Prognosis of scleroderma renal crisis: a long-term observational study

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Abstract

Background. Despite the efficacy of angiotensin-converting enzyme (ACE) inhibitors, the prognosis of patients with Scleroderma renal crisis (SRC) is characterized by a high rate of mortality and progression into end-stage renal disease (ESRD). Our aim was to evaluate the prognosis of SRC in our cohort of scleroderma patients.

Methods. We reviewed clinical charts of all our patients who developed SRC from 1980 to 2005. Outcome measures were ESRD, patients’ survival and SRC-related mortality. ESRD was defined as the need for chronic dialysis; survival was calculated from the time of SRC occurrence by Kaplan–Meier method. All patients were treated with ACE inhibitors and 10 patients were also treated with plasma exchange (PEx). Indications to PEx were concomitant micro-angiopathic haemolytic anaemia or intolerance to high doses of ACE inhibitors. SPSS package was used for calculation.

Results. Of 606 patients, affected with systemic sclerosis, who came at our observation during the aforementioned interval, 20 (3.3%) developed SRC. One year after SRC onset, 55% of patients developed ESRD. The survival rate was 70% at 1 year and 50% at 5 years; the mortality rate related to SRC was 35%. Notably, in the subgroup of patients treated with PEx, 20% developed ESRD; the survival rate was 90% at 1 year and 70% at 5 years; the mortality rate related to SRC was 10%.

Conclusions. Short-term prognosis of SRC has improved, but long-term prognosis remains disappointing. PEx in addition to ACE inhibitors seems to be a therapeutic option in patients with SRC who develop micro-angiopathy or are intolerant to high doses of ACE inhibitors.

Keywords: ACE inhibitors; end-stage renal disease; micro-angiopathy; plasma exchange; scleroderma renal crisis; survival rate

Introduction

Scleroderma renal crisis (SRC) is an uncommon but potentially fatal manifestation of systemic sclerosis (SSc), characterized by ‘malignant’ arterial hypertension, rapidly progressive renal failure and, in some cases, micro-angiopathic haemolytic anaemia [1]. Hypertensive retinopathy, encephalopathy with seizures and pulmonary oedema are severe complications of SRC.

SRC is due to a vasculopathy affecting intra-lobular and arcuate arteries of the kidneys with intimal proliferation leading to narrowing of the vessel lumen and to reduced blood flow which activates the renin–angiotensin system in the juxtaglomerular apparatus, with subsequent severe arterial hypertension [2–4].

Vascular hyperactivity can be associated with conditions such as ‘a renal Raynaud phenomenon’, and might contribute to intimal thickening leading to decreased cortical perfusion in the kidney [5]. Indeed, a higher frequency of SRC was observed during winter [6].

Risk factors for SRC include diffuse cutaneous SSc, elevated skin score, short duration of the disease (<3 years), anti-RNA-polymerase III antibodies [7–11], and prior exposure to drugs such as cyclosporine and/or glucocorticoids (>15 mg prednisone/die) [12–14].

SRC was reported in up to 10% of SSc patients and represented the leading cause of death before 1970. The outcome of SRC has dramatically improved since the introduction of treatment with angiotensin-converting enzyme (ACE) inhibitors, which block the activation of renin–angiotensin system. In a prospective study carried out in a cohort of 108 SRC patients, the 1-year survival rate was 76% in those treated with ACE inhibitors and 15% in those who were ACE inhibitors free [15]. Despite the improvement, SRC remains a life-threatening manifestation characterized by a high rate of mortality and progression into permanent dialysis [16].

In this retrospective study, we reported the long-term outcome of SRC patients in our cohort of SSc patients. Plasma exchange (PEx) has been used in the treatment of a variety of immunological disorders, including systemic rheumatic diseases [17, 18]. Over the last 25 years, we have extensively used PEx in the treatment of severe forms of SSc [19], and so we also reported our
experience with the use of this apheresis technique in addition to ACE inhibitors in patients with SRC.

**Materials and methods**

From 1980 to 2005, 606 patients were classified as affected with SSc, according to the American College of Rheumatology criteria [20], at the Rheumatology Unit of Padova University. Twenty of these patients (3.3%) developed SRC, defined as abrupt onset and rapidly progressive renal failure (doubling of serum creatinine above the value at baseline, in the absence of another defined cause) and/or malignant hypertension (systolic blood pressure ≥160 mmHg or diastolic BP ≥110 mmHg on at least two occasions). In seven patients, SRC was complicated by microangiopathic haemolytic anaemia [evidence of haemolysis assessed by plasma haptoglobin and lactate dehydrogenase (LDH) levels].

