Complete Ulcer Healing as Primary Endpoint in Studies on Critical Limb Ischemia? A Critical Reappraisal

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Objectives. Although complete ulcer healing is the mandatory primary efficacy criterion in current European guidelines for drug trials in critical limb ischemia (CLI), the appropriateness of this endpoint has been questioned for some time. We carried out a systematic review to assess the value of this endpoint in studies on reconstructive measures, considered to be the standard of care for CLI.

Methods. A computerized literature search (1985–2005) was performed to track down clinical studies on endovascular and surgical interventions by using the search terms CLI and ulcer healing and their synonyms.

Results. 1,914 papers on revascularization in CLI were identified. Complete ulcer healing was reported in 17 studies (0.9%). Among these, there were no randomized controlled trials, five prospective cohorts on endovascular procedures, and six retrospective cohorts for endovascular and surgical procedures, respectively. If healing rates or time to ulcer healing were available, they differed greatly between the studies without consistent correlation to types of therapy.

Conclusions. In past and current literature, complete ulcer healing is not a consistently reported criterion for success of revascularization in CLI. Thus, its appropriateness for efficacy assessment of drug studies in CLI patients has to be questioned.

Keywords: CPMP guidelines; Ulcer healing; Critical limb ischemia (CLI); Clinical studies; Revascularization.

Introduction

The European Committee for Proprietary Medicinal Products (CPMP) guidelines provide thorough methodological criteria for the conduct of confirmatory clinical drug trials. They are well accepted and form the basis for creating evidence in current medicine. For drug trials in patients with critical limb ischemia (CLI), the CPMP guidelines demand complete ulcer healing as the primary efficacy criterion.1 The appropriateness of complete ulcer healing as the sole primary efficacy parameter for drug trials in CLI has been questioned,2 since clinically important aspects such as time to and duration of response to treatment or the functional status of the patient are not considered. Notably, currently licensed and accepted drugs for CLI have been tested using a combined clinical endpoint consisting of partial and complete ulcer healing.3–9 Thus, the demand for complete ulcer healing as the sole primary efficacy parameter for confirmatory trials poses substantial difficulties to the assessment of already approved drugs and the implementation of future drug trials in CLI patients.

Surgical or endovascular revascularization is regarded as the standard of care for treating CLI patients. Hence, it is of interest to analyse whether and to what extent complete ulcer healing is used as a primary efficacy parameter in studies on reconstructive measures. We have therefore performed a systematic review of the literature (i) to provide information on to what degree complete ulcer healing is used as an
efficacy parameter in studies on endovascular or surgical interventions (ii) to evaluate the figures for complete healing rates and healing times in revascularization studies, and (iii) to discuss whether in the view of the results presented, complete ulcer healing may be considered appropriate as a sole primary endpoint for efficacy in CLI drug studies.

Methods

Search strategy

Computerized searches of the English and German medical literature from January 1985 to December 2005 were performed on Medline, BIOSIS, EMBASE and SciSearch. In addition, reference lists of retrieved articles were evaluated to identify relevant publications that might have been missed in the electronic database searches. Search terms were looked for in the title, abstract and keywords fields. To find out specifically how many of all revascularization studies focus on ulcer healing, first all studies dealing with endovascular and surgical interventions in CLI were identified, followed by scanning them for the term ulcer healing. Apart from the search terms CLI and ulcer, common synonyms of these terms were also employed: critical limb isch(a)emia, critical leg isch(a)emia, chronic critical leg isch(a)emia, end-stage isch(a)emia, limb-threatening isch(a)emia, isch(a)emia of the lower limb, lower limb isch(a)emia, Fontaine stage IV, PAOD, PAD, peripheral (arterial) occlusive disease stage IV, POAD, peripheral occlusive arterial disease, PVD, peripheral vascular disease; isch(a)emic ulcer, lower extremity ulcer, ulceration, isch(a)emic ulceration, chronic ulceration, ulcer area, isch(a)emic lesion, trophic lesion, chronic wound, gangrene, tissue loss.

