RHEUMATOLOGY

Rheumatology 2017;56:v12–v16
doi:10.1093/rheumatology/kex198

Points to consider when doing a trial primarily involving the heart

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Abstract

Cardiac involvement contributes to the severity of SSc and should carefully be investigated and managed in SSc patients. Although it is commonly sub-clinical, once symptomatic it has a poor prognosis. Several complementary tools (circulating biomarkers, electrocardiography, echocardiography, scintigraphy or MRI) allow the assessment of all the various cardiac structures (endocardium, myocardium and pericardium) and heart function. Treatment remains empirical but cardiac trials in SSc can add data to the treatment of this complication.

Key words: systemic sclerosis, heart, heart failure, arrhythmia, pericarditis, cardiac fibrosis, myocarditis

Rheumatology key messages

- Primary heart involvement is common in SSc and all the cardiac structures can be involved.
- Inclusion or exclusion criteria for trials on cardiac involvement must be carefully assessed including non-invasive and, potentially, invasive measures.
- Cardiac domains to be investigated include survival, myocardial contractility, cardiac rhythm or pericardial changes, or all of them.

REVIEW

Introduction and background

Cardiomyopathy in SSc is often subclinical but if symptomatic has a poor prognosis. Nearly any structure of the heart and pericardium can be affected by SSc. When sensitive tools are used it has been estimated to occur in up to 100% of SSc patients. Once cardiac involvement is clinically evident, it is recognized as a poor prognostic factor and a major cause of SSc-related mortality [1–6]. A meta-analysis suggested that cardiac involvement could be relevant in about 10–15% of SSc patients [7].

With the improvement in renal outcome, cardiac and pulmonary involvements have become major factors in determining the prognosis and outcome of this disease. Among 234 fatalities during prospective follow-up in the European Scleroderma Trials and Research group (EUSTAR) database, 128 died from causes related to SSc with cardiac involvement explaining 26% of cases (33 deaths). Amongst the cardiac causes of death 51% died of ventricular failure and 42% died because they had an arrhythmia [6].

Cardiac involvement may affect the endocardium, myocardium and pericardium, separately or concomitantly. As a consequence, pericardial effusion, auricular and/or ventricular arrhythmias, conduction disease, valvular regurgitation, myocardial ischaemia, myocardial hypertrophy and heart failure have been reported. In addition, pulmonary arterial hypertension, renal and lung involvement can adversely affect cardiac status. However, one should keep in mind that primary myocardial involvement is one of the most frequent cardiac complications of the disease (when sensitive tools are used) and may be life-threatening. This work will focus on primary myocardial involvement in patients without systemic or pulmonary hypertension and without significant renal or parenchymal involvement of the lung and will suggest points to consider when designing a trial to treat cardiac involvement in SSc.

The pathogenesis of primary heart involvement is not well defined, but SSc vascular lesions generally result in

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Submitted 30 June 2015; revised version accepted 12 April 2017

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impairment of the microcirculation. Despite the predominance of vascular abnormalities and documented ischaemia, the prevalence of atherosclerotic coronary artery disease seems slightly higher in SSc compared with that of the general population. Although higher than in the general population, it occurs less frequently than in more inflammatory conditions like RA.

Unfortunately, valid measures of heart involvement in SSc are few. Objective measures such as EKG, 24 h-Holter [8–11], echocardiography [12–16], scintigraphy (thallium tracer to measure perfusion and technetium to measure contractility) [17–20], and MRI [21–26] are not validated prospectively in SSc, or at best very partially validated. The validity of these measures in other cardiac conditions is summarized in Table 1.

Although many of these tests are used in routine clinical practice, their validation is incomplete and remains an issue of the highest priority in SSc. The authors therefore recommend that some degree of validation of some of these tests should be undertaken either before starting heart trials or concomitant with heart trials. Some of these tests may be used as exploratory or even secondary outcome measures in clinical trials but should not yet be used as primary outcome measures in cardiac SSc. Another critical issue is the low incidence of cardiac events and, therefore, it seems reasonable to combine different cardiac outcome to obtain a sufficient number of events.

