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Scleroderma (D Khanna, Section Editor)

Management of Renal Involvement in Scleroderma

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Opinion statement

The major renal manifestation of systemic sclerosis is scleroderma renal crisis (SRC). This condition is characterized by accelerated phase hypertension and acute kidney injury (AKI). The management of renal crisis was revolutionized by the introduction of angiotensin-converting enzyme (ACE) inhibitors more than 30 years ago, although in the current era, there is still a significant proportion of patients who have poor outcomes. Recognizing patients at high risk is a key part of the management of SRC. In particular, patients with early diffuse skin involvement from scleroderma and those who have the anti-RNA polymerase III autoantibody are at significantly increased risk for renal crisis. In these patient groups, we recommend avoidance of significant corticosteroid doses and regular home blood pressure monitoring. These measures should reduce the incidence of SRC and ensure its early diagnosis when it does appear. There is no role for ACE inhibitor prophylaxis of SRC. Patients with SRC should be hospitalized and receive careful supportive care. The condition presents with renal, hematological, and cardiac complications in the context of a complex multisystem rheumatological disease, so good inter-disciplinary care is a key goal to improve outcomes. The specific treatment for SRC remains ACE inhibitors, which should be titrated to the highest tolerated dose and continued indefinitely in all patients, regardless of renal recovery or establishment on dialysis. Other antihypertensives can be used *in addition* to achieve optimal blood pressure control. Patients with SRC can recover renal function after more than 2 years on dialysis, so renal transplantation should not be undertaken during this early period.

Introduction

Systemic sclerosis (SSc) has the highest disease-related mortality of all autoimmune rheumatic conditions. In recent years, the predominant cause of death has been cardiopulmonary complications of the disease [1]. Historically, the complication of SSc associated with the highest mortality was scleroderma renal crisis (SRC), which was almost universally fatal until the late 1970s [2]. Since the development of angiotensin-converting enzyme inhibitors (ACEi), SRC has been considered a treatable complication of SSc. However, there are still many patients who do not survive or do not recover independent renal function, so improving the diagnosis and management of this medical emergency remains an important goal for rheumatologists and nephrologists.

Kidney disease in systemic sclerosis

There is a broad spectrum of renal involvement in scleroderma. Like other organs affected by SSc, the kidney is subject to chronic, progressive parenchymal fibrosis and vasculopathy. Reflecting this pathology, the prevalence of chronic kidney disease (CKD), as defined by urinary abnormalities or a reduced estimated glomerular filtration rate (eGFR), was as high as 50 % in an unselected series of scleroderma patients, although slowly progressive chronic kidney disease is very uncommon (E. Kingdon, C.P. Denton Abstract 2003). In addition, other specific kidney diseases, including ANCA-associated vasculitis [3] and interstitial nephritis [4], are seen in the context of SSc. However, the most clinically significant renal manifestation in scleroderma is still SRC, and this review will concentrate on that topic.

Definition of scleroderma renal crisis

Scleroderma renal crisis is defined as the new onset of accelerated arterial hypertension and/or rapidly progressive oliguric renal failure occurring in the context of SSc. Neither hypertension nor a rise in serum creatinine in isolation can be presumed to be diagnostic of SRC. There are many other likely causes of acute kidney injury (AKI) in this patient population, and in a complex multisystem disorder, a rise in creatinine secondary to circulatory dysfunction (so-called pre-renal AKI) or drug-related causes should always be suspected. There have been some differences between the criteria used to define SRC in different studies, which may account for some of the different outcomes reported. Consensus criteria for the definition of SRC are summarized in Table 1 below [1].

Pathogenesis of scleroderma renal crisis

The pathology of SSc is typically described as a triad of autoimmunity, vasculopathy, and fibrosis, and dysfunction in all three of these three areas has been demonstrated in the kidney in patients with SSc [5]. Having said that, renal crisis is principally an impairment of arterial blood flow in the kidney.

