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Points to consider—Raynaud's phenomenon in systemic sclerosis

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Abstract

RP is an exaggerated vasospastic response to cold or emotion. Randomized, double-blind, placebo-controlled trials with either parallel group or cross-over trials should be mainly considered. Cross-over design, which is good for early phase trials of immediate or very short-term outcomes, is important in a condition as heterogeneous as RP: a wash-out period between treatment arms should always be included to minimize the possibility of a period (carry-over) effect. Duration of RP trials is usually constrained by the need to complete these over a single season, usually winter when the weather is colder. For cross-over trials, each treatment arm tends to be 4 weeks or less. Frequency and duration of attacks, and the Raynaud's Condition Score are widely used outcome measures. There is increasing interest in physiological laboratory endpoints, for example laser Doppler imaging at least for early phase trials.

Key words: systemic sclerosis, Raynaud's phenomenon, connective tissue diseases, rheumatic diseases, clinical trials, nailfold capillaroscopy, digital ulcers, vasodilators, gangrene, microcirculation

Rheumatology key messages

- The majority of patients with SSc-related RP should be offered treatment.
- Randomized, double-blind, controlled trials to test new RP therapies remain the standard.
- Most definitive trials of RP will need to be multicentre to achieve adequate power.

REVIEW

Introduction

RP is essentially an exaggerated vasospastic response to cold or emotion (stress) [1, 2]. In the classic triphasic response, the digits turn white (ischaemia), then blue (hypoxia) and then red (reperfusion). When mild, RP is uncomfortable but has minimal impact on quality of life [3]; this is the situation for many patients with primary (idiopathic) RP.

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At the other extreme, RP, when associated with CTDs such as SSc (secondary RP), can progress to irreversible tissue injury with skin ulceration and sometimes gangrene; digital skin ulceration occurs in the order of 50% of patients (probably more) at some point in their disease course [4–6]. Gangrene may also occur in patients with underlying CTD, particularly SSc, although much less frequently than digital ulceration [7].

These points to consider for a clinical trial in SSc derive from general experience, literature when available and consensus among experts. Thus while the evidence may be Class A through D, the Recommendations are often Class C, except where noted.

Objective

To suggest points to consider in conducting clinical trials in SSc-associated RP. Clinical trials specifically targeting digital ulceration (an end point of severe digital ischaemia) are considered elsewhere.

Trial design

We recommend that strong consideration be given to designing randomized, double-blind, placebo-controlled

trials, although sometimes a comparator drug (e.g. a calcium channel blocker [8]) is included rather than placebo. Trials may be either parallel group [9–12] or cross-over trials [13]. A cross-over design, which is good for early phase trials of immediate or very short-term outcomes, has the advantage of allowing each patient to act as his/her own control, and this is important in a condition as heterogeneous as RP. A disadvantage of the cross-over trial is that there may be a period effect, although a washout period between treatments [13] can minimize this.

Single-dose studies, examining acute effects of vasodilators, can be considered at an early stage of drug development [14] and are usually of cross-over design. Duration of RP trials is usually constrained by the need to complete these over a single season, usually winter when the weather is colder in the latitudes where there are large temperature differences. For this reason trial duration is usually short. For parallel group trials, duration has usually been 4–6 weeks [9, 11, 15] but may be up to 4 months [16].

For cross-over trials, each treatment arm tends to be 4 weeks or less [13]. If the study question is more broad ranging than short-term safety and efficacy in RP, for example, if effects on peripheral vascular structure and/or vascular remodeling are being examined (even if indirectly), then a longer duration may be appropriate [10]. Because SSc-related RP is a long-term condition, there is a good rationale for long term trials (i.e. 2–3 years) [10].

Methods

Inclusion criteria

In addition to having SSc and RP, a patient must have sufficiently frequent attacks to allow a realistic measurement of improvement. Therefore, studies usually specify for inclusion a minimum number of attacks per week [9, 11, 15].

