Title

UK Scleroderma Study Group (UKSSG) Guidelines on the Diagnosis and Management of Scleroderma Renal Crisis

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Introduction

Systemic sclerosis (SSc) is a multisystem connective tissue disease of uncertain aetiology that is characterised by inflammation and fibrosis in the skin, internal organs and vascular abnormalities. Scleroderma is classified according to the pattern of skin involvment, including limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) systemic sclerosis(1).

Scleroderma renal crisis (SRC) is the most important renal complication in SSc and is characterised by the acute onset of severe hypertension (often described as accelerated or malignant) together with acute kidney injury (AKI). It is estimated to occur in 10-15 % of patients with dcSSc and very rarely (1-2 %) in lcSSc (2,3). The reported median duration of SSc at the time of SRC is 7.5 months (range 0-200 months) with 66% of patients suffering SRC within one year of diagnosis of SSc (2,4). It is unknown why only a minority of patients with SSc develop SRC. A second major or multiple minor triggers as well as genetic susceptibility are likely, in addition to SSc. As part of the UK Scleroderma Study Group (UKSSG), we developed guidelines on the diagnosis and management of Scleroderma Renal Crisis (SRC) based on best available evidence and observational clinical experience.

Risk Factors associated with SRC

Major risk factors for the development of SRC include early dcSSc, rapidly progressive skin disease, tendon friction rubs, recent high-dose corticosteroid use (e.g. prednisolone or equivalent at >15 mg/day) and positive RNA Polymerase III (ARA) antibody. In the Australian Scleroderma cohort study, independent of corticosteroid exposure, the presence of ARA conferred a 25% risk of developing SRC and was measurable in 59 % of SRC patients in one cohort (2,5).

Other risk factors for SRC include hormone replacement therapy (HRT), pericardial effusion, cardiac insufficiency, high skin score and large joint contractures (6). Anaemia, thrombocytopenia and new cardiac events may arise as early consequences of the SRC rather than representing true risk factors yet they serve as useful alerts to the possibility of SRC.

To aid early identification of the occurrence of renal crisis in high risk patients we recommend home blood pressure monitoring twice weekly for all patients with dcSSc who are within 4 years of diagnosis. Blood pressure targets should be individualised according to the patients' own normal BP readings (see below).

Diagnosis of SRC

The diagnosis of SRC is summarised in Table 1. Clinically, SRC is characterised by the development of accelerated hypertension together with acute kidney injury. If a

patient with SSc has an elevated blood pressure (BP) of >150/85 mmHg or an increase of ≥20 mmHg from their usual systolic BP on two occasions in 24 hours, they should be assessed urgently with blood tests and urinalysis. If there is a significant increase in serum creatinine (either an absolute increase of 26.5 µmol/L or an increase of 50% from the baseline value) or urine dipstick shows proteinuria (>2+) and/or haematuria (1+), they should be started on an angiotensin converting enzyme inhibitor (ACEi) immediately and admitted to hospital for further assessment.

Most patients with renal crisis presenting to clinicians complain of non-specific symptoms including fatigue and dyspnoea. Other typical clinical features are those seen in accelerated hypertension of any cause: there may be headache, blurred vision or other encepholopathic symptoms, including seizures.

In addition to the above there may be evidence of microangiopathic haemolytic anaemia (MAHA), oliguria, cardiac failure and tachyarrhythmias. MAHA or intra-vascular haemolysis is present in approximately 50% of patients with SRC and is evidenced by reduced platelet counts, red cell fragments, reduced serum haptoglobin levels, red cell fragments and schistocytes on blood film together with massively elevated lactate dehydrogenase (LDH) levels. Echocardiogram will often demonstrate a reduced left ventricular ejection fraction and pulmonary oedema is common in SRC. However, these findings typically result from dramatically increased peripheral resistance and effective outflow tract obstruction rather than primary myocardial dysfunction. Tachycardias and tachyarrythmias are also seen in this group, which has a high prevalence of concomittant myocardial fibrosis.