After the diagnosis of SRC, all patients continued their regular treatment and, in addition, they were treated with increasing doses of ACE inhibitors (captopril, enalapril or ramipril). Unfortunately, three patients were intolerant to high doses of ACE inhibitors and developed systemic arterial hypertension without any improvement of renal function. These three patients and another seven, who developed micro-angiopathic haemolytic anaemia, were treated with PEx in addition to ACE inhibitors.

Outcome measures were end-stage renal disease (ESRD), patient survival, overall mortality and SRC related mortality. ESRD was defined as the need for permanent dialysis. The study was approved by the Local Ethics Committee (University of Padova-Azienda Ospedaliero di Padova, Italy).

**Clinical and laboratory assessment**

At baseline, every 4 months for the first 2 years, and every 6 months thereafter, patients underwent a complete clinical evaluation and routine laboratory tests, including white blood cell count, urinalysis, glucose, BUN, serum creatinine, C-reactive protein, aspartate aminotransferase, alanine aminotransferase and LDH.

Auto-antibodies were tested at baseline. Anti-nuclear (ANA) and anti-centromere antibodies were detected by indirect immunofluorescence technique, using HEP-2 cells as a substrate. Anti-extractable nuclear antigens (ENA) antibodies (anti-Scl70, anti-U1RNP, anti-Ro/SSA and anti-La/SSB) were tested by counterimmunoelectrophoresis technique, using sera provided by the Center for Disease Control (Atlanta, GA) as control. Anti-RNA polymerase III antibodies were detected by an immunoenzymatic test.

Skin thickening was assessed using the modified Rodnan skin score [21]. Pulmonary function tests and diffusing capacity for carbon monoxide (DLco), chest radiography, high-resolution computed tomography (HRCT) of the lungs, electrocardiogram (ECG) and Doppler echocardiogram were regularly performed during follow-up, according to the current recommendations [22, 23] based on disease cutaneous form (limited versus diffuse) and disease severity [24].

Lung involvement (interstitial lung disease) was diagnosed if DLco was ≤70% of predicted and forced vital capacity was ≤75% of predicted or interstitial changes were noted on chest radiogram or on HRCT. Heart involvement was defined in the presence of conduction defects or arrhythmias on ECG and/or left ventricular diastolic dysfunction on echocardiogram. In patients with suspected pulmonary arterial hypertension (PAH) and estimated systolic pulmonary arterial (PA) pressure ≥40 mmHg by Doppler echocardiogram, right heart catheterization was performed and PAH diagnosed in presence of mean PA pressure >25 at rest. Gastrointestinal involvement was considered if symptoms related to gastro-oesophageal reflux, dysphagia and bowel alterations were present.

**PEx procedure**

PEx procedure was carried out according to the following treatment schedule: two to three sessions per week during the first month, then one session per week for 2 months, followed by one session every 2 weeks for maintenance. In each session, 70–100% of the plasmatic volume was treated using a 4% human albumin solution as the replacement fluid. PEx was discontinued when a sufficient renal function (serum creatinine <300 μmol/L and serum urea <15 mmol/L) remained stable for at least 1 month or when the patient required dialysis.

**Survival and causes of death**

Patients’ survival was calculated from the time of the SRC occurrence. The causes of death were defined on the basis of clinical data and, when available, by post-mortem examination. We considered as cause of death the pathologic event which mostly contributed to determining the death. According to causes of death, we distinguished overall mortality and mortality related to SRC.

**Statistical analysis**

SPSS package was used for calculation. Student’s t-test for paired data was performed to estimate differences of skin score and biochemical data at study entry and after 1 year. Univariate analysis of survival was performed by Kaplan–Meier method. We considered the time of SRC diagnosis as the baseline evaluation and the time of death or the last visit as the end of follow-up.

**Results**

Twenty patients developed SRC, 14 women and 6 men, mean age 45.5 ± 14.9 years at the time of SSc onset, and 49.0 ± 12.1 years at the time of SRC onset. The mean duration of SSc was 3.7 ± 4.8 years at the time of SRC occurrence. Sixteen patients had the diffuse (median skin score 20.5, range 15–32) and four the limited (median skin score 5.5, range 5–7) cutaneous form of SSc. Intestinal lung disease was detected in 12 cases, heart involvement in 6 and gastrointestinal alterations in 13. No patients developed PAH. Anti-RNA polymerase III antibodies were positive in 11 patients, anti-Scl70 in 7 and anticientromere in 2. Demographic, clinical and serological data of patients are reported in Table 1.