Selection criteria

Reviews, case reports and studies with less than 10 patients were not eligible. Studies were selected for analysis if they fulfilled the following criteria: Ulcers had to be of ischemic origin, hence studies with neuropathic, postoperative, mixed arterial/venous, and pressure ulcers were excluded, as were those with ulcers due to thromboangiitis obliterans. Only studies applying surgical or interventional therapeutic measures that are recommended in the relevant guidelines were taken into account, which excluded such measures as spinal cord stimulation or sympathectomy. After checking the publications, just those studies were selected that presented clear quantitative data on rates of complete healing and the time needed for healing.

Results

The computerized search identified 1914 studies dealing with surgical or endovascular interventions in CLI. After searching the retrieved articles for the term ulcer healing and its synonyms, only 88 remained (Fig. 1). On carefully checking these papers and applying the inclusion and exclusion criteria mentioned above, just 17 studies were considered acceptable for the present review, namely 6 bypass studies and 11 studies on endovascular interventions, some of which were combined with bypass surgery. None of the 17 studies was randomized or controlled, and only 5 were prospective. In none of the prospective studies, however, was complete ulcer healing defined as the only primary efficacy endpoint. In all studies and surveys, respectively, ulcer healing was one of several efficacy parameters such as limb salvage or patency rates. Nearly all trials included diabetic as well as non-diabetic patients. A characterisation of disease severity of PAD at baseline in terms of ankle pressure, ankle-arm-index or equivalent parameters (toe pressure, tcPO2, plethysmography) was available only in two studies. Only two trials presented exact data on healing rates separately for diabetic and non-diabetic patients.

Fig. 1.
non-diabetic patients. Due to the great heterogeneity of all studies, a pooled analysis of the data was not possible.

**Ulcer healing following vascular surgery**

No prospective studies in vascular surgery with data on complete ulcer healing and healing times were found. Only 6 retrospective surveys reported on such data. Apart from debridement, an intensive special wound treatment (e.g. skin grafting, fibroblast-derived dermal substitute) was utilized in two studies. The four remaining studies did not provide any details on local wound treatment. In all studies minor amputations were performed if appropriate, to improve wound healing. Moreover, in two studies clinical outcome was influenced by secondary interventions. While exact figures on repeat operations (176 interventions in 112 patients) were given in one of these papers, no such data were given in the other. Two studies evaluated ulcer healing only in patients with grafts that had remained patent throughout the entire follow-up.

Healing rates (37–96%), and particularly healing times (0.4–48 months), differed considerably throughout the studies with a broad variability of follow-up ranging from 6 months to 5 years (Table 1).

**Ulcer healing following endovascular or combined endovascular and surgical intervention**

Six retrospective surveys and 5 prospective but uncontrolled studies on interventional measures were identified that provided data on complete ulcer healing and healing times. As with the vascular surgery trials, healing rates (15–100%) as well as healing times (1–30 months) showed large variations among the studies and included almost always minor amputations as a part of the therapeutic strategy (Table 2).

In four studies the reported healing rates did not relate to the entire study population, but only to successfully recanalized patients or those for whom complete follow-up data were available. In two studies the results of two differently treated patient groups (PTA and bypass) were evaluated together. One retrospective survey thoroughly investigated wound healing in 85 patients, among them “many” diabetics (no figures reported). These patients received comprehensive local ulcer management (e.g. topical growth factors) in a specialized wound care center in addition to endovascular interventions. In contrast, no details of local ulcer treatment were given in eight studies. Secondary interventions were performed in all but two of the studies.

**Discussion**

As the present review documents, ulcer healing is rarely reported as an efficacy parameter in clinical studies on revascularization therapies in CLI. Less than 1% of all studies provided data on complete ulcer healing and healing times. Most notably, among these there was no single randomized controlled study. Methodological quality of the studies was poor and varied considerably so that none of the