Inclusion criteria usually include the ACR/EULAR 2013 criteria [17, 18] but may also allow recruitment of patients who fulfil any validated criteria for SSc. The LeRoy and Medsger criteria include either an SSc-specific autoantibody and/or abnormal nailfold capillaroscopy [19, 20] and so allow inclusion of patients likely to have SSc (and who often have severe RP) but who do not (at least as yet) fulfil the 2013 criteria. Other options such as stratification by RP type will allow for balance between the treatment groups.

Confounding variables

Because most drugs examined in clinical trials of RP have vasoactive effects, patients who have any underlying disease that might jeopardize assessment of vasodilation, or in whom special caution is required, are generally excluded, for example, patients with ischaemic heart disease or cerebrovascular disease.

In phase 3 trials inclusion criteria should be as broad as possible, so if potential confounding medications are to be allowed, then washout, stratification, stability on the medications with continued frequency of RP and accounting of potential confounding medications will be important.

Smoking has effects on the vasculature. Although it could be strongly argued that smokers should be excluded from clinical trials of RP, this may make results of the study less generalizable. If smokers are to be allowed, the duration and intensity of smoking should be recorded and accounted in the analysis. Therefore data on smoking should be collected at the baseline visit.

As for concomitant and confounding medications, confounding illnesses need to be considered and accounted. They can be excluded, although this may hinder recruitment. Recording the concomitant illnesses and including them in the analysis and/or allowing a limited number of concomitant illnesses that are stable are other alternatives.

Outcome variables

Frequency of Raynaud's attacks, duration of Raynaud's attacks and the Raynaud's Condition Score are outcome measures [21] that are sensitive to change and that are widely used in clinical trials. The only fully validated Raynaud's phenomenon measure is the Raynaud's Condition Score [20]. It is a daily self-assessment incorporating frequency, duration, severity and impact of RP attacks on a 0–10 ordinal scale [21].

Other measures that can be used are patient's and physician's assessment of RP activity on a visual analogue scale measures of disability (e.g. the HAQ Disability Index) and of psychological impact [21].

If these measures, which are not validated in SSc, are to be used as primary measures, it is advisable to do a small study to validate them before using them as a primary measure in a phase 3 trial. If it is chosen to use one of the unvalidated measures without prior validation, it might be advisable to use it/them as a secondary or exploratory measure or use it/them in phase 2 trials [11].

A recent large study showed that a combination test improved test characteristics compared with individual measures. This should be considered during trial design [22]. There is increasing interest in physiological laboratory endpoints, for example, thermography, laser Doppler imaging [23] and finger systolic pressure measurements [24]. Although most require further evaluation, these are possible endpoints for early phase trials, although not feasible for phase 3 multicentre clinical trials.

Exploratory endpoints may be appropriately investigated in small open-label [25] or single dose studies [26]. Microvascular structural abnormalities, as assessed by nailfold capillaroscopy [27], may be an end point in clinical trials of vascular remodelling agents in patients with SSc-related RP, as recently shown [28–30]. Other end-points may be appropriate depending on the mechanism of action of the drug being evaluated [31, 32]. Digital ulceration is often included as an end point in clinical trials of RP but is discussed elsewhere.

Analysis

A full analytic plan is required before starting a clinical trial. At a minimum, analyses should include patient disposition

(as a table or figure) and another table describing patient groups at enrolment including demographics, ancillary disease characteristics and baseline values for outcome measurements. Comparisons among the groups to establish baseline uniformity are strongly recommended.

Most definitive trials of Raynaud's phenomenon will need to be multicentre to achieve adequate power and power analysis prior to starting a trial should be strongly considered, especially for phases 2 and 3 trials. Phase 1 trials may not require power analysis. A predefined analysis plan that includes an algorithm to deal with missing data and drop-outs (and the reasons for dropping out) should also be strongly considered.

Safety and publication

Finally, safety issues must be carefully evaluated in designing new trials [33]. Results should be presented wherever possible according to the CONSORT guidelines [34].

Conclusion

The majority of patients with SSc-related RP should be offered treatment. Randomized, double-blind, controlled trials to test new RP therapies remain the standard. Most trials of RP will need to be multicentre to achieve adequate power.

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