyspnoea, hypertension (240/120 mmHg), headaches and vomiting. The patient was exhibiting anaemia (haemoglobin 10.2 g/l), with leucocytosis ( $16\,000/\text{mm}^3$ ), neutrophilia ( $13\,500/\text{mm}^3$ ), thrombocytopenia ( $80\,000/\text{mm}^3$ ) and evidence of azotaemia (creatinine  $329\ \mu\text{mol/l}$ , urea  $29.8\ \text{mmol/l}$ ).

This patient exhibited a number of risk factors for SRC, including a short disease course, recent corticosteroid therapy and HRT. At this stage in a case such as this, it would be reasonable to suspect SRC. In order to confirm diagnosis, one may wish to pursue a renal biopsy. However, this may not be absolutely necessary as SRC could be confirmed by a rapidly progressive oliguric renal insufficiency and arterial hypertension.

Following confirmation of SRC diagnosis, a patient such as this could be treated using the regimen described by Teixeira *et al.* [26]. Treatment could be initiated with captopril 6.25–12.5 mg every 8 h, and increased to 50 mg three times daily [26]. If blood pressure were to remain elevated at 72 h, calcium channel blockers could be added, and if unsuccessful, supplemented with intravenous  $\alpha/\beta$  blockers and/or minoxidil. If oliguric renal insufficiency remains unresolved, dialysis may be initiated until improvements in renal function are observed. Patients who remain on dialysis after 2 yrs should be listed for renal transplantation.

### Improving outlook for SRC—modifying endothelin overactivity

Evidence is growing for a role of dysregulation in the endothelin system in patients with SRC. Levels of ET-1 are increased in SSc patients with hypertensive renal crisis [27] and increased expression of both ET-1 and ET-1 receptors is detectable in the small renal arteries of SRC patients [13]. *In vivo* studies suggest that organ-specific activation of the endothelin system is responsible for the development of hypertensive nephropathy in renin- and angiotensin-mediated hypertension [28].

Specific polymorphisms in the endothelin receptor B genes exist in increased frequency in patients with dcSSc, alongside increased carriage frequencies of specific ET-1 receptor A alleles in SSc patients with anti-RNA polymerase antibodies [29]. This finding of associations between endothelin receptors A and B and specific SSc subsets, especially those at risk of SRC, supports a role of endothelin and its receptors in the pathogenesis of SSc and associated renal crisis.

A small open-label study using bosentan in patients with SSc-related renal crisis has been conducted in London, the results of which are awaited.

### Conclusion

An estimated 15% of SSc patients may develop SRC, which presents as an abrupt onset of hypertension and acute renal failure, and is associated with poor long-term survival. Major risk factors for the development of SRC are early dcSSc, rapidly progressive skin disease, ANA speckled pattern status and recent corticosteroid therapy. Patients with SRC may recover renal function within 3 yrs, although mortality is highest in those who do not. Prognosis is worse for males, for patients aged >53 yrs and for patients who present with normal blood pressure. Deaths are most common in patients who do not recover renal function.

Early, aggressive therapy with angiotensin-converting enzyme inhibitors is essential, and can be supplemented with other anti-hypertensive agents if required. However, patients who present in renal failure without hypertension or without a prior diagnosis of SSc present serious diagnostic challenges. Dysregulation in the endothelin system has recently been identified in SRC patients, and may be amenable to treatment using endothelin receptor antagonists.

### Rheumatology key messages

- SRC occurs in 5–10% of SSc patients.
- Risk factors for SRC are early dcSSc, rapidly progressive skin disease, anti-RNA polymerase antibodies and corticosteroid therapy.

