Effect of dihydropyridine calcium channel blockers and glucocorticoids on the prevention and development of scleroderma renal crisis in an Italian case series

G. Montanelli, L. Beretta, A. Santaniello, R. Scorza

Referral Centre for Systemic Autoimmune Diseases, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico and University of Milan, Italy.
Gaia Montanelli, MD
Lorenzo Beretta, MD
Alessandro Santaniello, MD
Raffaella Scorza, MD
Please address correspondence to: Dr Lorenzo Beretta,
Referral Centre for Systemic Autoimmune Diseases, Fondazione IRCCS,
Ospedale Maggiore Policlinico and Università di Milano,
Via Pace 9, 20122 Milano, Italy.
E-mail: lorberimm@hotmail.com
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ABSTRACT

Objectives. Scleroderma renal crisis (SRC) is a relative rare yet dramatic event in the history of systemic sclerosis (SSc). Several factors that may precipitate or protect from the development of SRC have been described in previous case-control studies. To date, no attempt has been made to evaluate these factors in an observational fashion.

Methods. Retrospective data from 410 SSc patients with disease duration <5 years at referral were evaluated in an observational fashion for the development of SRC within 5 years from the first visit at our centre. Baseline characteristics as well as the use of steroids or dihydropyridine calcium-channel blockers (CCB) were analysed via the Cox regression method with time-dependent covariates.

Results. In the multivariate model the diffuse subset the disease (HR=5.728 CI_{95}=2.199–14.918, p<0.001) and the use of prednisone (HR=1.015 CI_{95}=1.004–1.026, p=0.006) resulted to be predictors for the development of SRC, with a risk to develop SRC increased by 1.5% for every mg of prednisone/day consumed the trimester prior SRC. Contrariwise, the risk to develop SRC was highly reduced in those who were prescribed CCBs (HR=0.094 CI_{95}=0.038–0.236, p<0.001).

Conclusion. Steroids exhibits a weak effect on the risk to progress toward SRC in our case series, whilst dihydropyridines CCB appeared to be protective against that. Further larger prospective studies are warranted to better define the role of CCB in this setting or as a background therapy for SSc.

Introduction

Systemic sclerosis (SSc) is a chronic systemic autoimmune disease characterised by vascular damage, immune deregulation and cutaneous and visceral fibrosis. Renal involvement is a relatively rare (1-6), yet dramatic event in the history of SSc, which is plagued by high morbidity and mortality rates (7). The use of angiotensin-converting enzyme (ACE)-inhibitors has consistently improved the prognosis of scleroderma renal crisis (SRC) (8), nonetheless 30–50% of patients is still expected to need permanent haemodialysis or to die within 5 years from the onset of kidney disease (9). In the vast majority of patients, SRC is characterised by the abrupt development of arterial hypertension, oliguria and rapidly progressive renal failure, however, 10% of subjects with a rapidly progressive deterioration of renal function may not experience hypertension at all (10).

The mechanisms implied in the pathogenesis of SRC are not completely understood, even though several lines of evidence suggest that vasculopathy plays a predominant role in the development and in the progression of the renal disease. Increased platelet aggregation, overt intimal hypertrophy and proliferation leading to the pathognomonic “onion bulb” lesions, are typically observed in renal biopsies from SRC patients (11). These factors associated with vascular hyper-reactivity are responsible for a decreased renal blood flow with consequent renal ischaemic damage. Hypoperfusion may eventually lead to the activation of the renin-angiotensin-aldosterone system, further enhancing vasoconstriction and hyperplasia, thus strengthening and amplifying a pathological vicious circle (12).

