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Points to consider in renal involvement in systemic sclerosis

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Abstract

This article discusses points to consider when undertaking a clinical trial to test therapy for renal involvement in SSc, not including scleroderma renal crisis. Double-blind, randomized controlled trials *vs* placebo or standard background therapy should be strongly considered. Inclusion criteria should consider a prespecified range of renal functions or stratification of renal function. Gender and age limitations are probably not necessary. Concomitant medications including vasodilators, immunosuppressants and endothelin receptor antagonists and confounding illnesses such as diabetes, kidney stones, hypertension and heart failure need to be considered. A measure of renal function should be strongly considered, while time to dialysis, mortality, prevention of scleroderma renal crisis and progression of renal disease can also be considered, although they remain to be validated. Detailed, pre-planned analysis should be strongly considered and should include accounting for missing data.

Key words: renal, kidney, systemic sclerosis, clinical trials, points to consider

Rheumatology key messages

- Randomized trials of 52 weeks to assess chronic renal involvement in SSc should be considered.
- Confounding illnesses, cutaneous disease and SSc subsets need to be considered in assessing renal involvement.
- Creatinine clearance, despite problems, is a reasonable outcome for SSc renal involvement.

REVIEW

Introduction

Many forms of kidney involvement are reported in SSc, although the most studied event and most dramatic is scleroderma renal crisis (SRC), which is seen today in ~3% of SSc patients [1]. SRC remains uncommon in lcSSc and the rate in the dcSSc group seems to be stable over time [2]. This aspect of SSc is well defined, but because it is rare, it requires large, long-term trials, which are not possible [3–8] and will therefore not be addressed here. Asymptomatic and slowly progressive renal involvement, on the other hand, is present in 60–80% of SSc patients, although clinically apparent renal involvement is uncommon. In more than half of asymptomatic SSc patients, renal function demonstrates clinical markers of renal damage (proteinuria, elevation of serum creatinine, hypertension, etc.) [9–11]. These patients, with evidence of underlying chronic renal disease but without confounding illnesses such as diabetes or hypertension existing prior to the onset of their SSc, may be the most appropriate patients for SSc renal outcome trials. We suggest points to consider when designing and conducting a clinical trial of non-SRC renal disease in SSc.

Trial design and duration

At present, there is insufficient evidence to definitively establish the design of studies regarding non-SRC renal disease in SSc. For this reason, expert opinion and experience are often relied upon in this points to consider. When relying on expert opinion, the designation EP will be used throughout.

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Double-blind, randomized controlled trials (RCTs) *vs* placebo or standard background therapy should be strongly considered [12–24] (EP). A study of non-SRC in SSc patients might be done in those who have mild renal compromise and up to a certain amount of proteinuria. Since many of these patients will have comorbid diseases (e.g. diabetes mellitus, hypertension, congestive failure) and/or use medications that could affect the outcome (e.g. antihypertensives, angiotensin-converting enzyme inhibitors), one could exclude such comorbidities or medications, include them in a regression analysis or consider other ways to allow for such potential confounders.

Because there is a lack of predictive markers of renal involvement in SSc, it is currently impossible to recommend a definitive duration for controlled trials. However, study durations of at least 52 weeks may be useful to assess improvement in renal function (EP). The following parameters can be considered, although, as noted below, most are not validated in SSc *per se*: change in blood pressure, serum creatinine, creatinine clearance (at baseline $<60\%$), proteinuria, urine creatinine:protein ratio (on spot urine), urinary sediment, time to a certain level of renal impairment, etc. [13, 14, 20–25] (EP). Open-label, long-term follow-up (such as follow-up for 1–4 years) can be considered for purposes of following adverse events and for determining definitive, dichotomous endpoints such as those outlined below.

Inclusion criteria

For uniformity of populations, most would consider limiting patients to those who fulfil ACR/EULAR criteria or the very early criteria for SSc [29–31]; patients can be grouped into subsets of diffuse or limited disease within the general definition, as these two groups of patients may have different proclivities for renal disease (EP). There are no data indicating a predilection by gender and nearly any age may be affected, so these two patient characteristics need not be considered.