With these caveats, we recommend the following points to consider for testing therapies for SSc cardiac disease of primary origin. To make the recommendations comprehensible, the heart involvement will be divided into three areas: contractility, arrhythmias, pericardium. Where commonalities exist, recommendations will refer to the whole heart. Where separation is necessary, recommendations will be separated into paragraphs.

The hypothesis supporting a clinical trial in cardiac SSc would be that therapy of the myocardial involvement with the relevant therapy will improve long-term outcomes (e.g. mortality from cardiac causes, time to clinical worsening, occurrence of overt dysfunction, arrhythmia, pericarditis) of SSc-cardiac involvement

In clinical trials looking at cardiac heart failure from other origins than SSc, the main outcome measures are global mortality, cardiovascular mortality or first hospitalization. The low prevalence of significant SSc cardiac disease would preclude the possibility of recruiting enough patients to use such outcomes. Other key outcomes are left ventricular (LV) ejection fraction, dyspnoea class, natriuretic peptides or quality of life, which are relevant in SSc and are more feasible than clinical events. Nevertheless the sensitivity to change of these cardiac outcomes would need validation in SSc.

Design and duration

Strong consideration should be given to trials that are randomized, double blind controlled trials either on standard therapy background or *versus* an active control. While not evidence-based, the below represent reasonable recommendations. For improvement of long-term outcomes the trial duration should be of >12 months taking into account that trials of 1–3 years' duration are frequent in other indications.

Outcome variables

Outcome variables used in cardiovascular trials can be considered, including cardiac mortality (as in other indications, this needs to be adjudicated by a separate, dedicated committee); myocardial contractility evidenced by LV or right ventricular (RV) dysfunction on echocardiography (reduced ejection fraction <50%), congestive heart failure based on symptoms and brain natriuretic peptide (BNP) or N-terminal prohormone of BNP (NT-pro-BNP); new onset of sustained atrial fibrillation; pericardial effusion (moderate or large pericardial effusion defined by an effusion >10 mm or circumferential). These outcome variables, although not validated in SSc, might be considered separately or in combination and may be validated as part of the trial if they are considered as exploratory outcomes.

Other outcomes could be regarded as exploratory (if carried out without validation during the trial) or secondary (if validation is carried out before study) such as the following: symptoms, among which dyspnoea is probably primary (measured using a validated scale); measures of contractility such as pulsed Doppler or scintigraphy or MRI [with measurement of LV ejection fraction (LVEF), RV ejection fraction (RVEF), LV filling, RV filling]; biomarkers; and measures of rhythm or conduction.

Table 1 Validity of measures or tools in general cardiac conditions

	Face	Content	Construct	Criterion	Reliability	Sensitivity to change	Feasibility
EKG	Y	Y	Y	PV	N	N	Y
Echocardiography	Y	Y	Y	Y	Y	Y	Y
Scintigraphy							
Thallium	Y	Y	Y	PV	Y	N	Y
Technetium	Y	Y	Y	PV	Y	N	Y
Cardiac MRI	Y	Y	Y	Y	Y	Y	N
Natriuretic peptides	Y	Y	Y	PV	Y	Y	Y

Y: Yes; N: No; PV: partially validated.

Survival data could be considered for collection although it is unlikely to be a discriminative outcome measure because death is rare in SSc clinical trials. In non-SSc trials that study cardiac involvement, outcome measures that are considered include hospitalization, clinical worsening, death and functional class. These measures would require validation in SSc, if used.

Biomarkers have been surrogate markers in various cardiac conditions and accumulating data point to their apparent usefulness in SSc, particularly for natriuretic peptides (other than NT-pro-BNP) and troponin [27].

Although not yet endorsed by any guideline, given the prognostic significance of clinically relevant arrhythmias and conduction defects and the poor sensitivity of electrocardiography, 24-h Holter monitoring might be included in the assessment tools as an exploratory outcome [28]. The six-minute walk distance is not recommended as an outcome for measuring cardiac involvement in SSc [29, 30].