Although the etiology of SSc-associated kidney disease remains elusive, several studies have been conducted in the effort to determine which factors may precipitate/protect from the development of SRC. A disease duration of less than 4 years (1, 13), a diffuse
and rapidly progressive skin thickening (13, 14), a recent onset of anaemia or cardiac events – particularly pericardial effusion or congestive heart failure (13, 14) – and the presence of anti-RNA polymerase III antibodies were reported as clinical predictors of SRC (1). Furthermore, a number of therapies, including cyclosporine and corticosteroids, has been reported as a precipitant factors for SRC; nonetheless not all the studies on steroids provided univocal data and controversial results have been obtained reworking the data from randomised controlled clinical trials (14). Conversely, to date, only the presence of anti-centromere antibodies has been described as protective against the development of SRC (13), whilst no exhaustive analysis has ever been provided to clearly define the effect vasoactive drugs commonly used in the treatment of scleroderma vasculopathy (15) may have on the prevention of SRC.

In the present retrospective observational study we analysed the factors associated with the development of SRC. We particularly focused on the role of glucocorticoids in the effort to determine if a correlation between the consumed daily dose and SRC exists, evaluating, at the same time, the effect of vasoactive drugs such as calcium-channel blockers (CCB) and iloprost, on the risk for SRC.

**Material and methods**

**Patients**

Four hundred and ten consecutive patients with a diagnosis of SSc, made according to the preliminary criteria for the classification of SSc proposed by the American College of Rheumatology (ACR) (16) and referred to our outpatient clinic between 1990 and 2011, were considered for the analysis. A previous survey in Italy reported that the incidence of SRC is higher in the first years of illness (2); accordingly, only patients with disease duration ≤5 years were included in the study. Disease duration was calculated from the first non-Raynaud feature clearly attributable to SSc (2). This inclusion criterion allowed us to select a population enriched for subjects at risk for SRC, dampening the possibility to produce a biased estimate of SRC-associated risk factors. All the eligible patients were categorized as having the limited cutaneous (lcSSc) or the diffuse cutaneous (dc-SSc) subset of the disease, according to LeRoy et al. (17), and the patients’ autoantibody profile was determined by reviewing the patients’ medical records. Antinuclear antibodies (ANA) were determined by indirect immunofluorescence on Hep, cells (Kallestad, Chaska, MN, USA) using a standardised technique (18); extractable nuclear antigens (ENAs) were determined by a commercial enzyme-linked immunosassay (ELISA) (Diamedix, Miami, FL, USA). The data were observationally handled from the year of referral onward and we considered the following baseline characteristics for the analysis: the percentage values for the forced vital capacity (FVC) and for the diffusion lung capacity for carbon monoxide (DLco); the presence of a right ventricular systolic pressure (RVSP) ≥45 mmHg on echocardiography (19); the presence of muscle involvement, defined as weakness with elevated creatinine phosphokinase ≥2 times the laboratory upper normal values; the presence of systemic inflammation, defined as the presence of an erythrocyte sedimentation rate (ESR) ≥25 mm/h without evidence of concurrent infection (20) and the presence of digital ulcers, defined as the loss of surface epithelialisation (21).

Observation time was set to 5 years and it was divided in 3-month time-intervals (e.g. 20 trimesters). For each trimester, information about the occurrence of SRC, the average daily dose of prednisone and the use of dihydro-pyridine calcium-channel blockers or therapy with cyclic Iloprost (22) was retrieved. No data about other vaso dilators were retrieved, because for clinical practice we do not prescribe them for the treatment of SSc-related Raynaud’s phenomenon, consequently, the exposure to them in our patients is very low to allow for a reliable analysis. Hypertensive and normotensive SRC were defined as reported by Teixera et al. (6). Hypertensive SRC was defined by rapidly progressive oliguric renal insufficiency with no other explanation and/or rapidly progressive hypertension occurring during the course of SSc. Normotensive SRC was defined by an increase in serum 50% over baseline or serum creatinine >20% of upper limit of normal and one of the following five features: proteinuria >2+ by dipstick, haematuria >2+ dipstick or >10 red blood cells/high-power field, thrombocytopenia, <1*10⁹ cells/mm³, haemolysis defined as anaemia not due to others causes and either schistocytes or other red blood cell fragments seen on blood smear, or increased reticulocyte count, or renal biopsy findings consistent with SRC.

All the patients referring at our clinic at the first visit gave written consent to allow the use of their data for epidemiological studies; the present research complies with the ethic rules of our hospital and was approved by the regulatory board of our institution.