Endothelial injury, with increased vascular permeability and subsequent intimal proliferation, is an early event in scleroderma kidney disease. The resulting luminal narrowing, particularly in the interlobular and arcuate arteries, results in reduced blood flow to the renal cortex, which is likely to be a key stage in the evolution of SRC.

In addition to endothelial injury, endothelial cell activation has been implicated in the development or progression of renal crisis. Increased circulating levels of endothelin-1 [6] and soluble vascular adhesion molecules (s-VCAM-1) [5] have been shown to be associated with SRC. Staining of SRC renal biopsies has demonstrated increased tissue concentration of ET-1 and increased expression of both subtypes of the endothelin receptor [7, 8•].

One chronic result of decreased renal cortical perfusion is hyperplasia of the juxtaglomerular apparatus, the major site of renin production in the kidney [9]. At the time of renal crisis, patients have marked elevation in peripheral levels of

Table 1. Diagnostic criteria for scleroderma renal crisis

Diagnostic criteria (essential)	
New onset BP >150/85 mmHg or Increase ≥20 mmHg from usual systolic BP	obtained at least twice over 24 h
A decline in renal function, defined as an increase in serum creatinine of ≥10 % (confirmed with repeat testing where possible)	
Supportive evidence (desirable)	
Microangiopathic hemolytic anemia on blood film	
Findings consistent with accelerated hypertension on retinal examination	
Microscopic hematuria on urine dipstick and/or red blood cells on urine microscopy	
Oliguria or anuria	
Renal biopsy with typical features of SRC including onion skin proliferation within the walls of intrarenal arteries and arterioles, fibrinoid necrosis, glomerular shrinkage	
Flash pulmonary edema	

renin. Given the dramatic response to therapeutic inhibition of the renin-angiotensin system in SRC patients (and previously to nephrectomy), it is likely that renin overproduction has a central role in the evolution of the condition [2]. However, hyperreninemia is uncommon prior to the acute onset of SRC and when detected is not predictive of future crisis [10], so it remains unclear what precipitates the acute crisis in a subgroup of patients with renal vasculopathy.

There is no specific evidence regarding the role that autoimmunity plays in SRC, but the marked contrast between the frequency of SRC in patients with anti-centromere antibody (<1 %) and those with anti-RNA polymerase III (33 %) provides hope that a better understanding of the role these antibodies play in the pathophysiology of SSc in general will further our understanding of renal crisis specifically [11].

Epidemiology

SRC is seen in around 10 % of the SSc population overall and 20–25 % of patients with the diffuse subtype. Seventy-five percent of SRC cases occur less than 4 years after the first symptom attributable to SSc [10], and in one renal crisis series, it was the presenting symptom of SSc for 22 % of patients [12•]. Males are proportionately more likely to be affected than females [13], and in one study, African-Americans were three times as likely to be affected as Caucasians [14].

Predicting renal crisis

Given the predisposing factors that have been identified in SRC cohort studies, careful baseline assessment will allow us to identify patients at increased risk of renal crisis and manage them appropriately. These risk factors are summarized in Table 2. With regard to scleroderma phenotype, patients with diffuse cutaneous SSc (dcSSc) are at the greatest risk, i.e., patients with skin thickening on

Table 2. Risk factors for scleroderma renal crisis

Increased risk of SRC	No increased risk of SRC
Disease symptoms <4 years	Previous acute or chronic hypertension
Diffuse skin involvement	Abnormal urinalysis
Rapid progression of skin thickening	Preexisting chronic kidney disease
Anti-RNA polymerase III antibody	Pathological abnormalities of renal blood vessels
New cardiac events	Anti-topoisomerase/anti-centromere antibodies
Pericardial effusion	
Congestive heart failure	
New anemia	
Recent high-dose corticosteroid exposure	

the proximal limbs or trunk. Of this patient subgroup, 20–25 % will develop renal crisis [15•], and they make up 75–80 % of SRC cases.

