Review

Scleroderma Renal Crisis

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ABSTRACT. Scleroderma renal crisis (SRC) is characterized by malignant hypertension and oligo-anuric acute renal failure. It occurs in 5% of patients with systemic sclerosis (SSc), particularly in patients with diffuse disease during the first years. SRC is more common in patients receiving corticosteroids, the risk increasing with increasing dose. The disease is sometimes triggered by use of nephrotoxic drugs and/or intravascular volume depletion. Left ventricular insufficiency and hypertensive encephalopathy are typical clinical features. Thrombotic microangiopathy is detected in 43% of cases, and anti-RNA-polymerase III antibodies are present in one-third of patients. Renal biopsy is not necessary if SRC presents classical features. However, biopsy may help to define the prognosis and guide treatment in atypical forms. The prognosis of SRC has greatly improved with the introduction of angiotensin-converting enzyme (ACE) inhibitors. However, the 5-year survival for SSc patients with full SRC remains low (65%). The treatment of SRC relies on aggressive blood pressure control with an ACE inhibitor, combined with other antihypertensive drugs if needed. Dialysis is frequently indicated but can be stopped in about half of patients, mainly those with good blood pressure control. Patients who need dialysis for more than 2 years qualify for renal transplantation. (J Rheumatol First Release May 15 2014; doi:10.3899/jrheum.131210)

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The term scleroderma renal crisis (SRC) was proposed in 1952 by Moore and Sheehan[1] who first described the typical histopathological lesion of the disease. SRC is an infrequent complication of systemic sclerosis (SSc). It presents as recent onset, accelerated-phase hypertension (HTN) and/or rapidly deteriorating renal function, frequently accompanied by microangiopathic hemolysis[2]. Although the disease is now well described, the pathogenesis remains poorly understood. Before the late 1970s, SRC was almost uniformly fatal[3]. Since the introduction of angiotensin-converting enzyme (ACE) inhibitors, survival has greatly improved and the 1-year mortality rate decreased from 85% to 24%[4]. However, despite aggressive antihypertensive therapy, 5-year survival with SRC is only 65%[5,6,7,8]. In addition, exposure to certain drugs, particularly corticosteroids (CS), represents an additional risk factor for SRC[9,10].

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Pathophysiology and Renal Pathology

The pathogenesis of SRC is incompletely understood[11]. The typical arterial "onion-skin" lesion results from vascular intima, which leads to a narrowing of the vessel lumen and reduced blood flow[12]. Other mechanisms such as vascular hyperreactivity can occur; Cannon, *et al* reported a "renal Raynaud's phenomenon [RP]", responsible for decreased renal perfusion[13], and Traub, *et al*[3] reported an increased frequency of SRC during winter.

Cortical blood flow was found significantly decreased in patients with SRC or progressive renal failure, whereas SSc patients without renal involvement showed normal renal blood flow[13]. However, Doppler ultrasonography and renal perfusion scintigraphy fail to identify patients at risk for SRC[14,15].

Activation of the renin-angiotensin-aldosterone system plays an important role in the pathophysiologic process of SRC. There is evidence of a juxtaglomerular apparatus hyperplasia, and blood pressure can usually be controlled with high-dose ACE inhibitors[16]. However, elevated plasma

renin level does not predict the development of SRC[17,18]. Because vascular changes and hyperreninemia may be present in patients with asymptomatic SSc, additional factors are probably involved in triggering SRC. A number of factors responsible for reduced renal blood flow, such as sepsis, dehydration, cardiac arrhythmia, congestive heart failure, and use of nephrotoxic drugs such as nonsteroidal antiinflammatory drugs (NSAID)[18] may trigger SRC. In addition, the role of pregnancy *per se* is debated[19,20].