Inclusion criteria for a cardiac treatment trial

Criteria for inclusion to consider include SSc by ACR/EULAR 2013 classification criteria and/or the LeRoy sub-classification; patients with a specific (or several) cardiac abnormalities; gender; age $\geqslant$18 for studies of adults; disease duration 5–20 years (as cardiac involvement is thought a late complication in SSc); allowing immunosuppressive medications, pulmonary or GI medications (all if stable $\geqslant$3 months). There needs to be careful consideration regarding concomitant medications used to treat RP, pulmonary drugs plus cardiac medications (as they could interfere with the test therapy, if allowed, they need to be carefully accounted throughout). Patients with minor contractility alterations could be considered (LVEF $<$55% but $>$40%) including those with abnormal myocardial velocities/strain or diastolic dysfunction.

Exclusion criteria for a cardiac treatment trial

Exclusion criteria to consider include symptomatic heart involvement: dyspnoea class III or IV, symptoms of heart failure, arrhythmia, symptomatic pericarditis, LVEF $<$ 40%; concomitant diseases such as pre-capillary pulmonary arterial hypertension (PAH) (defined by haemodynamic measurements through heart catheterization); severe lung disease [31]; active myositis [32]; overlap with lupus, polymyositis or RA; ischaemic heart disease; selected laboratory abnormalities (may be governed by the particular therapy); concomitant medications (may be governed by the particular therapy); renal crisis (past or present); renal insufficiency [33]; renal dialysis or total parenteral nutrition (unless the stopping of these modalities is to be studied as an outcome); and previous haematopoietic stem cell, lung, renal, cardiac transplantations. As in any trial, laboratory abnormalities and concomitant therapies that are affected by the test therapy need to be considered as possible exclusion criteria.

If there is myocarditis, this needs urgent attention as it has a different prognosis from myocardial involvement due to microcirculatory impairment such as is expected in SSc *per se* and specific immunosuppressive therapy might be needed.

Analysis

The analysis plan should be pre-specified and should include descriptive analysis that is sufficiently clear to understand the groups involved and their similarities/differences. Primary and secondary/exploratory outcomes should be delineated. Power analysis should be considered, when appropriate. Consideration of how to deal with missing data should be part of the analysis plan. Adverse events should be systematically included and carefully described.

Conclusion

Primary heart involvement is common in SSc and all the cardiac structures can be affected. When clinically relevant, cardiac involvement in SSC is a complication with potentially high morbidity and mortality. Despite this, long duration trials (1–3 years) in late disease (5–20 years) may be needed. Exclusion criteria will require consideration of the multiple medications and concomitant illnesses that can confound cardiac evaluation, including PAH. Cardiac domains that should be considered include survival, myocardial contractility, cardiac rhythm and/or pericardial changes.

Supplement

This paper is part of the supplement titled Points to consider: systemic sclerosis and was funded by an unrestricted educational grant from EULAR.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: Y.A. received research grants or honorarium from Actelion, Bayer, Bristol-Myers Squibb, Boehringer, ChemoMab, Genentech/Roche, Galapagos, Inventiva, Medac, Pfizer, Sanofi/Genzyme and Servier. O.D. had consultancy relationships and/or has received research funding from 4 D Science, AbbVie, Actelion, Active Biotec, Bayer, BiogenIdec, Bristol-Myers Squibb, Boehringer Ingelheim, ChemoMab, EpiPharm, espeRare foundation, Genentech/Roche, GlaxoSmithKline, Inventiva, iQone Healthcare, Lilly, medac, Mepha, MedImmune, Pharmacyclics, Pfizer, Sanofi, Serodapharm and Sinoxa in the area of potential treatments of scleroderma and its complications and has a patent mir-29 for the treatment of systemic sclerosis licensed. D.K. is supported by the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases K24 AR063120 and has received investigator-initiated grants and acts as a consultant to Actelion, Bristol-Myers Squibb, Bayer, Corbus, Cytori, ChemoMab,

GlaxoSmithKline, Genentech/Roche and Sanofi-Aventis. D.E.F. has received grant/research support from AbbVie, Actelion, Amgen, Bristol-Myers Squibb, Corbus, National Institutes of Health, Novartis, Pfizer and Roche/Genetic and consulting fees from AbbVie, Actelion, Amgen, Bristol-Myers Squibb, Cytori, Novartis, Pfizer and Roche/Genentech. All other authors have declared no conflicts of interest.

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