Defining success in clinical trials of diabetic foot wounds: the Los Angeles DFCon consensus

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ABSTRACT

Regulatory requirements for new products should be guided by clinical trials that protect the public by a thorough evaluation of safety and efficacy, while not creating unnecessary barriers to their development and ultimate approval. While healing a wound is the ultimate goal of treating an individual with a diabetic foot ulcer, achieving this goal is physiologically complex requiring the initiation and interaction of many events and therefore unlikely to be achieved by one compound. We believe that developing new, more meaningful, study outcomes or end points in wound care trials would both aid in determining the true efficacy of wound management modalities and facilitate the product development cycle. The primary guidance from the US Food and Drug Administration to industry in this field was published in 2006. This document, while helpful and largely in concert with current knowledge of wound healing, needs to be substantially improved. We therefore convened an interdisciplinary task force comprising experts in various aspects of wound care to attempt to achieve consensus in defining primary outcomes and potential secondary endpoints for various classes of wound-healing modalities.

Key words: diabetes • ulcer • healing • outcomes • consensus • FDA • amputation • infection

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INTRODUCTION

Regulatory requirements for new products should be guided by clinical trials that protect the public by a thorough evaluation of safety and efficacy, while not creating unnecessary barriers to their development and ultimate approval. As clinicians and scientists focused on wound healing, we strive to practice evidence-based medicine whenever possible. However, so few wound-healing therapies have been rigorously evaluated. Many that have been subjected to robust interrogation are ultimately shown to be not able to achieve Food and Drug Administration (FDA) approval. This is in many cases because outcomes that are mandated by guidance are not always germane to a modality's specific mechanism of action.

Key Points

- regulatory requirements for new products should be guided by clinical trials that protect the public by a thorough evaluation of safety and efficacy, while not creating unnecessary barriers to their development and ultimate approval
- we are eager to provide innovative safe and efficacious therapeutic technologies to our patients, but are also concerned about the criteria used to define 'success' in trials of products to heal diabetic foot ulcers
- specifically, the FDA currently requires all new wound care therapeutics to be able to heal a wound

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Key Points

- developing new, more meaningful, study outcomes or end points in wound care trials would aid both in determining the true efficacy of wound management modalities and in facilitating the product development cycle
- it is unreasonable to judge technologies by the outcomes that they were not designed to achieve
- in the several-month course required for healing most diabetic foot wounds, clinicians use various products to achieve various goals; in fact, successful wound healing may be viewed as a sequence of achieving smaller triumphs
- the most definitive claim for a wound-healing product is that it accelerates the rate, or increases the incidence, of total wound closure

We are eager to provide innovative safe and efficacious therapeutic technologies to our patients, but are also concerned about the criteria used to define 'success' in trials of products to heal diabetic foot ulcers. Some of these criteria are unnecessary or possibly not clinically meaningful. Specifically, the FDA currently requires all new wound care therapeutics to be able to heal a wound. However, wound healing is an orchestrated process requiring the interactions of many cell types and homeostatic mechanisms. While healing a wound is the ultimate goal of treating an individual with a diabetic foot ulcer, achieving this goal is physiologically complex requiring the initiation and interaction of many events and therefore unlikely to be achieved by one compound. We believe that developing new, more meaningful, study outcomes or end points in wound care trials would aid both in determining the true efficacy of wound management modalities and in facilitating the product development cycle.

The primary guidance from the US FDA to industry in this field was published in 2006. (1) This document, while helpful and largely in concert with current knowledge of wound healing, needs to be substantially improved. We therefore convened a task force comprising experts in various aspects of wound care to attempt to achieve consensus in defining primary outcomes and potential secondary endpoints for various classes of wound-healing modalities. The task force was co-chaired by the immediate past and current chairs of the American Diabetes Association (ADA) Foot Care Interest Group (AJMB and DGA) and included panel members with expertise and leadership in primary care, infectious diseases and microbiology, orthopaedic and vascular surgery, dermatology and podiatric medicine and surgery. Each member of this task force was instructed to conduct an independent literature review prior to the convening of the task force. Furthermore, all were provided with the most recent FDA guidance document for contemporaneous review during the task force writing sessions.

DIFFERENT THERAPIES, SAME ENDPOINT?