Use of a number of substances (e.g., cocaine)[21] and medications including cyclosporine[22] and CS[5,7,9,23] has been implicated in SRC. A case-control study found that in the 6 months before SRC onset or the first visit for medical care, patients with SRC more frequently showed use of a medium-dose to high-dose CS (≥ 15 mg/day prednisone) than did controls (36% vs 12%; OR 4.37, 95% CI 2.03–9.43)[23]. We recently reported that in a cohort of 50 SSc patients with SRC, 30 (60%) had been exposed to a CS before SRC onset[7]. The OR for developing SRC with CS exposure during the preceding 3 months and 1 month was 24.1 (95% CI 3.0–193.8) and 17.4 (2.1–144.0), respectively. In addition, Helfrich, *et al* found an association of high-dose CS (> 30 mg/day) and normotensive SRC[9]. However, patients with normotensive SRC have often been exposed to a CS, and confounding variables cannot definitively be ruled out. Nevertheless, from the current literature, which documents an association of CS dose and risk of SRC, we strongly suggest avoiding medium-dose to high-dose CS therapy for SSc.

The mechanism by which CS may trigger SRC has not been elucidated. Endothelin 1 (ET-1) might be involved because increased circulating levels of ET-1 were found in SSc patients with SRC and in those with pulmonary arterial HTN[24,25]. In agreement are immunohistological findings of Kobayashi, *et al* revealing the expression of ET-1 and ET-1 type B receptor in kidney biopsies of 2 patients who died of SRC[25]. Further evidence was obtained from Penn, *et al* who reported that ET-1 and both ET A and B receptor expression were increased in SRC biopsies[26]. However, the mechanism by which CS could increase the circulating levels of ET-1 and/or increase the expression of ET-1 and ET-1 type B receptor in the kidney remains to be determined, as are other mechanisms by which CS could be associated with SRC, including effects on prostacyclin, blood pressure, fluid shifts, confounding, and more.

Renal biopsy is not necessary to confirm the diagnosis of classical SRC. However, a number of research groups are performing systematic renal biopsy to better evaluate the prognosis of SRC[8]. In atypical clinical presentations, renal biopsy is mandatory to confirm the diagnosis. In all cases, renal biopsy is performed after blood pressure control. With severe thrombocytopenia, renal biopsy can be performed by jugular vein catheterization.

In severe SRC, vascular occlusion and tissue ischemia may lead to grossly visible renal infarcts and subcapsular hemorrhages[27]. Characteristic changes in arteries and arterioles are the pathologic hallmarks of SRC[28]. Larger arteries appear normal or may reveal nonspecific changes, whereas small arteries and arterioles, especially in the interlobular and arcuate arteries, undergo severe changes. The characteristic pathologic onion-skin lesion results from vascular intimal thickening, proliferation of endothelial cells and vascular smooth muscle cells, hyperplasia, or similar conditions (Figures 1 and 2)[29]. The mucinous intimal change mostly consists of glycoprotein and mucopolysaccharides. Fibrinoid necrosis may be present in arterial walls without other signs of vasculitis. Fibrin deposits may also be found in the thickened intima. These vascular changes lead to a narrowing and occlusion of the vessel lumen[30]. Notably, in contrast to lesions encountered in malignant HTN in the absence of SSc, in renal biopsies of patients with developing SRC, the media of interlobular arteries are often thinned and surrounded by periadventitial and adventitial fibrosis (Figure 2). In addition, glomerular and tubular changes are frequent, as a result of ischemia (Figure 2). Glomerular changes may vary considerably. Some glomeruli may have subnormal aspects, and others can be ischemic[28]. However, capillary walls are thickened, with a double contour aspect on silver or periodic acid-Schiff staining, accumulation of glomerular intracapillary eosinophilic material corresponding to fibrin thrombi, and lesions observed in thrombotic microangiopathy[28]. Mesangiolysis may also be present. The juxtaglomerular apparatus is prominent, especially in cases with severe occlusive arterial and arteriolar lesions. Juxtaglomerular hyperplasia may be seen[31]. Immunoglobulin and complement deposits may be detected in small arteries[32,33]. However, many of these pathologic changes can also be seen in patients with SSc in whom SRC does not develop or in patients experiencing malignant HTN in the absence of SSc.

Prevalence and Predictive Factors

The prevalence of SSc is still poorly documented, with disparity among states and countries[34]. It ranges between 200 and 260 cases per million in the United States and Australia[35,36], 20 and 50 cases per million in Asia[37], and 100 and 200 cases per million in Europe[38,39].