Patients who are destined to develop dcSSc but do not yet have the typical diffuse skin changes make up a further 15–20 % of SRC cases. Identifying early diffuse patients is therefore of particular importance. These patients have usually had sclerodermatous symptoms for less than 1 year. They typically have polyarthritis/arthralgias, puffy or swollen hands and legs, and carpal tunnel syndrome [16]. Palpable tendon friction rubs can be an important clue—these occur at some point in 65 % of patients with dcSSc [17] but fewer than 5 % of patients with limited disease,

Autoimmune serology can also help us to identify patients at significant risk of SRC. Anti-RNA polymerase III is a scleroderma-specific antibody that is seen almost exclusively in dcSSc, and 24 to 33 % of patients with this antibody develop SRC [18, 19]. The frequency of this antibody in scleroderma in published cohorts from Asia or Southern Europe ranges from 6 to 9 %, so it is not surprising that these countries have a low frequency of renal crisis compared with the USA and the UK, where the frequency is of RNA polymerase III is more than 20 % [18]. Renal crisis occurs in 10 % of patients with anti-topoisomerase antibody, the most common antibody associated with dcSSc [20]. The anti-centromere antibody, typically seen in limited cutaneous SSc, is a protective factor for renal crisis [21].

Management of patients at high risk of renal crisis

Early identification

All patients with scleroderma should have regular blood pressure monitoring together with urinalysis and serum biochemistry to detect impaired renal function. Patient education regarding the risk of renal crisis and its presentation is important, and patients should be aware of the potential presenting symptoms of accelerated hypertension, including headache, blurred vision, altered mental state, breathlessness, and palpitations.

For patients with early dcSSc (within 4 years of diagnosis), we recommend home BP monitoring twice weekly. Patients should be given individualized blood pressure targets and instructions to seek medical review if their blood pressure is above these.

Typically, patients who go on to have renal crisis do not have hypertension prior to the acute onset, and the rise in blood pressure is rapid. In cases where blood pressure is checked regularly, normal blood pressures have been seen as recently as 24 h prior to the diagnosis of SRC [14].

Corticosteroid exposure

An association between corticosteroid use and the development of SRC has been described since the 1950s [22, 23]. A recent meta-analysis estimated that the incidence of SRC among patients exposed to >15 mg prednisolone a day or equivalent was approximately twice that is seen in the remaining SSc population [24•]. It is not easy to interpret the significance of this association. Renal crisis is most prevalent among patients with early, aggressive disease: the same group who are likely to be treated with high steroid doses. A case–control study of patients with renal crisis compared to other patients at high risk (according to the clinical risk factors described above) found that those who had received >15 mg prednisolone were three times as likely to be diagnosed with SRC in the following 6 months [25]. We recommend that high-dose steroids should be used with great caution and very close monitoring in patients with early dcSSc.

ACE Inhibitors prior to renal crisis

There is no evidence to support the use of ACE inhibitors as a preventative treatment in high-risk scleroderma patients, according to retrospective studies [12•, 26•], and indeed this may be harmful. A recent prospective study of 75 patients with renal crisis found that those who had been on ACE inhibitors prior to the diagnosis of SRC had more than two times the risk of death in the year following SRC [27]. The authors propose several possible hypotheses for this unexpected finding. It may be that partial ACE inhibition masked the cardinal finding of hypertension at the onset of renal crisis and therefore lead to late diagnosis of these patients. It might also be that the group of patients who developed clinically detectable renal crisis despite taking an ACE inhibitor were in a resistant group with an intrinsically poor prognosis. Finally, they propose confounding by indication, i.e., that the preceding hypertension or cardiac failure for which the ACE inhibitor was prescribed was responsible for the excess mortality in these patients.

Clinical presentation of SRC

As with other causes of accelerated hypertension, patients may complain of severe headache, blurred vision, or other encephalopathic symptoms, including seizures in the most severely affected. As in other forms of AKI, patients may occasionally present with oliguria or with obviously uremic symptoms. The majority of patients will be nonspecifically unwell, complaining of increased fatigue, headache, or occasionally dyspnea. High-risk patients should be taught to take these symptoms seriously and to check their own blood pressure if they occur.