At the time of SRC occurrence, five patients were taking β-blockers, four cyclosporine, one cyclophosphamide, one azathioprine and one methotrexate. Ten patients were also taking glucocorticoids at a low dosage (seven at a dosage of ≤15 mg/day and three at a dosage of 25 mg/day), 15 oral vasodilators and 5 intravenous prostanooids.

In the first year after SRC onset, 11 of 20 patients (55%) developed ESRD and six of which died due to SRC complications (30%). The skin score and the biochemical data of all patients at the study entry (T0) and after 1 year (T1) are summarized in Table 2. The 5-year survival rate was 50% and the mortality rate related to SRC was 35%.

Ten patients were treated with PEx in addition to ACE inhibitors because they were intolerant to high doses of ACE inhibitors or developed micro-angiopathic haemolytic anaemia. They were seven females and three males, mean age 44.09 ± 9.67 years and mean duration of the disease 2.72 ± 3.67 years at SRC onset. Eight patients had diffuse cutaneous form (median skin score 19.1, range 15–32) and two limited cutaneous form (skin score 5 in both cases). Anti-RNA polymerase III antibodies were detected in seven patients, anti-Scl70 in two, and anti-centromere in one.

All patients had been taking ACE inhibitors before undergoing PEx. The duration of PEx treatment varied from patient to patient ranging between 1 and 10 months; the mean number of sessions per patient was 28 ± 12 (range 12–46). PEx procedures were well tolerated by all patients.
One year after the SRC occurrence, we observed a significant decrease in the serum levels of creatinine, urea and LDH and a significant increase of Hb and haptoglobin (Figure 1). Skin score decreased significantly over this period ($T_0 = 16.3 \pm 7.68$ versus $T_1 = 7 \pm 3.8$, $P = 0.004$).

One year after the onset of SRC, 7 of the 10 patients preserved or recovered sufficient renal function to avoid dialysis, 2 developed ESRD requiring permanent dialysis and subsequently underwent renal transplantation, and 1 patient died as a result of SRC complications. In this group of patients, the 5-year survival rate from SRC onset was 70% and SRC related mortality was 10%; two other patients, who initially improved, died of cancer after 15 and 18 months, respectively. The cumulative survival

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**Table 2.** Skin score, renal function tests and haemoglobin in patients with SRC at study entry ($T_0$) and at 1-year follow-up ($T_1$)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Treatment before SRC</th>
<th>PEx</th>
<th>Skin score</th>
<th>Serum creatinine (μmol/L)</th>
<th>Serum urea (mmol/L)</th>
<th>Haemoglobin (g/dL)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>$T_0$</td>
<td>$T_1$</td>
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<td>$T_1$</td>
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<tr>
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<td>5</td>
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</tr>
<tr>
<td>3</td>
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<td>No</td>
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<td>Yes</td>
<td>15</td>
<td>3</td>
<td>641</td>
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</table>

All patients were treated with ACE inhibitors and 10 of them with ACE inhibitors and PEx.

SRC, Scleroderma renal crisis; PEx, plasma exchange; D, deceased.
curves of all patients and of those treated with PEx are reported in (Figure 2).

**Discussion**

Despite the efficacy of ACE inhibitors, the prognosis of patients with SRC remains disappointing. Steen et al. [16] assessed the outcome of 145 patients affected with SRC treated with ACE inhibitors: 19% died within 3 months, 19% were treated with permanent dialysis, 23% with temporary dialysis, 38% did not require dialysis. De Marco et al. evaluated 18 patients with SRC and observed a 5-year survival rate of 50% [25]. In a study carried out in a South Australian Scleroderma cohort, of 539 patients, 16 cases of SRC (2.8%) were identified, 5 patients required dialysis (3 long-term and 2 temporary dialyses). The 5-year mortality rate in this study was 31% [26]. In a retrospective single-centre study, of 110 patients treated with ACE inhibitors, 64% developed ESRD and entered into dialysis; however, in 23% of them, renal function recovered and they were able to withdraw dialysis, whereas the remaining 41% of cases were treated with permanent dialysis. Overall survival at 1 and 5 years from SRC onset was 82 and 59%, respectively, and patients in whom renal function recovered were those with the most favourable prognosis [27]. Finally, in a French retrospective study on a cohort of 50 patients with SRC, 94% of whom were treated with ACE inhibitors, the 1-year and 5-year mortality rate was 22 and 31%, respectively. Eight (16%) patients who required dialysis were able to discontinue the treatment after a median period of 9.8 months [28].