SRC occurs in about 4% to 6%[40,41] of patients with SSc, predominantly in those with diffuse SSc[18,40]. Historically, SRC occurred in up to 25% of patients with SSc, whereas in a more recent work involving the database of the European League Against Rheumatism Scleroderma Trials and Research group, it occurred in less than 5% of those patients[40] and in less than 2% of patients with limited cutaneous SSc[2,18,40].

Steen, *et al* and others[18,42] identified a number of risk factors that predict the occurrence of SRC[43]. Among these are SSc duration < 4 years, diffuse and rapidly progressive

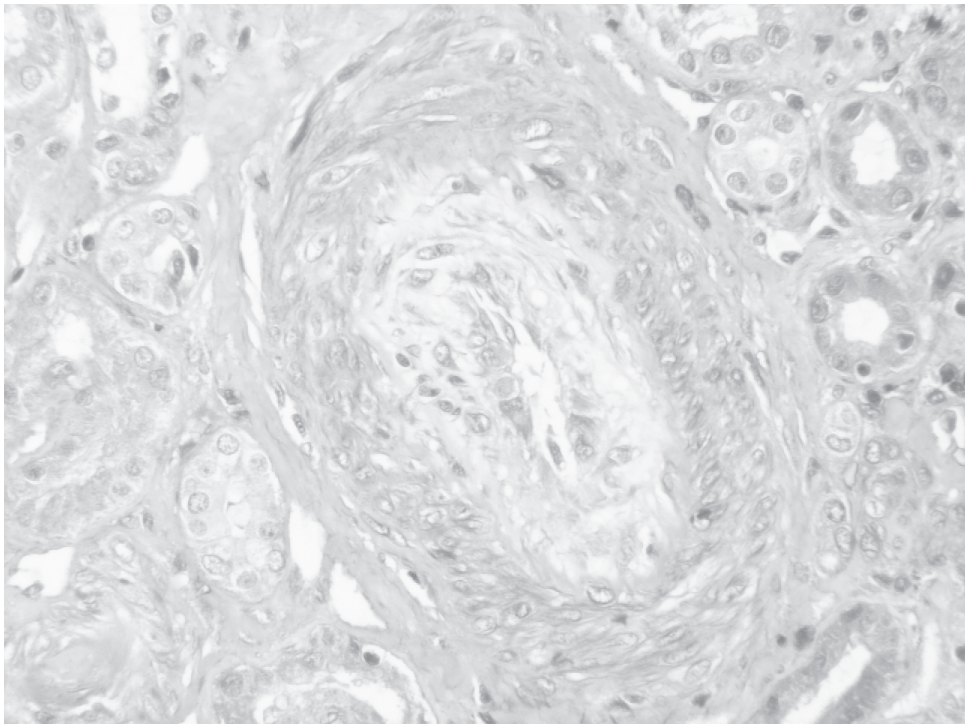

Figure 1. Trichrome light green: chronic injury in an interlobular artery with mucoid changes and endothelial proliferation. Magnification 250×.