**Statistical analysis**

Cox regression with time-dependent covariates was used to determine which factors were associated with the development of SRC (23). Firstly, univariate Cox regression was conducted and variables significant at the 0.01 level were further considered for multivariate analysis. Owing to the low number of events in our population, the 0.01 threshold was used instead of the canonical 0.05 threshold, so as to minimise Type I error. Before conducting multivariate Cox regression, we checked the occurrence of multicollinearity among the candidate features; in this case, the least explicable variable was not included in the multivariate model. To conduct the multivariate Cox regression analysis, the forward stepwise procedure was chosen. Results from univariate and multivariate models are expressed as hazard ratios (HRs) with their relative 95% confidence intervals (CI₉⁵) throughout the manuscript. For descriptive statistics, continuous variables are expressed as mean±standard deviation (SD), except when skewed; in the latter case, median and interquartile range (IQR) values are reported. The SPSS software version 18.0 (SPSS Inc, Chicago, IL, USA) was used to conduct all the statistical analyses.
Results
Baseline demographic and clinical characteristics of our population are reported in Table I. Twenty-two patients (5.4%) developed SRC within 5 years from referral; overall nineteen hypertensive SRC (86% of the total) were observed. The median time elapsed between the first visit at our centre and the onset of renal involvement was 9 months (IQR: 1.8–14 months); the overall median disease duration at the onset of SRC was 12 months (IQR: 6.7–34.8 months).

Two hundred and twenty-one patients (53.9%) were treated with corticosteroids and 142 patients received cyclical therapy with i洛prost (34.6%); the vast majority of the patients (n=368, 89.8%) had been treated with dihydropyridine CCB. Overall, exposure to CCBs was equal to 5498/6308 trimesters (87.2%), whilst steroids were used in 1993 out of 6308 trimesters analysed (31.6%), with a mean dose/trimester of 5.4 mg prednisone/day and a mean maximum dose/trimester of 17.4 mg prednisone/day. Steroids were used in 24 cases (10.9%) to treat myositis, in 74 cases to treat lung involvement (33.4%), in 65 cases to treat skin involvement (29.4%), in 24 cases to treat articular involvement (11%) and in the remaining cases to treat a miscellaneous of conditions. No differences were observed between patients who received CCB and those who did not as far as any of the baseline clinical or demographic variables were concerned.

Significant results from univariate and multivariate Cox regression analysis with time-dependent covariates are reported in Table II; all the other studied covariates that do not appear into the table were not significantly associated with SRC occurrence. Overall, 55.6% of instances had a type II censoring, type I censoring rates were equal to 39%. Univariate analysis sorted out the following variables as significantly associated with the occurrence of SRC: the dcSSc subset (HR=6.797, CI: 2.769–16.683), the male gender (HR=5.13, CI: 2.147–12.261) and the use of steroids (HR=1.015, CI: 1.004–1.026) resulted to be predictors for the development of SRC, whilst the use of CCB was associated with a reduced risk for that complication (HR=0.962, CI: 0.914–0.991). Overall, the results indicate that the risk to develop SRC is increased by 1.5% for every mg of prednisone/day. Cumulatively, the exposure to CCB in subjects who did or did not experience SRC was thus distributed: 8/22 trimesters with SRC (36.4%), 5490/6286 trimesters without SRC (87.3%).

Discussion
SRC is one of the most dreadful complication of SSC and, even if the early use of ACE-inhibitors has dramatically improved SRC survival (8), its occurrence is still plagued by high morbidity and mortality rates. Several studies have been conducted in order to sort out the factors that may predict or protect from the occurrence of SRC. Amongst clinical and serological factors, corticosteroids have emerged as a relevant risk-factor for the development of SRC, with a 3-fold estimated risk for those who were treated with any dose of steroid, according to a previous report by Steen and co-workers (13). Nonetheless, reworking the data from the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial (14), the association between corticosteroids consumption and SRC was