Renal biopsy is helpful to resolve diagnostic uncertainty as to the cause of acute kidney injury (where there is a positive ANCA screen for example) and also to assess renal prognosis. The risk of haemorrhage is increased in the context of uncontrolled hypertenison, so biopsy should not be performed until the patient's BP is well controlled, the clinical condition of the patient is stable and the platelet count has recovered.

Management of SRC

Acute management of SRC involves general supportive care with thoughtful BP control (Figure 1). Prompt BP control is essential if hypertensive encephalopathy or cardiac de-compensation dictate it. Otherwise, moderate, steady reduction in BP (10% reduction in systolic BP per day) is likely to optimise chances of renal recovery. The use of an ACEi in the early stages is now standard and there is evidence that continuation of these agents even if the patient becomes dialysis dependent improves the chances of recovering renal function and becoming dialysis independent (7,8). There is no evidence that a short-acting ACEi (e.g. captopril) should be preferred to a long-acting agent (e.g. ramipril) unless the patient has marked cardiovascular instability. Beta blockers are relatively contraindicated given the risk of reducing cardiac output in the face of massively raised peripheral

resistance. The choice of other agents is largely dependent on patient response.

Angiotensin Receptor Blockers (ARBs) are an alternative where ACEi is not tolerated although there is some evidence they may not be as effective (9,10). The use of prophylactic ACEi in at risk patients with SSc is not recommended and it may result in worse outcomes (11,12). Conventional intra-venous vasodilators (e.g. GTN) are effective where rapid reduction in BP is required. Intravenous prostaglandin analogues (e.g. Iloprost) also provide effective blood pressure control and may have the added advantage of discouraging platelet/vascular endothelial activation.

Around 60% of patients with SRC will progress to requiring renal replacement therapy (RRT) at some point, despite appropriate BP management (2,13). The choice of RRT is between continuous methods—haemofiltration or peritoneal dialysis (PD)—or intermittent haemodialysis (HD). Historically, a large majority of patients has been treated with HDdue to the greater availability of this modality. However, intravascular instability in the early stages of SRC means that continuous modalities may be preferable where available and ptractical for the patient.

For dialysis dependent patients, renal transplantation is an option but careful consideration needs to be given to the timing of transplantation as renal recovery can occur up to two years following SRC (2). Post-transplant immunosuppression needs to be considered carefully as calceneurin inhibitors (ciclosporin and tacrolimus) are renal vasoconstrictors associated with an increased risk of SRC (14,15). Furthermore, co-existing cardiac and pulmonary disease may dictate suitability for listing. Although in general renal transplantation offers superior survival in SRC patients (16), graft survival is reduced compared to the general renal transplant population and recurrence of scleroderma may play a role in this poor post-renal transplant outcome (10,17).

Conclusion

Despite recent improvements in overall survival in SSc and advances in organ-based therapies, SRC remains an important complication of the disease. An estimated 15 % of SSc patients may develop SRC, which presents as acute onset hypertension and acute kidney injury. Current strategies to reduce the associated morbidity and mortality include identifying at risk patients to aid early diagnosis and ACEi therapy should be lifelong in all patients, regardless of whether they require renal replacement therapy. Patients with SRC may recover renal function up to 3 years after the crisis, most often within 12 to 18 months. Deaths are more frequent in patients who do not recover renal function.

Table 1 Diagnosis of 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 hrs
Acute Kidney Injury stage 1 or higher: >50% increase in serum creatinine from stable baseline or an absolute increase of 26.5 µmol/L)
Supportive evidence (desirable)
Microangiopathic haemolytic anaemia on blood film, thrombocytopaenia and other biochemical findings consistent with haemolysis
Findings consistent with accelerated hypertension on retinal examination
Microscopic haematuria 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 oedema