The presenting blood pressure at the onset of SRC is variable, but a large majority has significant hypertension. Ninety percent have BP levels greater than 150/90 mmHg, and 30 % have diastolic recordings greater than 120 mmHg. A blood pressure in the normal range is seen in around 10 % of cases. However, these patients usually have a significantly raised BP compared

to their own baseline measurements. An increase of 20 mmHg in either the systolic or diastolic pressure would be potentially diagnostic in this setting. All changes in BP in patients with SSc require further investigation and monitoring. The diagnosis of "normotensive renal crisis" requires other clinical features or investigation findings, primarily rapidly progressive unexplained AKI and/or microangiopathic hemolytic anemia (MAHA).

Patients may present with symptoms and signs secondary to hyperreninemia and accelerated hypertension, including signs of congestive cardiac failure, pericardial effusion, or arrhythmias. Fundoscopy may demonstrate grade III/IV hypertensive retinopathy.

Laboratory findings

There is usually both proteinuria and microscopic hematuria on dipstick urinalysis. Proteinuria is mild or moderate (generally <2 g per day), and microscopy can show granular casts [28]. Serum creatinine is typically at least 150 % of baseline value at presentation. This is stage 1 acute kidney injury in the most recent international consensus guidelines for AKI care [29]. It is worth noting that in SSc patients with low muscle mass, the creatinine value will commonly reach this threshold without rising above the normal range values quoted by most laboratories. Creatinine can rise rapidly in the first few days following and will usually continue to rise even once blood pressure has been adequately controlled.

There is serological evidence of MAHA in around half of patients. One series found a reduced platelet count in 50 % of SRC patients and red cell fragments in 52 % [12•]. Other evidence of hemolysis, including a reduced serum haptoglobin level and/or a raised lactate dehydrogenase, should be sought.

Even in a patient with obvious cutaneous signs of scleroderma, the presence of MAHA and accelerated hypertension or the findings of thrombotic microangiopathy on kidney biopsy can occasionally raise the possibility of a primary hemotological diagnosis, i.e., thrombotic thrombocytopenia purpura (TTP) or atypical hemolytic uremic syndrome (aHUS). The distinction is clinically important as plasmapheresis, the primary acute treatment for TTP or aHUS, has not been demonstrated to benefit patients with SRC. There are several reported cases of TTP and scleroderma in the literature [30–33]. Fever and hemorrhagic manifestations were the principal clinical findings that differentiated these cases from SRC. Levels of the metalloproteinase enzyme ADAMTS13, which are reduced in TTP [34], were normal in a small study of patients with SRC (K.S. Torok et al. "Scleroderma renal crisis and thrombotic thrombocytopenic purpura—are they related," American College of Rheumatology abstract 2008). However, in most institutions, results of the ADAMTS13 assay will not be available early enough to affect the immediate clinical management. Given the remaining diagnostic uncertainty in this field, if a diagnosis of TTP or HUS is suspected in a scleroderma patient, we recommend that an ACE inhibitor should be used in conjunction with plasmapheresis.

Imaging

Renal ultrasound is typically unremarkable in SRC but may be useful in some patients to rule out urinary tract obstruction as a cause of AKI.

Echocardiography can show pericardial effusions and left ventricular systolic dysfunction, which are common findings secondary to the increased afterload on the heart. Signs of pulmonary hypertension are sometimes seen on echo, but in the SRC cohort, this is almost always a transient secondary phenomenon caused by accelerated hypertension rather than chronic pulmonary arterial hypertension.

Renal pathology

In the acute setting, the main diagnostic benefit of renal biopsy is to exclude other pathologies. In the longer term, it may help to inform renal prognosis (see below). Biopsy needs to be delayed until the patient is clinically stable with good blood pressure control and the platelet count has recovered.