Table I. Demographics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SSc (n=410)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, n (%)</td>
<td>364 (88.8%)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>51.6 ± 12.9</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>dcSSc, n (%)</td>
</tr>
<tr>
<td>12 (4–28)</td>
<td>105 (25.6%)</td>
</tr>
</tbody>
</table>
| Autontibodies, n (%) | ANA | 388 (94.8%)
| 102 (24.9%) |
| 162 (39.5%) |
| 154 (37.6%) |
| 14 (3.4%) |
| 95.3 ± 19 |
| 74.4 ± 20.7 |
| 112 (27.4%) |
| 24 (5.9%) |
| 123 (30%) |

Table II. Factors associated with scleroderma renal crisis (SRC).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>CI</td>
</tr>
<tr>
<td>dcSSc</td>
<td>6.797</td>
<td>2.769–16.683</td>
</tr>
<tr>
<td>Male gender</td>
<td>5.13</td>
<td>2.147–12.261</td>
</tr>
<tr>
<td>Prednisone, mg/day</td>
<td>1.028</td>
<td>1.018–1.038</td>
</tr>
<tr>
<td>FVC, % of predicted</td>
<td>0.961</td>
<td>0.93–0.973</td>
</tr>
<tr>
<td>Disease duration (months)**</td>
<td>0.099</td>
<td>0.041–0.241</td>
</tr>
<tr>
<td>Presence of ACAs**</td>
<td>0.72</td>
<td>0.01–0.539</td>
</tr>
</tbody>
</table>

Results from Cox regression analysis with time-dependent covariates. dcSSc: diffuse systemic sclerosis; FVC: forced vital capacity; ACAs: anti-centromere antibodies; HR: hazard ratios; CI: 95% confidence intervals or the HRs. *Not included in the multivariate model due to multicollinearity with dcSSc. **Not included in the multivariate model (p-values from univariate analysis above 0.01 screening threshold).
found to be less crucial: prednisone had a causative role only in presence of high skin scores and joint contractures together, exerting no effect when considered alone. In our study, the use of prednisone (or equivalent) was found to be associated with the occurrence of SRC both after univariate and multivariate analysis. Differently from previous studies, rather than establishing a cutoff value for the dose of corticosteroids, we treated prednisone as a continuous variable and handled it observationally in a time-dependent fashion; the resulting estimated risk for SRC in those who made use of prednisone versus those who did not was found to be rather weak (1.5% per mg/prednisone/day). A much higher risk for SRC was observed in patients with the dcSSc subset, in accordance with previous reports (2, 13, 14). Owing to the limited number of subjects included in our analysis, it was difficult to model for interaction terms and/or to conduct a stratified analysis to assess the risk for renal complications in those with the dcSSC who were given steroids. Nonetheless, even if in our population the risk of SRC associated with prednisone would appear negligible, it seems reasonable to be advise caution in prescribing high-dose steroids to dcSSc patients.

To date, no pharmacological therapy has proved effective in protecting against the risk of developing SRC in SSC patients. On the contrary, in our study, the use of CCB was found to be associated with a dramatic reduction in the risk for SRC. As for clinical practice, the vast majority of our patients (89.8%) is prescribed first or second generation dihydropyridines (mainly nifedipine, but also perdipine or amlodipine) during the course of their illness. Presently, it is not possible to define the precise mechanism by which this class of drugs may reduce the risk for SRC, even if it seems reasonable to speculate that this may be somewhat related to their vasoactive properties. CCBs block L-type calcium channels preferentially acting on the peripheral circulation and are considered a first-line therapy for the treatment of Raynaud’s phenomenon (15). However, several studies also demonstrated that dihydropyridines act on the kidney vascular bed, selectively vasodilating the afferent arteriole with almost no effect on the efferent arteriole (24, 25). Preglomerular vasoconstriction, intimal fibrosis and endothelial tissue remodelling are prominent features that can be observed in the pathogenesis of scleroderma renal disease, decreasing kidney perfusion and leading to an impaired glomerular filtration rate (11, 12). In this critical situation, hypoperfusion activates the renin-angiotensin system, giving rise to angiotensin II levels in order to maintain a stable glomerular filtration rate via postglomerular arteriolar vasoconstriction. Dihydropyridines were shown to antagonise the vasoconstrictive action exerted by angiotensin II on the preglomerular arteriole (26, 27), preserving its effect on the efferent arteriole and exerting thus a preferential augmentation of glomerular filtration rate and filtration fraction, eventually counteracting the trigger events of SRC. These peculiar properties of dihydropyridines may also explain their observed capability of reducing renal sufficiency secondary to cyclosporine therapy (27). Of interest and similarly to SRC, cyclosporine-induced nephrotoxicity is thought to be partially caused by vasoconstriction of the glomerular afferent arterioles (28).