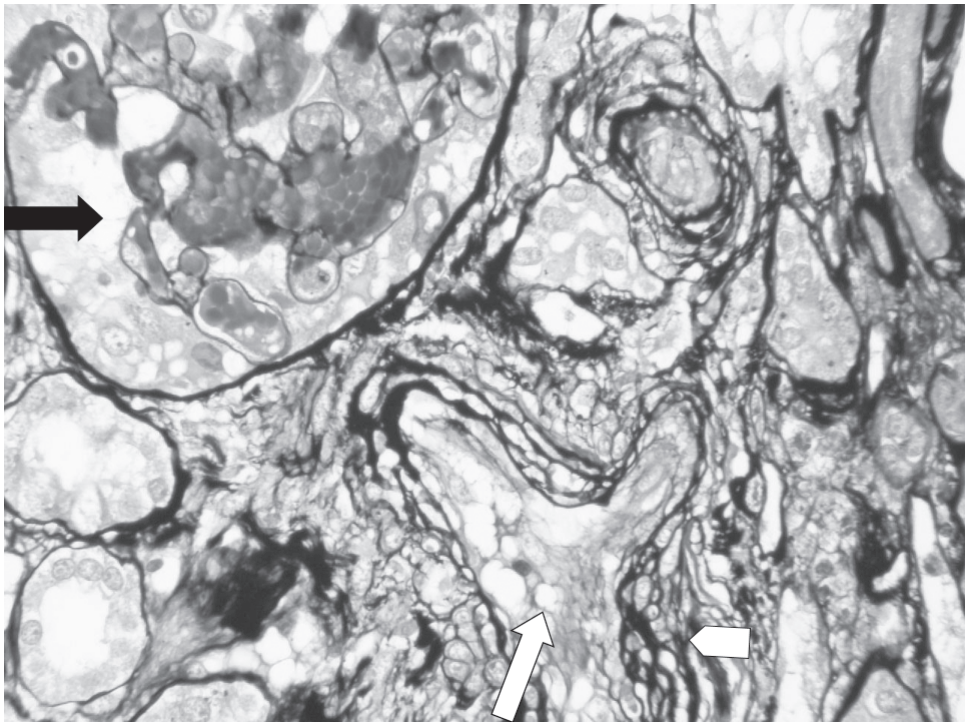

Figure 2. Jones periodic acid-Schiff staining of scleroderma renal crisis: interlobular artery with mucoid changes and concentric intimal fibroplasia with "onion-skin" changes (white arrow), enlarged vascular diameter, perivascular fibrosis (truncated white arrow), and ischemic glomerulus (black arrow). Magnification 250×.

skin thickening, and new anemia and new cardiac events (e.g., pericardial effusion or congestive heart failure).

Another important risk factor is the presence of anti-RNA polymerase III antibodies. The prevalence of such antibodies varies among countries, being high in the United States[44] and Sweden[45], with a prevalence of 28% and 22%, respectively; intermediate in Australia, with a prevalence of 15.3%[46]; and low in Asia, with a prevalence of 6% in Japan[44] and 3.4% in South Korea[47]. In Europe, the prevalence of anti-RNA polymerase III antibodies varies from 7.8% in Italy[48], 8.7%[49] to 9.4%[50] in France, and 12% in the UK[51]. These differences might be explained, at least in part, by genetic factors.

In our cohort of patients with SSc in France, among those with anti-RNA polymerase III antibodies, multivariate analysis revealed that anti-RNA polymerase III antibodies were independently associated with diffuse SSc, renal insufficiency, and absence of pulmonary fibrosis. Interestingly, in a study conducted in Australian patients, in multiple regression analysis, after adjustment for other covariates, anti-RNA polymerase III antibodies were independently associated with renal crisis, diffuse disease, joint contractures, and malignancy diagnosed within 5 years of onset of SSc skin disease[46].

The proportion of patients with SRC who had anti-RNA polymerase III antibodies was 31%[50] and 38%[49] in 2 French series; 29.4%, 33.3%[51], and 59%[8] in the UK[51]; and 28% in the United States[52], all higher than the level observed in Italy (15%)[53].

Another major issue is the use of a CS (prednisone) at > 15 to 20 mg/day[23]. Our study of 50 patients with SRC revealed that 30 (60%) had been exposed to a CS before SRC onset, and intake of CS during the preceding 3 months and 1 month was associated with SRC (OR 24.1 and 17.4, respectively), suggesting a potential role of CS in inducing SRC[7]. As well, the case-control study of Steen and Medsger found that exposure to a high-dose CS (≥ 15 mg/day prednisone or equivalent) in the 6 months before SRC onset or the first medical visit was more frequent among SRC patients than among controls (36% vs 12%)[23]. Thus, CS might play a role in inducing SRC. In line with these data, high-dose CS should be avoided in patients at risk of SRC. SRC has been reported after cyclosporine treatment.

Finally, patients at risk of SRC should be followed closely and their blood pressure monitored at least weekly.