The renal pathological findings in SRC are broadly the same as those seen in other causes of accelerated hypertension [4]. Fibrinoid necrosis is seen either in arterial walls or in the subintima in small arteries and arterioles (characteristically the interlobular and arcuate arteries). The resulting intimal thickening leads to narrowing or total obliteration of the lumen and a typical "onion skin" appearance (Fig. 1). Adventitial and peri-adventitial fibrosis, an indication of chronic vasculopathy seen in patients with SRC, is rarely seen in accelerated hypertension without scleroderma. Glomeruli are collapsed with wrinkling of the basement membrane. Interestingly, unlike in other renal diseases, the extent of interstitial scarring does not have prognostic value, whereas markers of acute vascular injury (including fibrinoid necrosis and thrombosed vessels) do predict poor renal outcome [4, 12•].

Treatment

General considerations

Patients with SRC are in a high mortality group and need aggressive inpatient management. In addition to close monitoring and renal replacement therapy (RRT) when required, higher level care of the unwell patient with renal crisis might include ventilatory support, where there is severe pulmonary edema, and sedation or anti-seizure medications for hypertensive encephalopathy.

ACE inhibitors

Immediately on diagnosis of SRC, an ACEi should be introduced or the dose increased if the patient is already taking one [35]. A short-acting ACE inhibitor (e.g., captopril) may be preferable in a hemodynamically unstable patient, but there is no evidence that it is preferable in general to a once-daily medication. ACEi resistance is more typical than oversensitivity, and our practice is to initiate a long-acting drug as soon as possible and escalate the dose daily to maximum. We recommend that any rise in serum creatinine after increasing ACEi dose should not trigger dose reduction or ACEi cessation. There is no evidence in scleroderma renal crisis that renal function can be spared or improved by minimizing ACEi dose. The eventual goal is to reach the pre-SRC blood pressure, but in the absence of hypertensive encephalopathy or cardiac

