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LETTER TO THE EDITOR

Designing clinical trials to bring wound products to market

Dear Editor,

Few novel products supported by rigorous research have reached the wound healing market in the last decade. This has been in part because of a number of failed or inconclusive studies resulting in low-level evidence (1,2). Many of these products have failed to progress from a phase II trial to a phase III trial, where the likelihood of success would be expected to be greater, based on better data on which to design an appropriate trial. A variety of reasons might account for trial failure ranging from ineffectiveness of study product to financial costs of drug or device development. However, one key element may be study design. Although it might appear possible that a single wound healing product is a panacea for all wounds at all times, it is more logical to assume that a product alters or enhances the biology of certain wounds at certain times. Certain products might be better for stimulating refractory wounds, while others improving healing of less difficult wounds (3,4). Therefore one would suppose that no single product is appropriate for the management of all wounds and that a logical course would be to study those wounds that have the highest likelihood of healing with any given product.

The need for new products exists. For example, for patients with venous leg ulcerations, from 30% to 75% of patients respond to standard care including multi-layered compression bandages over a 6-month time period (5) but due to a refractory subset, venous ulcers cost the health care system billions of dollars annually (6). Clinical predictors of leg ulcer healing have been described for those with a low likelihood of healing (7).

Several studies have showed that using wound size and wound duration can predict the likelihood of healing of venous leg ulcers (8,9). Among those Margolis et al. developed a simple predictive model to stratify patients on the likelihood of healing with standard of care using compression bandages (5,10). They found that wounds of small size (<5 cm^2) and of short duration (<6 months) (Margolis score 0) healed quite well with standard care (93% of the time with compression therapy by 24 weeks), those possessing one of those factors (large size or long duration but not both) (Margolis score 1) healed 65% of the time, and those of long duration and large size (Margolis score 2) healed infrequently, only 13% of the time. This information can be used as a historical control to determine the potential benefit of novel therapies under development and have the potential to be used to help future clinical trial design. Thus this model can help determine whether a product has its relative effect on easy (perhaps speeding healing), relatively difficult (increasing healing or time to healing) or exceedingly difficult (increasing healing) to heal venous ulcers.

As an example, recent technological developments have led to the creation of intact keratin (non hydrolysed) products suitable for topical application, for example, a keratin-based hydrogel (11,12). After Institutional Review Board approval, an open-label study to determine the effect of topical keratin dressings (Keratec International, Christchurch, New Zealand), either a keratin-based hydrogel or keratin-based foam (depending on the amount of exudate) plus compression therapy was performed for the treatment of venous ulcers. Patients were stratified by Margolis score, as described above, and seven patients with refractory venous ulcers with a Margolis score 2 were enrolled. Baseline planimetry and photography were performed at baseline, weekly and at the end of this study. Dressings were changed at least weekly and more often if required. By 12 weeks, five of the seven (71·4%) patients healed, greater than the 13% predicted to heal by 24 weeks.

This would imply for future larger trials, instead of allowing all patients with venous ulcers to be enrolled, limiting patients with refractory venous ulcers based on size and duration, would lend the best chance to optimise success. Using pilot data and intelligent trial design to propose larger and more expensive trials would allow for more efficient and cost-efficient trials. Most importantly, this would allow for design of more rational larger studies and provide a better chance for new treatments for success.

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