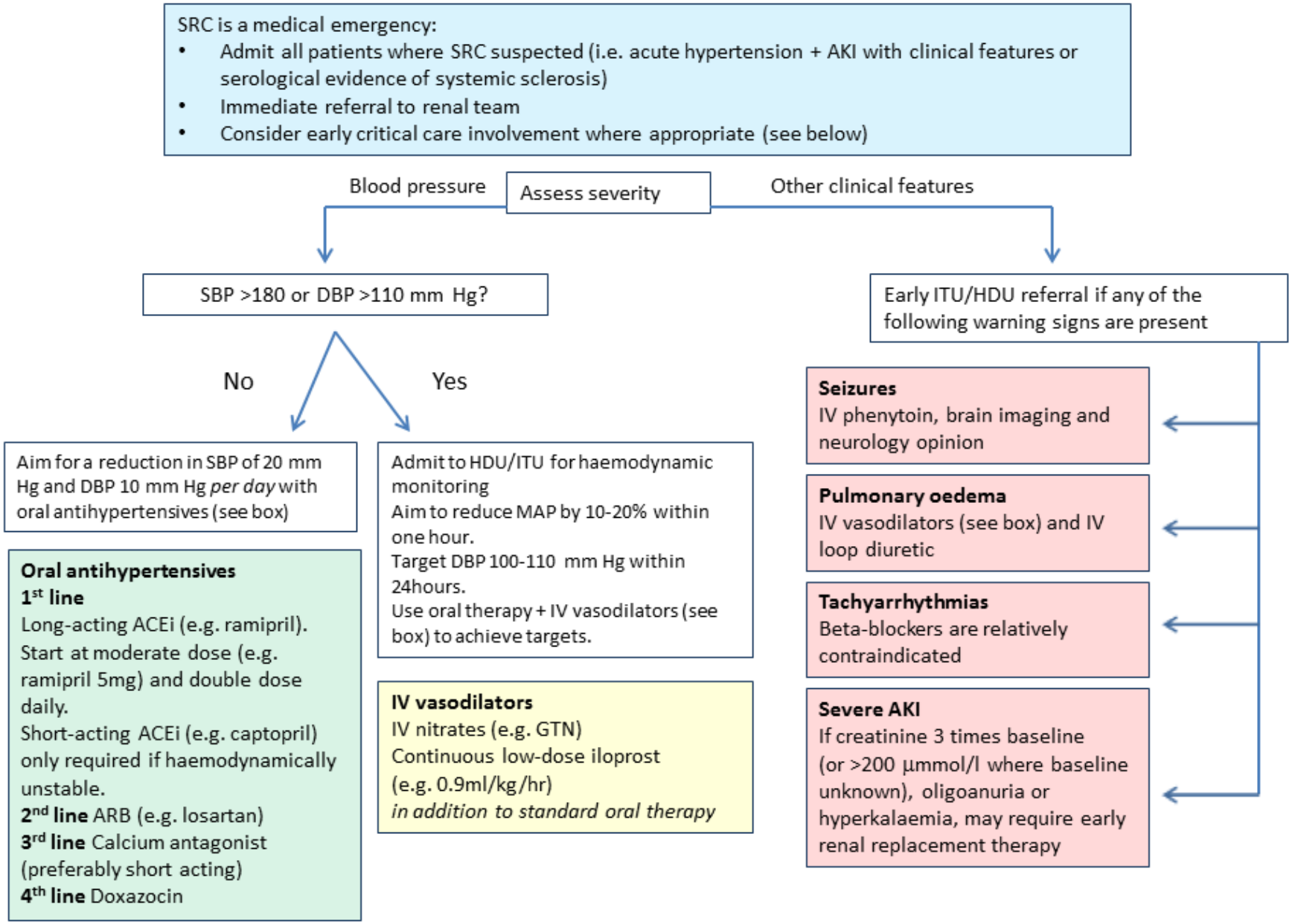

Figure 1: Management of scleroderma renal crisis.

ACEi – Angiotensin converting enzyme inhibitor, AKI - Acute kidney injury, ARB – Angiotensin receptor blocker , DBP - Diastolic blood pressure, HDU - High dependency unit, ITU - Intensive therapy unit, MAP - Mean arterial pressure, SBP - Systolic blood pressure.

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