A history of HTN, urinary abnormalities, increased serum creatine, antitopoisomerase 1 or anticentromere antibodies and pathologic abnormalities in renal blood vessels preceding the onset of SRC have not been found associated with increased occurrence of SRC.

Clinical Features

The main clinical features of SRC in published data for cohorts are in Table 1. On average, 90% of patients with SRC present with blood pressure > 150/90 mmHg. Clinical signs of SRC are mainly malignant HTN with hypertensive encephalopathy, congestive heart failure, and arrhythmia. Hypertensive encephalopathy is characterized by acute or subacute onset of lethargy, fatigue, confusion, headaches, visual disturbances (including blindness), and seizures[54]. Some of these signs are nonspecific and must be interpreted in the clinical context of patients at risk. If inadequately treated, hypertensive encephalopathy may lead to cerebral hemorrhage, particularly in the presence of thrombotic microangiopathy, and result in coma and death. Of note, seizures, either focal or generalized, may be the first manifestation of SRC. Another clinical observation is rapidly progressive dyspnea due to congestive heart failure, which is related to HTN and/or diastolic left ventricular dysfunction in the context of oliguria. Some patients may present with large pericardial effusion. Finally, pulmonary hemorrhage has been life-threatening in some cases[9].

Normotensive SRC. In 10% of cases, SRC occurs in the absence of significant HTN[7,55]. Patients with normotensive SRC are often exposed to a CS; two-thirds present with thrombotic microangiopathy and their prognosis is worse than those with HTN[7,9]. Distinguishing autoimmune thrombotic thrombocytopenic purpura due to SRC from other causes of thrombotic microangiopathy may be difficult but is mandatory because treatments differ. However, with the availability of accurate assays for ADAMTS13 activity, these distinctions should now be more evident[56].

SRC without SSc. SRC can occur in patients without evidence of skin thickening[57,58]. Thus, in a patient presenting with malignant HTN, SSc should be considered. Clinical features that help identify patients with SSc in this context are recent-onset RP, acute onset of fatigue, weight loss, polyarthritis, swollen hands and lower legs, carpal tunnel syndrome, and tendon friction rubs. Usually, after a few months, patients show skin thickening that progresses to a diffuse form of SSc.

Pregnancy and SRC. Whether there is an increased risk of SRC during pregnancy remains a matter of debate[20]. In pregnant women with SSc, it is sometimes difficult to differentiate preeclampsia from SRC. Importantly, renal function is usually normal in preeclampsia. Elevation of liver enzymes may orient the diagnosis in the direction of eclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count).

In patients with a history of SRC, there is a tendency to consider that pregnancy is contraindicated. However, it is difficult to make a global recommendation, and a patient-tailored strategy is probably mandatory. Thus, in a patient with normal renal function and controlled HTN, pregnancy may probably be conducted. Whether ACE inhibitors (which are contraindicated during the second and third trimester of pregnancy) should be interrupted remains a matter of debate.

Table 1. Main clinical and biological manifestations of scleroderma renal crisis from the literature.

	Steen, et al[2]	Walker, et al[6]	DeMarco, et al[5]	Penn, et al[8]	Teixeira, et al[7]	Guillevin, et al[72]	Hudson, et al[70]
Type of study	R	R	R	R	R	R	P
No. patients	195	16	18	110	50	91	75
Age, yrs	50	54	45	51	53	53	52.5
Sex, % males	25	31	17	21	26	22	33.3
Symptoms < 4 years, %	76	69	100	66 (< 1 y)	86	79 (< 3 y)	32 (< 1 y)
Diffuse SSc, %	83	100	100	78	86	85.7	74.7
Antitopoisomerase 1 antibodies, %	20	6	ND	17.2	32	31	25.3
Anticentromere antibodies, %	1	ND	ND	1.8	0	3.4	4
Hypertension, %	90	94	ND	ND	88	85.7	93.3
Systolic/diastolic BP, mmHg	184/108	203/113	130/76	193/114	189/111	184/107	ND/ND
Pericarditis, %	53	ND	ND	ND	6	ND	33.3
Left ventricular insufficiency, %	25	56	39	31	46	46	ND
Arrhythmia, %	ND	ND	ND	ND	18	ND	ND
Seizures, %	8	12	ND	ND	10	ND	ND
Hypertensive encephalopathy, %	ND	ND	ND	ND	34	58	ND
Intracerebral hemorrhage, %	ND	ND	ND	ND	10	ND	ND
Thrombotic microangiopathy, %	30	81	ND	59	46	56	ND
Platelet count < 150,000/mm^3, %	39	ND	ND	50	ND	ND	ND
Hematuria, %	38	ND	ND	ND	42*	42*	ND
Proteinuria, %	63 (> 0.25 g/d)	ND	ND	ND	53 (> 0.5 g/d)	68	ND

