Digital ulcers and outcomes assessment in scleroderma

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Ischaemic ulcerations of the fingertips are common in SSC and a source of pain and disability. Healing has been demonstrated with intravenous iloprost and two studies with bosentan have demonstrated reduction in the occurrence of new digital ulcers (DUs) over 4–6 months of treatment. Both bosentan studies showed no benefit in healing DU and because of this, net DU burden is no different between drug and placebo and accordingly secondary measures of outcome including pain and hand functionality are inconsistently affected. While it is likely an artefact, it remains unclear that current outcome measures including the Scleroderma Health Assessment Questionnaire (SHAQ), the UK Functional Score and the Michigan Hand Questionnaire are sensitive to change in the domain of digital ischaemia. Major events including amputation and hospitalization occur too infrequently to serve as practical measures of outcome in trials. Future studies of DU therapies will benefit from development of an ulcer-specific measure of outcome.

KEY WORDS: Digital ulcers, Scleroderma, Systemic sclerosis, Outcome measures.

Introduction

Oclusive vasculopathy is the hallmark lesion of all forms of SSc. In addition to RP, ~30% of the patients per year develop ischaemic digital tip ulcerations [digital ulcers (DU)] [1]. DUs are a source of pain and reduced functional capabilities and represent the initial event in a sequence of events leading to tissue loss, infection, gangrene and occasionally amputation. For this reason, a strategy for facilitating healing and/or preventing occurrence of DUs is mandatory in SSc patients.

Many factors are implicated in the pathogenesis of critical tissue ischaemia, all of which apply to consideration of DUs in the setting of SSc. These include (i) impaired afferent vasoemotion (RP, intimal hyperplasia of arterioles), (ii) impaired efferent vaso-motion (impaired venous drainage secondary to local extrinsic pressure effects), (iii) disrupted microvasculature including capillary and lymphatic, (iv) leucocyte and platelet activation and adherence to injured endothelium and (v) haemorheological alterations typical of SSc. The disease is also characterized by insufficient angiogenesis and defective vasculogenesis contributing further to tissue ischaemia. The refractory nature of DUs may in fact be explained by these complex pathophysologies although many approaches to intervention seem possible.

The clinical impact

Two large retrospective studies have attempted to define the clinical impact of DUs. The Pittsburgh Scleroderma Database identified 2080 subjects, predominantly Caucasian women, and determined that 58% of them had experienced at least one DU during their course of SSc [2]. In 32% of the cases, DUs persisting for >6 months were associated with severe complications as gangrene or need for amputation or sympathectomy in 9.5%. In the Royal Free Hospital database, 17% of 1168 patients were categorized as having ‘severe’ digital vasculopathy including gangrene or critical digital ischaemic events [3]. DUs are encountered regularly in both lcSSc and dcSSc. Smoking is associated with more persistent and severe ulcers.

In the RAPIDS-2 trial of bosentan vs placebo, 11% of 198 subjects had undergone amputation with a calculated annual incidence of 1–1.4% (Seibold et al., submitted). These data are similar to the Pittsburgh database wherein 11% of the subjects had undergone amputation. Of those patients with DUs persisting for >6 months, amputation rates increased to 22%. Precise data on need for hospitalization for intravenous antibiotic, pain management or parenteral prostacyclin are lacking. In the Royal Free Hospital database, 38% had been admitted for hospitalization although elective use of iloprost was a dominant explicit reason [3].

The assessment of DUs

Assessment of DU impact is challenging. In fact, assessment of DUs in the context of therapeutic trials offers some surprising issues. A critical base issue is how to determine whether or not a fingertip lesion is indeed an ulcer as opposed to a local infection, an area subtended by calcinosis or an area of ischaemic demarcation. In a recent exercise, experts rated photographs of various digital lesions. Intra-observer variability was excellent (κ = 0.81) but inter-observer variability was disappointingly low (κ = 0.48). In short, an individual clinician seems reasonably consistent but reliable guidelines for judging digital lesions will need to be developed to assure clinical research consistency [4]. In the past, the efforts to ‘measure’ the length and depth of DUs as outcome have failed. Therefore, the only direct parameter remains today the healing of DUs and as an indirect parameter the measurement of hand function. The clinical utility of healing DUs was established in a large controlled trial of intravenous iloprost [5]. Using a rigorous definition requiring healing of at least 50% of all ulcers present at baseline, HAQ scores improved statistically significantly at 3, 6 and 9 weeks of follow-up. However, two major placebo-controlled trials of bosentan failed to affect overall HAQ although small effects were noted in subdomains of the HAQ, e.g. dressing ability [1, Seibold et al., submitted]. In both trials, bosentan was ineffective in healing of established DUs and no effect on RP was shown. Benefit of bosentan was limited to reduction of the occurrence of new DUs (30–48%). Although this effect was statistically significant, there remain critically important issues in defining the attendant benefits to treated patients. In RAPIDS 2, a large trial (198 subjects) of 24-week duration, the small effect of prevention was subsumed by higher rates of healing on placebo. Thus at the end of 24 weeks of drug therapy, there were no differences between active treatment and placebo in net DU burden, pain, measures of activities of daily living by HAQ or UK Functional Score (UKFS) or in hospitalization rates (Seibold et al., submitted).

Clinical outcomes instruments have been developed which focus on patient ratings of hand function including the UKFS [6] and the Michigan Hand Questionnaire [7]. Pilot validation studies...
have suggested that SSc hand function is dominantly an issue of ability to grip objects and that fingertip lesions are a minor contribution to patient ratings of hand functionality.

Conclusions
Thus, in the area of DUs, the challenges to the clinical research community are considerable. Subjects enjoy reduced pain and improved function from agents with strong yet short-lived effects such as iloprost. Agents with more subtle effects, e.g. bosentan, effects on prevention offer an immeasurably low benefit on pain, function and quality of life and cannot be endorsed as appropriate for the overwhelming majority of patients. It is possible that development of clinical instruments of high specificity to the clinical impact of DUs would facilitate future trials of other potentially useful interventions.

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References

Rheumatology key messages
- Digital ischaemic ulcers are common in scleroderma.
- Intravenous iloprost facilitates healing whereas bosentan has effects in preventing ulcer occurrence.
- Studies of DU-related outcomes are rendered difficult by clinical definitions, insensitivity to change of functional measures and low event rates of major complications.
- An outcome panel specific for assessment of DUs is needed.