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### References

- 1 DeMarco PJ, Weisman MH, Seibold JR *et al.* Predictors and outcome of scleroderma renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. *Arthritis Rheum* 2002;46:2983–9.
- 2 Walker JG, Ahern MJ, Smith MD *et al.* Scleroderma renal crisis: poor outcome despite aggressive antihypertensive therapy. *Intern Med J* 2003;33:216–20.
- 3 Denton CP, Black CM. Scleroderma – clinical and pathological advances. *Best Pract Res Clin Rheumatol* 2004;18:271–90.
- 4 Rodnan GP, Benedek TG. An historical account of the study of systemic sclerosis (diffuse scleroderma). *Ann Intern Med* 1962;57:305–19.
- 5 Steen VD. Renal involvement in systemic sclerosis. *Clin Dermatol* 1994;12:253–8.
- 6 Steen VD, Costantino JP, Shapiro AP *et al.* Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med* 1990;113:352–7.
- 7 Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis* 2007;66:940–4.
- 8 Penn H, Howie AJ, Kingdon EJ *et al.* Scleroderma renal crisis: patient characteristics and long-term outcomes. *Q J Med* 2007;100:485–94.
- 9 Steen VD. Scleroderma renal crisis. *Indian J Med Sci* 2007;61:71–2.
- 10 Steen VD, Medsger TA Jr. Long-term outcomes of scleroderma renal crisis. *Ann Intern Med* 2000;133:600–3.
- 11 Cannon PJ, Hassar M, Case DB *et al.* The relationship of hypertension and renal failure in scleroderma (progressive systemic sclerosis) to structural and functional abnormalities of the renal cortical circulation. *Medicine* 1974;53:1–46.
- 12 Lee S, Lee S, Sharma K. The pathogenesis of fibrosis and renal disease in scleroderma: recent insights from glomerulosclerosis. *Curr Rheumatol Rep* 2004;6:141–8.
- 13 Kobayashi H, Nishimaki T, Kaise S *et al.* Immunohistological study endothelin-1 and endothelin-A and B receptors in two patients with scleroderma renal crisis. *Clin Rheumatol* 1999;18:425–7.
- 14 Teixeira L, Mouthon L, Mahr A *et al.* Mortality and risk factors of scleroderma renal crisis: a French retrospective study in 50 patients. *Ann Rheum Dis* 2008;67:110–6.
- 15 Bryan C, Howard Y, Brennan P *et al.* Survival following the onset of scleroderma: results from a retrospective inception cohort study of the UK patient population. *Br J Rheumatol* 1996;35:1122–6.
- 16 Steen VD, Medsger TA Jr, Osial TA *et al.* Factors predicting development of renal involvement in progressive systemic sclerosis. *Am J Med* 1984;76:779–86.
- 17 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.
- 18 Steen VD. Scleroderma renal crisis. *Rheum Dis Clin North Am* 2003;29:315–33.
- 19 Bunn CC, Denton CP, Shi-Wen X *et al.* Anti-RNA polymerases and other autoantibody specificities in systemic sclerosis. *Br J Rheumatol* 1998;37:15–20.
- 20 Tormey VJ, Bunn CC, Denton CP *et al.* Anti-fibrillar antibodies in systemic sclerosis. *Rheumatology* 2001;40:1157–62.
- 21 Kingdon EJ, Knight CJ, Dustan K *et al.* Calculated glomerular filtration rate is a useful screening tool to identify scleroderma patients with renal impairment. *Rheumatology* 2003;42:26–33.
- 22 Van den Born BJ, Honnebiel UP, Koopmans RP. Microangiopathic hemolysis and renal failure in malignant hypertension. *Hypertension* 2005;45:246–51.
- 23 Helfrich DJ, Banner B, Steen VD *et al.* Normotensive renal failure in systemic sclerosis. *Arthritis Rheum* 1989;32:1128–34.
- 24 Medsger TA Jr, Masi AT, Rodnan GP *et al.* Survival with systemic sclerosis (scleroderma). A life-table analysis of clinical and demographic factors in 309 patients. *Ann Intern Med* 1971;75:369–76.
- 25 Steen VD. Treatment of systemic sclerosis. *Am J Clin Dermatol* 2001;2:315–25.
- 26 Teixeira L, Servettaz A, Mehrenberger M, Noël LH, Guillevin L, Mouthon L. [Scleroderma renal crisis.] *Presse Med* 2006;35:1966–74.
- 27 Vancheeswaran R, Magoulas T, Efrat G *et al.* Circulating endothelin-1 levels in systemic sclerosis subsets – a marker of fibrosis or vascular dysfunction? *J Rheumatol* 1994;21:1838–44.
- 28 Maki S, Miyauchi T, Kakinuma Y *et al.* The endothelin receptor antagonist ameliorates the hypertensive phenotypes of transgenic hypertensive mice with renin-angiotensin genes and discloses roles of organ specific activation of endothelin system in transgenic mice. *Life Sci* 2004;74:1105–18.
- 29 Fonseca C, Renzoni E, Sestini P *et al.* Endothelin axis polymorphisms in patients with scleroderma. *Arthritis Rheum* 2006;54:3034–42.