* Hematuria documented with dipstick measurement or urinalysis. SSc: systemic sclerosis; BP: blood pressure; ND: not documented; P: prospective; R: retrospective.

Differential Diagnosis

In case of acute renal failure with SSc, a number of differential diagnoses should be considered[43]. Renal arterial stenosis can present with malignant HTN. Hypovolemia can mimic SRC. It may be provoked by dehydration, third-space sequestration in case of gut involvement, and intestinal paresis from use of diuretics or NSAID, cardiac failure, and/or arrhythmia. However, SRC can also occur by chance in this setting. Crescentic glomerulonephritis associated with antineutrophil cytoplasmic antibodies with antimyeloperoxidase specificity may cause renal insufficiency in patients with SSc[59,60]. However, malignant HTN and thrombotic microangiopathy are absent in these cases. There is evidence of microscopic hematuria, and the diagnosis is finally confirmed by renal biopsy, which identifies extracapillary glomerulonephritis, without evidence of involvement of interlobular arteries or arterioles. Vasculitis may appear at other sites[61]. Autoimmune thrombotic thrombocytopenic purpura unrelated to SRC may be difficult to identify. Usually patients do not present with malignant HTN. A low ADAMTS13 activity is a key feature of autoimmune thrombotic thrombocytopenic purpura, which would help distinguish it from SRC-related thrombotic microangiopathy. In case of doubt, a renal biopsy should be performed, using the transjugular vein route. Renal toxicity of D-penicillamine is well documented, responsible for proteinuria and membranous nephropathy. Proteinuria in the nephrotic range can be due to toxicity of NSAID. Finally, in a prospective observational study, Steen, *et al* observed that only 5% of 675 patients with diffuse SSc presented unexplained renal abnormalities over a mean of 12.5 years[60]. It is very difficult to state on this small proportion of patients, and it is difficult to make sure, even from prospective studies, that we did not miss a drug intake or specific exposure.

Laboratory Findings

Serum creatine level can be markedly increased at presentation. Even after control of blood pressure, it can increase during several additional days. Urinalysis frequently shows mild proteinuria (0.5–2.5 g/l). Microscopic hematuria, often detected by dipstick measurement, corresponds to hemoglobinuria in most cases.

Thrombotic microangiopathy, defined by hemolytic anemia and thrombocytopenia, occurs in 43% of patients with SRC[7]. The detection of schistocytes indicates that hemolysis is related to mechanical disruption of red blood cells. Thrombocytopenia is usually moderate; platelet count is > 50,000/mm^3 in most cases and almost always returns to the normal range after blood pressure control.

Antinuclear antibodies are common. Of note, antitopoisomerase antibodies, found in 30% of patients with diffuse SSc, are not predictive of the occurrence of this manifestation. However, anti-RNA polymerase III antibodies, detected almost exclusively in diffuse SSc, can identify patients at risk. In fact, SRC will develop in 33% of these patients[62]. Detection of anti-RNA polymerase III antibodies is particularly useful in patients without skin involvement, notably in very early diffuse SSc. Remarkably, patients with anticentromere antibodies and SRC have rarely been reported.