Among the other analysed factors, the presence of ACAs in the univariate analysis confirmed its negative association with SRC as observed by Penn et al. (1); similarly to the English case-series, it is difficult to ascertain whether this inverse risk-association is due to a protective effect of ACAs or is somehow related to the absence of RNA-polymerase III antibodies, a strong risk-factor for SRC in some populations (1, 29), albeit not in Italy (2), and whose occurrence is mutually exclusive with ACAs (29). The retrospective design of the study, dating back to the early 90’s, indeed prevented us from a thorough collection of this datum. Penn et al. (1) identified a median of disease duration of 7.5 months in patients with renal complication and 69% of SCR developed within 1 year of the diagnosis of SSC. In our population, the median disease duration at SRC was 12 months and 73% of SRC occurred within 15 months from the diagnosis. Therefore, our observation confirms that SRC is a precocious manifestation in the disease course. In our population, 5.4% of patients develops SRC; this datum contrasts with the SRC incidence of 13% described in the American (5) or north European SSC-patients (1), but it is in accordance with previous studies performed in Mediterranean area (2, 4). The low prevalence of SRC and the inclusion criteria we applied prevented us from observing a large number of cases in our population and, thus, to conduct more sophisticated analyses that might have better elucidated the role of steroids and CCB on the prevention or on the progression of SRC, as for instance, the search for interaction terms. Also, the low prevalence of SRC in our series and the need to avoid the risk to describe spurious results (e.g. to lower Type I error) was inevitably accompanied by a low power to detect significant effects from other factors described elsewhere (1, 13, 14). The number of events per predictor (EPV) variable we used in the multivariate analysis (e.g. 22/4=5.5) may suggest a significant departure from the empirical “rule of thumb” of 10 EPV and thus the presence of a significant bias in our analysis. Yet, as shown in (30), this rule is by far too conservative and the presence of 5–9 EPV is sufficient to keep low the bias in risk estimation and type I error rates as well as to adequately estimate confidence interval coverage.

As with any observational data, extreme caution should be applied in the evaluation of results, being the risk of the so-called “survivor bias”, not negligible (31): patients who do not experience the event of interest may preferentially be exposed to treatment (e.g. steroids or CCB) leading to spurious associations. However, as noted in (32), this risk is negligible when Cox regression with time-dependent covariates is applied; indeed this technique, which we applied both in the univariate and multivariate analysis, is regarded as the optimal choice to address the survivor bias issue.

To our knowledge, this is the first time CCB emerged as a significant inversely related risk factor for the development...
of SRC. It is nearly impossible to explain the divergence of our results from the two reports that have, at least partially, addressed the question (13, 14); a direct comparison between our and these studies is not feasible, due to the completely different methodological approach employed for the analysis (e.g. retrospective survival study with time-dependent covariates vs. case-control) and to the strikingly different exposure to this class of drugs. Overall, even if our findings should be carefully gauged in light of the above-mentioned considerations and of the retrospective design of the study, our results may help to cast new light on the possible systemic effects of CCBs already described in SSc case series such as the prevention of pulmonary hypertension in lcSSc patients (33), the amelioration of myocardial perfusion (34) and the prevention of left ventricular dysfunction (35). Larger observational studies are thus needed to confirm these preliminary findings, which are supported by the physiological properties of dihydropyridines.

References