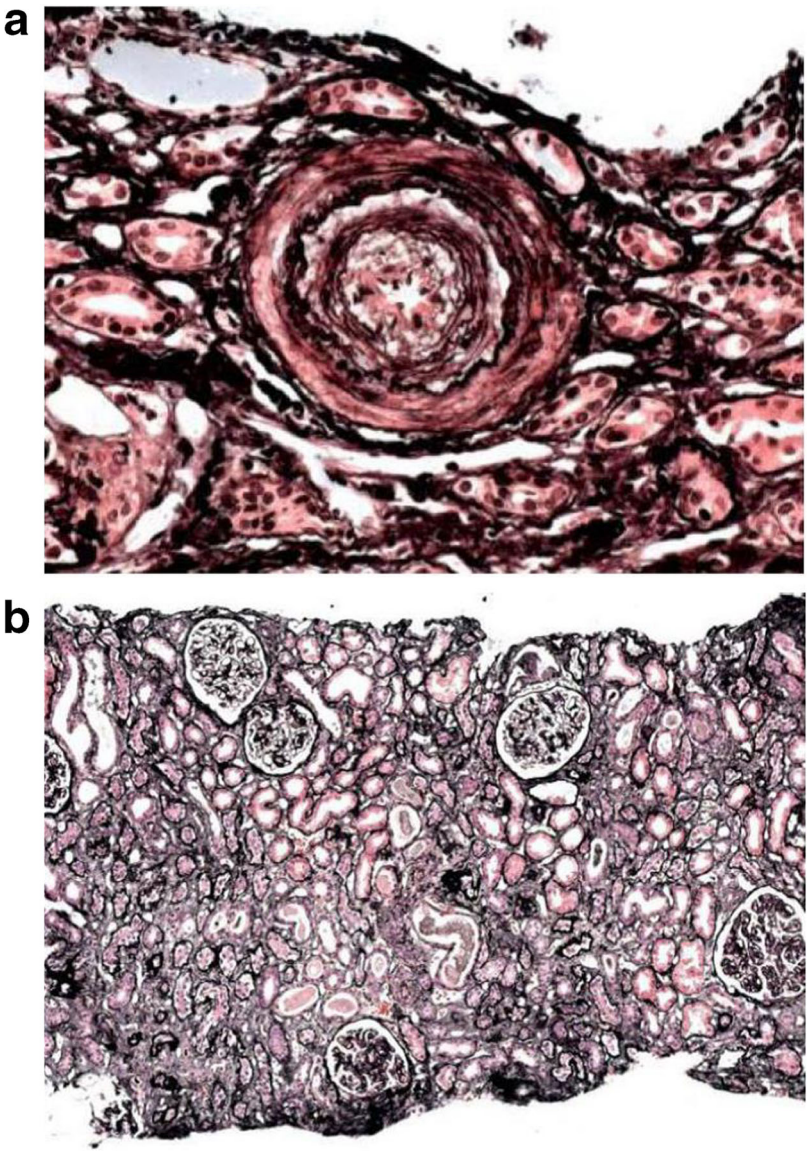

Fig. 1. Renal biopsy findings in SRC. **a** An interlobular artery showing, loose, concentric intimal thickening superimposed on a ring of smooth muscle inside the internal elastic lamina. This suggests a recent acute vascular injury superimposed on a chronic vasculopathy. **b** Cortex in a kidney affected by SRC. Glomeruli show acute ischemic shrinkage. Tubules show acute ischemic damage and early atrophy.

decompensation, a steady reduction in the blood pressure of around 10 % per day is preferable to dropping it precipitously.

Other antihypertensives

Given the dramatic survival benefit conferred by antagonizing one part of the renin-angiotensin system (RAS) in SRC, we might be optimistic about the benefits of blocking other parts of this endocrine axis. There are reports suggesting that angiotensin receptor blockers (ARBs) alone are less effective that ACEi in treating SRC [36, 37]. There is no evidence regarding the role of direct renin inhibitors. Our practice is to add an ARB to treatment once the ACEi is in the therapeutic range and to introduce other antihypertensives including calcium channel blockers, doxazosin and clonidine if blood pressure remains above the target on ACEi and ARB combination therapy. Beta-blocking drugs are

contraindicated in SRC due to effects on peripheral circulation and intravenous antihypertensives are not usually indicated, although nitrate infusion is sometimes required when pulmonary edema complicates SRC.

Endothelin receptor antagonists (ERAs)

Endothelin receptor antagonists have been demonstrated to have significant outcome benefit in both PAH and digital ulceration in patients with SSc. This has raised the question of their utility in renal crisis, another vasculopathic manifestation of SSc, and this drug type has been used in selected scleroderma patients with renal crisis [38]. As discussed above, high circulating levels of ET-1 and upregulation of the endothelin receptor have been demonstrated in SRC. Polymorphism in the endothelin ligand receptor axis has been associated with SRC [39], whereas polymorphism in the ACE axis has not [40], so it is possible that activation of the endothelin system is a key event in the evolution of the condition. In a recent open label pilot study, the nonselective ERA bosentan was given to six patients with SRC. Although not significant, there was a trend towards lower rates of dialysis and better recovery of renal function in these patients [8•]. At least two further studies of this drug class in SRC are ongoing.

Other drug treatments

The prostacyclin analogue Iloprost is an additional way to reduce the systemic vascular resistance in SRC and has been shown specifically to increase blood flow within the kidney in patients with SSc [41]. The role of immunosuppression in the context of acute SRC has not been defined.

Renal replacement therapy

In the US and UK case series since the advent of ACEi, the number of SRC patients who progressed to needing RRT was around 60 % compared to >90 % prior to the availability of ACEi [12•, 42]. The most commonly used form of RRT in the acute phase is intermittent hemodialysis (HD), but continuous hemofiltration is occasionally required for patients with marked hemodynamic instability. In the general chronic RRT population, peritoneal dialysis (PD) is associated with better preservation of residual renal function than HD [43, 44], and this may be a particular consideration in the SRC group, given the potential for late recovery of renal function. PD in this patient group is not uncommon—in a case series which included all patients with scleroderma who received RRT in Australia or New Zealand between 1963 and 2005, 50 % of patients had PD [45], Despite this, there are currently no data directly comparing outcomes of PD and HD after renal crisis.