### Table 1. Studies with complete ulcer healing following vascular surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>CLI-patients (n)</th>
<th>Healing time</th>
<th>Complete ulcer healing including minor amputation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichmann et al., 1990</td>
<td>retrospective</td>
<td>80 (34 diabetics)</td>
<td>2.2 years (mean)</td>
<td>68% after 5 years</td>
</tr>
<tr>
<td>Nicoloff et al., 1998</td>
<td>retrospective</td>
<td>112 (53 diabetics)</td>
<td>range: up to 5 years</td>
<td>76% at last follow-up</td>
</tr>
<tr>
<td>Brochado Neto et al., 2000</td>
<td>retrospective</td>
<td>11 (4 diabetics)</td>
<td>5.2 months (mean)</td>
<td>64% at last follow-up</td>
</tr>
<tr>
<td>McCulloch et al., 2003</td>
<td>retrospective</td>
<td>74 (36 diabetics) (93 limbs)</td>
<td>range: 0.4–48.3 months</td>
<td>37%</td>
</tr>
<tr>
<td>Woelfle et al., 2003</td>
<td>retrospective</td>
<td>34 (27 diabetics)</td>
<td>19 months (median)</td>
<td>51%</td>
</tr>
<tr>
<td>Woelfle et al., 2003</td>
<td>retrospective</td>
<td>211 (94 diabetics)</td>
<td>range: 6–43 months</td>
<td>66%</td>
</tr>
</tbody>
</table>

* in patients that healed.

b within follow-up.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>CLI-patients (n)</th>
<th>Revascularization</th>
<th>Healing time</th>
<th>Complete ulcer healing including minor amputation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al., 1990</td>
<td>prospective not randomised uncontrolled</td>
<td>27 (17 diabetics)</td>
<td>laser angioplasty</td>
<td>6–24 months</td>
<td>Only 18 successfully recanalized patients were evaluated: 31% (5/18)</td>
</tr>
</tbody>
</table>
| Crew et al., 1994   | retrospective                        | 85 ("many" diabetics) | (a) iliac stent (7 limbs)  
(b) PTA femoropopliteal (42 limbs)  
(c) rotational atherectomy tibioperoneal (47 limbs)  
plus comprehensive wound management in a specialized wound care center | 5 months (mean)  | Results (after 5 months) include additional bypass surgery because of restenosis:  
(a) 100%  
(b) 90%  
(c) 72% |
| London et al., 1995 | retrospective                        | 53 (26 diabetics) | PTA iliacal, femoropopliteal, infrapopliteal                                     | 7.5 months (median)  | 79% (27/34) of limbs after 7.5 months (median) |
| Konradsen et al., 1996 | retrospective                       | 39 (15 diabetics) | 9 PTA  
33 bypass                                                                 | 6 months  | data of all patients with different interventions:  
55%  
70%  
75% |
| Hanna et al., 1997  | prospective not randomised uncontrolled | 29 diabetics     | PTA infrapopliteal (in 2 patients rotational atherectomy)                        | 12 months (mean)  | 60% of patients within follow-up of 20 months (median); cumulative ulcer healing rates:  
3 months: 15%  
6 months: 40%  
12 months: 54%  
24 months: 81% |
| Mlekusch et al., 2002 | retrospective                       | 40 (32 diabetics) | PTA femoropopliteal                                                               | 5 months (median)  | 60% of patients within follow-up of 20 months (median); cumulative ulcer healing rates:  
3 months: 15%  
6 months: 40%  
12 months: 54%  
24 months: 81% |
| Boccalandro et al., 2004 | prospective not randomised uncontrolled | 25 (20 diabetics) | laser angioplasty                                                                 | 13 months (mean)  | Only 21 patients with procedural success were evaluated: 86% (18/21) data of all patients with different interventions: 65% of limbs  
Only 20 patients were followed for 1 year: 55% (11/20)  
33% (4/12) of patients after 3 months (mean)  
Entire cohort (n = 32) after 1 year: 70% PTA; only 13 patients with successful PTA were evaluated: 69% (9/13) Bypass: no clear follow-up data |
| Losa et al., 2004   | prospective not randomised uncontrolled | 50 diabetics (59 limbs) | 38 PTA  
20 bypass                                                                 | 4.5 months (mean)  | 60% of patients within follow-up of 20 months (median); cumulative ulcer healing rates:  
3 months: 15%  
6 months: 40%  
12 months: 54%  
24 months: 81% |
| Atar et al., 2005   | prospective not randomised uncontrolled | 38 (27 diabetics) | PTA popliteal, infrapopliteal                                                     | 12 months  | 60% of patients within follow-up of 20 months (median); cumulative ulcer healing rates:  
3 months: 15%  
6 months: 40%  
12 months: 54%  
24 months: 81% |
| Clair et al., 2005  | retrospective                        | 19 (11 diabetics) | PTA femoropopliteal                                                               | 3 months (mean)  | 60% of patients within follow-up of 20 months (median); cumulative ulcer healing rates:  
3 months: 15%  
6 months: 40%  
12 months: 54%  
24 months: 81% |
| Jacqueminet et al., 2005 | prospective not randomised uncontrolled | 32 diabetics     | 25 primary PTA  
6 primary bypass  
36 secondary bypass after unsuccessful PTA                                        | 8.5 months (mean)  | 60% of patients within follow-up of 20 months (median); cumulative ulcer healing rates:  
3 months: 15%  
6 months: 40%  
12 months: 54%  
24 months: 81% |