In this study, we retrospectively reviewed 20 patients with SRC. In addition to their regular therapy, all patients were treated with increasing doses of ACE inhibitors (captopril, enalapril or ramipril) and 10 of which with PEx.

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**Fig. 1.** Renal function tests, haemolysis parameters and skin score in patients treated with ACE inhibitors and plasma-exchange (PEx). Hb, haemoglobin; LDH, lactate dehydrogenase.

**Fig. 2.** Five-year survival curve in patients with scleroderma renal crisis (SRC). PEx, Plasma exchange.
also, due to concomitant micro-angiopathic haemolytic anaemia in seven cases and intolerance to high doses of ACE inhibitors in three.

Our data confirm the poor prognosis of SRC: 55% of patients developed ESRD and 30% died within the first year after the onset of SRC; the 5-year survival rate was 50%. Finally, three of our patients died of cancer and the mortality related to SRC was 35%.

The mortality ratio observed was higher than that reported by others which ranged between 19 and 50% [25–29]. There are some potential explanations for this discrepancy. The mean baseline serum levels of creatinine were higher in our patients (627.3 μmol/L) compared with those observed in other studies which ranged between 248 and 452 μmol/L [16, 26, 28, 29]. In addition, the prevalence of anti-Scl70 antibodies was higher in our patients (50%) than in those reported by others, which ranged between 6 and 32% [26, 27, 28, 29]. Notably, it has been shown that anti-Scl70 antibody represents a marker of poor prognosis in SSC with SRC [11, 30, 31].

PEx has been used in the treatment of SSC since the 1980s. The rationale behind this therapy stems from evidence that humoral factors play an important role in the pathogenesis of disease [32–35]. By removing autoantibodies, cytokines, chemokines, circulating immune complexes, adhesion molecules, growth factors and other mediators, PEx seems to have a beneficial effect on disease immune pathways. Indeed, we observed a significant decrease in soluble interleukin-2 receptor and type III procollagen amino terminal propetide serum levels as well as in the number of circulating positive DR+ T cells in a group of SSC patients treated with PEx, suggesting that this treatment is able to affect some pro-fibrotic and immune activation markers [36]. The rationale of using PEx in the treatment of SRC is less clear. PEx might potentially remove immune or other plasma factors involved in renin–angiotensin system activation [37]. It has also been hypothesized that PEx might gradually decrease angiotensin II serum levels and aldosterone synthesis in refractory hypertensive patients [38].

In the last few decades, a number of studies carried out in small groups of patients affected by different subsets of SSC and treated with different treatment schedules have reported the effectiveness of PEx in improving cutaneous lesions and, in some cases, even visceral involvement [39–49]. Unfortunately, no randomized controlled trials are available to date, and according to the guidelines elaborated by American Society for Apheresis, current indication for PEx in SSC can be assigned to category III, whose definition is: ‘Optimum role for apheresis therapy not established. Decision making should be individualized’ [50].

In our study, 10 patients were treated with PEx plus ACE inhibitors and 7 were ‘responders’ since their renal function was preserved and sufficient to avoid dialysis. In this group of patients, the mortality rate was 30% and mortality related to SRC was 10%.

Thus, PEx added to the standard treatment seems to be an option in the management of a subset of patients with SRC, i.e. patients with micro-angiopathic haemolytic anaemia or intolerant to high doses of ACE inhibitors. Notably, these are conditions which can further worsen the prognosis of SRC both in terms of renal and patient survival. Overall, in our study the prognosis of patients treated with PEx in addition to ACE inhibitors was better than those treated with ACE inhibitors alone in terms of preserved or recovered renal function, 5-year survival rate and mortality due to SRC.

In conclusion, short-term prognosis of SRC has improved, but long-term prognosis remains disappointing. PEx in addition to ACE inhibitors seems to be a therapeutic option in patients with SRC who develop micro-angiopathy or are intolerant to high doses of ACE inhibitors.

Funding. This work was supported by ‘Ministero dell’Istruzione, dell’Università e della Ricerca’ [60A07-1030/09], Italy.

Conflict of interest statement. None declared.

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