Treatment

Early treatment of SRC is a major issue, and therefore prompt recognition of SRC is mandatory. The first report of successful results with an ACE inhibitor was in 1979[63]. Since then, no randomized study has been performed to demonstrate the efficacy of ACE inhibitors. Comparison with historical controls suggests a major therapeutic gain. Steen and colleagues reported their results of a single-center case-control study of 108 patients between 1972 and 1987. The 1-year survival was 15% without an ACE inhibitor versus 76% with an ACE inhibitor[4]. ACE inhibitor therapy must be initiated very early, at a low dose, with progressive increase to the maximal dose within 48 h[4]. A short to medium half-life drug should be chosen. Importantly, ACE inhibitor must be continued even if renal function is deteriorating. The treatment goal is to achieve blood pressure control as soon as possible. Angiotensin II receptor blockade (ATII) may be useful but is anecdotally less effective than ACE inhibitors, although clinical experience with these agents has been limited[64].

Continuous low doses of prostacyclin may be added to standard therapy[41] although there is no evidence that it improves short-term and longterm prognosis. Plasma exchange, which has been proposed in the setting of thrombotic microangiopathy, has no demonstrated efficacy and should not be performed, with the exception of the rare patients in whom SRC might develop in association with thrombotic microangiopathy related to antibodies directed at ADAMTS13 (Mouthon, *et al*, unpublished data).

Recently, from the identification of ET-1 in kidney biopsies from patients with SRC, ET receptor blockers in addition to an ACE inhibitor were found to have acceptable tolerance in a small, open study[26]. Serum ET-1 was elevated in patients with SRC compared with healthy controls ($p < 0.0005$), and ET-1 and both ET A and B receptor expression was increased in SRC biopsies[26]. Additional trials are necessary to document in a larger cohort of patients the efficacy of anti-ET receptor antagonists in addition to an ACE inhibitor in the acute phase of SRC, particularly in the medium term and long term. In this setting we are conducting a prospective multicenter open study, ReinBO, in 20 patients with SRC receiving ACE inhibitor therapy for fewer than 15 days in whom we are analyzing the effect of bosentan on the outcome of SRC.

With failure to normalize blood pressure with the maximal dose of an ACE inhibitor, additional antihypertensive therapy is needed. In such cases, most patients with SSc receiving calcium channel blockers should receive the maximal dose, orally or intravenously. In the absence of efficacy, additional treatments should be proposed, such as nitrates or other vasodilator agents[41]. Because relative hypovolemia is frequent in SRC, the use of diuretics or labetalol is a concern. Beta blockers cause concern for RP and digital ulcers and should also be avoided. Thus, as a third-line treatment, central antihypertensive agents such as minoxidil or prazosin can be proposed in the absence of blood pressure control. Immunosuppressive drugs, although recommended in patients with early diffuse SSc, have no proven beneficial effect in treatment of SRC. CS are theoretically contraindicated in patients with SRC and might play a role in the occurrence of SRC. However, there are no data supporting this statement in the literature.

Dialysis is needed in nearly half of patients with SRC. In patients under dialysis, blood pressure control is needed to offer the possibility of being removed from dialysis. SRC is a specific condition for dialysis because it may be temporary; up to 33% of patients may be removed from dialysis within 2 years after SRC onset[65]. Dialysis-dependence for 2 years means renal function will not return and transplantation is the only other option. In a series of 260 patients with SSc who underwent renal transplantation in the United States, the 5-year graft survival was 56.7%[66]. In that study, 5 patients developed a recurrence of the SRC on the renal transplant. The risk of recurrence of SRC after renal transplantation was increased in patients with early renal insufficiency after SRC onset.