As baseline renal function may determine outcomes or responses, strong consideration should be given to limiting patients to a specific range of renal function or to stratifying by renal function (EP); for example, limiting patients to those with a glomerular filtration rate (GFR) of 40–60 cm^3/min or stratifying patients into those with GFRs of 40–60 and >60 cm^3/min [11]. The utilization of patients with GFRs of 40–60 cm^3/min could theoretically improve sensitivity to change, as patients start with borderline function, allowing discernment of smaller changes to define progression to further renal dysfunction.

Concomitant therapies such as vasodilators, immunosuppressives and endothelin receptor antagonists could interfere with or confound the expected outcomes but ethically cannot be excluded, so one might consider accounting for their use in the study.

Exclusion criteria

Consideration of concomitant diseases is strongly recommended to prevent confounding. It may be necessary to exclude patients with overlap syndromes and concomitant illnesses or to stratify for these illnesses when analysing the study. Examples of diseases to consider include diabetes, kidney stones, arterial hypertension existing prior to the onset of SSc, vascular involvement of renal arteries, vesico-ureteric reflux, drug and/or toxic and/or other metabolic and/or post-infective induced nephropathy, heart failure, cancer, overlap with other diseases or connective tissue diseases such as vasculitides, APS, Goodpasture's syndrome and SLE (EP). A specific issue in renal involvement in SSc is ANCA-related glomerulonephritis [32–34], which should be carefully investigated and excluded from studies.

Outcome variables

Table 1 reviews the validity of the most commonly used measures of renal function in SSc. Serum creatinine concentration is commonly used as an index of renal function and has been validated in SSc [11, 25]. However, serum creatinine is modified by muscle mass and is not usually elevated until the GFR [11, 25] has fallen to $<50\%$ of normal. Inulin clearance remains the gold standard for the measurement of GFR [11, 20, 25, 35]. Multiple other outcome measures have been considered and are under investigation, including clearance methods employing radionuclides [11, 25]; creatinine clearance by the Modification of Diet in Renal Disease (MDRD) or Cockcroft–Gault formula may also be considered as indirect measures of GFR [25] (however, these have significant methodological problems that need to be considered); renal blood flow assessed by Doppler echography [20, 26] and markers of vascular injury, as well as other new markers. One could consider using any of these during a trial to validate them for future trials.

Renal survival (dialysis or transplantation), mortality, prevention of SRC or prevention of progression to chronic renal failure, the frequency and duration of dialysis and recovery of renal function may also be considered as outcome measures. Consideration should be given as to whether some of these will need to be validated in SSc before they can be used for registration trials [26–28, 36, 37, 38]. A real consideration for these clear dichotomous outcomes is that many of these latter methods require prolonged, large studies or follow-up if they are to be used as trial endpoints.

Analyses

Analysis should include, as a minimum, descriptive analysis and stratification of the population (if done as part of the study). Outcome statistical analysis can include analysis of variance, analysis of covariance, linear or logistic regressions, generalized estimating equations and survival analyses, among others. The primary outcome should be defined *a priori*. For proof-of-concept studies, testing for less traditional alpha values might be considered (e.g. alpha *P*-values of 0.10–0.15). A statistical power analysis should be considered before undertaking

Table 1 Validity of measures used when measuring renal involvement in SSc

Outcomes	Face	Construct	Criterion	Content	Reliability	Sensitive	Feasibility	Ready for clinical trials
Creatinine	Y	Y	Y	Y	Y	Y	Y	1°
Creatinine clearance (MDRD)	Y	Y	Y	Y	Y/N	Y	Y	1°
Proteinuria	N	Y	N	Y	N	Y	Y	2°
Renal blood flow	Y	Y	?	Y	?	?	Y	–
Renal histology	Y	Y	Gold standard	N	Y	N	N	–
Real survival (dialysis, transplant)	Y	?	Y	?	Y	N	N	–

Data taken from Merkel *et al.* [37]. ?: unknown; N: no; Y: yes.

the study. A strategy to account for missing data should be considered.

Conclusions

Clinically relevant renal involvement (non-SRC) in SSc is uncommon and randomized trials may require long-duration studies (because non-SRC renal progression is slow). Many non-SRC patients with renal involvement have common comorbidities and standard-of-care treatments cannot be denied. Innovative trial designs and outcomes (e.g. renal blood flow or surrogate biomarkers) may need to be considered, but such outcomes will require validation before being used.

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