To date, seemingly disparate wound treatment modalities have been assessed in nearly identical fashions because the FDA guidance document requires that for a product to be successful in a blinded randomised trial, those who receive the experimental agent must *heal* at a greater rate than those who did not receive it. Thus, therapies, designed to reduce the wound's bacterial load or signs of inflammation, have been evaluated with systems similar to those used for devices such as negative pressure vacuum systems (designed to simplify deeper wounds) or wound matrices (designed to serve as a scaffold for skin grafting). We believe that devices and pharmaceuticals designed to treat wounds should instead be assessed in a fashion appropriate to how they are used clinically. Ultimately, regulators and clinicians will decide whether the selected study outcomes are meaningful in the clinical context in which they see patients.

Similarly, we believe it is unreasonable to judge technologies by the outcomes that they were not designed to achieve. For example, we know that wound recurrence after healing is closely associated with the diligence of skin care and pressure off-loading once a wound has healed. These factors are likely to have a much greater influence on whether a subjects wound continues be healed than products applied in the first few weeks of a month-long healing period. Therefore, a wound-healing trial should not be required to include the current obligatory 3-month follow-up for wound recurrence. Removing such a requirement would substantially shorten most clinical trials and reduce their cost. Of course, an exception to this change would be a product that has the specific goal of decreasing the likelihood of wound recurrence.

In the several-month course required for healing most diabetic foot wounds, clinicians use various products to achieve various goals. In fact, successful wound healing may be viewed as a sequence of achieving smaller triumphs – for example, augmenting local blood supply, reducing levels of bacterial colonisation, alleviating pressure on the wound – whose net effect culminates in complete wound closure. Therefore, we believe that there should be intermediate end points, which may occur before the true endpoint but are also clinically meaningful, by which various technologies designed to influence one of these intermediate steps could more fairly be judged. As an example, the outline in Table 1 may represent clinically meaningful intermediate end points.

Table 1 Potential intermediate endpoints based on wound care category

1. Negative pressure wound therapy
   a. Development of granulation tissue
   b. Accelerated rate of wound closure
   c. Complete wound closure, with or without surgical intervention
2. Topical antimicrobials
   a. Reduction in bacterial colony counts
   b. Eradication of pathogens
   c. Reduction in local clinical signs of inflammation
   d. Reduction in odour
3. Acellular dermal matrices/scaffolds
   a. Accelerated rate of closure
   b. Complete wound closure with or without surgical intervention
4. Bioengineered tissues (cell-based therapies)
   a. Accelerated rate of closure
   b. Development of granulation tissue
   c. Prepared for skin grafting
   d. Complete wound closure with or without surgical intervention
5. Other topical prescriptives/dressings
   a. Accelerated rate of closure
   b. Complete wound closure with or without surgical intervention
6. Circulatory assist devices/hyperbaric oxygen
   a. Accelerated rate of closure
   b. Complete wound closure with or without surgical intervention
   c. Rate of change in local vascular monitoring

MEASURING AND DEFINING CLOSURE: A PLACE FOR SURROGATES?

Perhaps, the most definitive claim for a wound-healing product is that it accelerates the rate, or increases the incidence, of total wound closure. End points to establish such a claim have been highly controversial. It might be argued that complete reepithelialisation is only an intermediate healing milestone and, we believe, an inadequately defined one. There is no currently accepted and widely available technology for determining when a wound achieves this status. In fact, healing studies have shown that many wounds show an exponential decline in surface area as repair progresses. (2) Thus, even minor differences between observers deciding whether a wound is 99% or 100% reepithelialised can result in healing times that differ by weeks.

By contrast, using digital photography and computerised planimetric analysis leaves little ambiguity, if one defines an end point of 50% or 80% surface area healing compared with the initial wound measurement. Surrogate outcomes, which occur earlier than the true outcome but are believed to be representative of the true outcome, which reflect the specific mode of product action may also be appropriate for the evaluation and approval of wound care therapies. Many have been shown to be excellent predictors of ultimate wound healing. Several studies that have included evaluations of more than 20 000 individuals with diabetic foot ulcers have shown that changes in the size of a wound over the first 4 weeks of care can be used to successfully predict which wounds will heal at 3 and 6 months. (3–6) While surrogate outcomes are not intermediate end points, we believe that in many cases patients achieve benefit in reaching substantial, but only partial healing.

CONCLUSION

We believe that the economics of producing wound-healing products are currently unfavourable. Adjusting the regulatory burden to be more in concert with a new products' mode of action could enable more healing technologies to reach the public, while not jeopardising their safety. Meaningful end points of intermediate healing, for example, granulation, readiness for grafting, reduction of colonisation should become more acceptable, and in most cases studying wound recurrence should not be mandatory.

Key Points

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