Montanelli, *et al* recently reported in a retrospective analysis of 410 SSc patients with disease duration < 5 years that the risk to develop SRC was highly reduced in patients who were prescribed calcium channel blockers[67]. The use of a prophylactic ACE inhibitor remains a matter of debate because SRC develops in some patients with SSc taking those agents[7,41,68]. ACE inhibitor treatment has been proposed for treating other vascular manifestations in patients with SSc. No benefit was observed in the treatment of RP or digital ulcers in the QUINS trial[69], although that trial was conducted in patients with limited SSc or RP with antibodies, in whom the risk of SRC is presumably low. The use of an ACE inhibitor/ATII before SRC was somewhat associated with worse outcome in retrospective studies in dialyzed patients[7,8]. Analysis of pooled data from these 2 studies yielded an OR of 2.4 (95% CI 1.0–5.7, $p = 0.059$; chi-square value 3.64)[8]. Thus, whether a low-dose prophylactic ACE inhibitor protects against SRC or leads to increased risk of more severe SRC remains a matter of debate. Recently, a prospective, observational Web-based cohort study of incident SRC included 88 patients with SRC, including 13 lost to followup. In all, 18 patients (24%) received an ACE inhibitor immediately before SRC onset. In adjusted analyses, exposure to an ACE inhibitor prior to the onset of SRC was associated with an increased risk of death from the SRC (hazard ratio 2.42, 95% CI 1.02–5.75, $p < 0.05$ in the primary analysis and 2.17, 95% CI 0.88–5.33, $p = 0.09$ after posthoc adjustment for preexisting HTN). However, as stated by the authors, the wide CI, indicating considerable uncertainty around the precise magnitude of the risk and the possibility of residual confounding, remained an important limitation[70]. These

results need further confirmation, ideally from a randomized controlled trial in a large sample of patients.

Prognosis

The prognosis of SRC in large series is detailed in Table 2. Before the 1970s and the advent of ACE inhibitors, SRC almost always resulted in renal failure and death, usually within months. The use of an ACE inhibitor greatly improved the prognosis of SRC. Steen and Medsger and colleagues identified risk factors associated with poor outcome: male sex, older age, presence of congestive heart failure, serum creatine level > 3 mg/dl at the initiation of treatment, and more than 3 days to control blood pressure[4,65].

In the largest prospective observational cohort study to date, Steen and colleagues reported a good outcome for 60% of patients. More than half of those who required dialysis were able to discontinue it within 2 years, and the mortality rate was 15% at 2 years[4]. In 2 English and French publications[8,71], the mortality rate at 5 years was between 30% and 40%, corresponding to data from a North American multicenter randomized trial comparing high-dose versus low-dose D-penicillamine that showed 50% mortality[5], and from the South Australian Scleroderma Register, with 30% mortality despite aggressive antihypertensive treatment[6].

In the French cohort, 37/91 patients (40.7%) with SRC died versus 10.8% of controls ($p < 0.001$), and clinical outcomes were poor. In fact, 49 patients (53.8%) required dialysis, which was definitive for 38. Death was most frequent among patients undergoing dialysis who never recovered renal function (22 vs 2); and 13 patients with SRC who were never on dialysis died[72].

Finally, in the recent prospective international study, 36% of patients experiencing SRC died at 1 year, which is higher than the rate reported in retrospective studies[70]. Thus, incident cases of SRC may probably be missed in retrospective studies, and it will be important in the future to conduct prospective studies in this setting to confirm this result.

Overall, however, it is important to note that the longterm outcome is good for patients who survived the first year of SRC and are not undergoing dialysis.

SRC is a rare complication of SSc but remains severe. Prompt recognition and initiation of therapy with an ACE inhibitor offers the best opportunity for a good outcome. Nevertheless, the 5-year mortality remains unacceptable, and additional therapies are needed to improve the prognosis. Meanwhile, physicians should avoid intravascular hypovolemia treatment and therapy with CS and nephrotoxic drugs.

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Table 2. Prognosis of scleroderma renal crisis from the literature.

	Steen, et al[2]	Walker, et al[6]	DeMarco, et al[5]	Penn, et al[8]	Teixeira, et al[7]	Guillevin, et al[72]	Hudson, et al[70]
No. patients	195	16	18	110	50	91	75
Patients under dialysis, %	43	31	ND	64	56	54	53
Temporarily	23	6	ND	23	16	14	ND
Permanently	19	25	ND	42	22	39	25 (at 1 yr)
Died while under dialysis	ND	ND	ND	18	18	26	ND
Dead at 5 yrs, %	19*	31	50	41	31	40	36**

ND: not documented. * Early deaths. ** Deaths at 1 year.

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