*a* in patients that healed.  
*b* within follow-up.
reports would have met the CPMP criteria currently required for drug trials in CLI patients. Even basic clinical parameters such as ankle pressures were frequently lacking. Results in diabetics versus non-diabetics were usually not reported separately nor were CLI populations stratified for this important confounder as required by CPMP. Moreover, exact definitions of the standard of wound management was the exception and secondary interventions during follow-up were not reported consistently.

By analysing the healing rates and healing times, large variations among the 17 studies selected (12 retrospective surveys, 5 prospective but uncontrolled and non-randomized trials) were observed. In almost all studies minor amputations as well as secondary interventions were part of the therapeutic strategy. With a broad range of the length of follow-up lasting up to 5 years, healing times of 0.4 to 48 months and healing rates ranging from 15% to 100% were reported. Apart from variability in follow-up the vast differences in ulcer healing may be explained by the heterogeneity of ulcer origin, the degree of soft and bone tissue involvement and the different concepts of local ulcer treatment. In addition, a variety of comorbidities may have influenced the complex process of wound healing. Drug as well as revascularization trials would either require stratification for these multiple variables or would need rigorous inclusion and exclusion criteria in order to account for this heterogeneity. Whereas the first strategy will result in unrealistically high numbers of CLI patients to be included in a trial the latter will severely impede recruitment of patients and result in a highly selected study population.

In planning a confirmatory, randomized, double-blind and placebo-controlled drug trial in CLI patients based on the CPMP criteria for the proof of efficacy, it is necessary to have an estimate on the time and the percentage of complete ulcer healing for the drug as well as for placebo. Thus, studies on revascularization procedures which are considered the standard of care in CLI do not provide any reliable basis for a point estimate. Due to the broad variability of results reported it appears almost impossible to define the hypothesis and the necessary sample size for a confirmatory drug trial using complete ulcer healing as the primary efficacy criterion. Moreover, data on healing rates for placebo treatment are also missing.

If one were to insist on the same efficacy criteria for revascularization therapy as currently required for drug trials neither surgical nor interventional measures would be accepted as efficacious in CLI patients. By contrast, for methodologically sound revascularization studies in CLI, accepted efficacy criteria seem to be limb salvage or amputation-free survival; as a technical surrogate parameter graft patency may be given. In the recent BASIL trial, such endpoints served as a basis for meaningful conclusions for the comparison of bypass surgery versus angioplasty in CLI patients despite the heterogeneity of the patient population. Notably, complete ulcer healing was not even a secondary endpoint in this study. The inconsistency of the sole endpoint ulcer healing in CLI studies has also been recognized by Rutherford et al. in their revised version of the “Recommended Standards for Reports Dealing with Lower Extremity Ischemia.”

In view of the data presented, it appears justified to critically revise CPMP criteria for confirmatory drug trials. The definition of new endpoints for assessing the efficacy of therapeutic measures in CLI studies should be both clinically relevant and realistic, and should equally apply to pharmacotherapy and revascularization procedures. Thus, more appropriate alternative endpoints may include amputation-free survival, the functional status of the patient, and quality of life. Composite or response-based endpoints considering also the time to and duration of response have already been proposed by the Basel I conference and may form the basis for future discussions.

References


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