Recovery of renal function can continue for months or years after SRC and ACEi therapy should be continued indefinitely in all patients, whether or not they are on dialysis. In the US and UK case series described above, close to 50 % of patients initiated on RRT later recovered independent renal function to discontinue dialysis. In the UK series, the median time to becoming dialysis independent was 11 months (range 1–34 months) [12•]. In a large majority of both those who did not require dialysis and those who had temporary dialysis, eGFR continued to improve for at least 3 years after SRC diagnosis (see prognosis below).

Because of the possibility of late recovery of renal function, renal transplantation should not be undertaken for at least 12 months after the diagnosis of renal crisis. Calcineurin inhibitors (cyclosporine and tacrolimus) are renal vasoconstrictors and are associated with an increased risk of SRC [46, 47], so the choice of immunosuppressive regimen also needs careful consideration in this group of patients. There are case reports of recurrence of SRC both early and later after renal transplantation [37, 48], but overall, renal transplant improved survival in scleroderma compared to those who remained on dialysis [49].

Prognosis

Mortality

Prior to the use of ACE inhibitors, survival to 1 year in a patient with SRC was a rare event [14, 15•]. After ACEi use became widespread in the early 1980s, there was a dramatic improvement seen. Patients who "survive" renal crisis without the need for dialysis or only temporary dialysis have excellent outcomes with 5-year survival of 90 % [42]. However, we still have 40–50 % of patients who have a bad outcome with early deaths or permanent dialysis with all its problems. Reflecting these two cohorts, reviews that have looked at SRC outcome in this era have shown 5-year survival ranging between 50 and 70 % [12•, 26•, 27•, 50, 51]. Sadly, there is no clear trend towards improvement in these outcomes over the past 30 years. Risk factors for mortality in these studies included male sex, older age, and lower blood pressure at the time of diagnosis as well as the development of congestive cardiac failure.

Renal prognosis

Fifty-five of the 145 patients in Steen's series did not require RRT in the acute phase. Mean peak serum creatinine among these patients was 3.8 mg/dl (336 μmol/L). Seven years after diagnosis of SRC, their mean creatinine was 1.8 mg/dl (159 μmol/L). None went on to require RRT at a later stage. Thirty-four patients in the series had temporary dialysis. Their mean serum creatinine 6 years after SRC was 2.2 mg/dl (194 μmol/L). Two of these 34 patients progressed to end-stage renal failure requiring RRT within the follow-up period [42].

Survival on renal replacement therapy

The Australia and New Zealand series quoted above showed a median survival of 2.4 years for scleroderma patients on dialysis compared with 6.0 years for other patients [45]. In a US study of dialysis patients with scleroderma between 1992 and 1997, 2-year survival in the scleroderma group was 49 % compared with 64 % in all other patients [52]. Likewise, a review of scleroderma renal transplant cases from the United Network for Organ Sharing registry from 1987 to 1996 showed both lower graft and patient survival times than in renal transplant patients without systemic diseases [53].

Summary

Despite the marked improvement in outcome for the majority of patients with scleroderma renal crisis since the introduction of ACE inhibitors, there is a significant subgroup for whom mortality remains high.

Our ability to identify a subset of patients at high risk of developing the condition—those with early diffuse cutaneous systemic sclerosis in particular—offers hope that early diagnosis will improve this poor prognosis.

Recent important developments in this field include increasing evidence of the role of corticosteroids as a risk factor for SRC and recognition that ACE inhibitor prophylaxis is unlikely to be beneficial for high-risk patients. Potential new treatments for patients with renal crisis include endothelin receptor antagonists.

Compliance with Ethics Guidelines

Conflict of Interest

Edward P. Stern and Virginia D. Steen declare that they have no conflict of interest.

Christopher Denton reports grants and personal fees from Actelion pharmaceuticals, personal fees from GSK, personal fees from Genetech-Roche, and grants from Astra Zeneca, outside the submitted work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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