Data insufficient to recommend the use of PDGF gels

Sirs,

In their article entitled "Use of a platelet-derived growth factor gel (PDGF) in chronic diabetic foot ulcers", Agrawal et al (2009) concluded that there is a "growing body of evidence that suggests rhPDGF therapy improves clinical outcome in chronic diabetic foot ulcers". We dispute this claim: we believe the body of evidence for the effectiveness of PDGF gels is both slim and not growing.

The authors refer to the single, well-designed, study involving 382 participants with neuropathic foot ulcers that reported on the benefits of PDGF gel use (Wieman et al, 1998). The authors do not mention that the finding was not confirmed in a later study conducted in the USA involving 146 participants (Robson et al, 2005). Furthermore, it is known that a PDGF gel manufacturer sponsored a large European study, but the results were never published – possibly because they, too, were negative.

The present article describes a very small randomised controlled trial in which a total of 28 people with chronic diabetic foot ulcers were randomised to receive treatment with topical PDGF gel or placebo for a period of 12 weeks. The authors report a highly significant difference in healing between the two groups, but the results are difficult to assess – partly because of apparent weaknesses in trial design, and partly because of the way in which the data are presented.

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The principal weakness of the study design is that it does not appear to have been blinded, meaning that outcomes were assessed by observers who knew to which group each participant was allocated to, and may therefore have been susceptible to unintentional bias. The sponsor of the study is not given and no conflict of interest statement is made.

Other details of the conduct of the study are also either missing or confusing. Thus, the authors report that off-loading was "effective", but they do not describe how this was assessed. The study's inclusion criteria stipulate that only those who were "free of peripheral vascular disease" were randomised, and yet ulcers of Wagner grade 4 (localised gangrene) were permitted.

The numbers of participants recruited to a randomised controlled trial should be based on prior definition of a primary endpoint (the principal difference sought between the groups) and a sample size calculation. None is provided, although the main difference reported is in ulcer area. The authors, however, do not describe how this was measured and this is crucial – especially in a non-blinded study. The actual mean "circumferential area" at baseline in the PDGF gel treated group was 55.61 cm^2. If the term "circumferential area" is synonymous with "cross-sectional area", this indicates that the average ulcer area was roughly 10 x 5 cm. Ulcers of such size are obviously very unusual in routine clinical practice and this also undermines the confidence of readers trying to assess this work.

It is also not clear if the analysis was completed blind to group allocation, and whether it was by intention to treat (i.e. comparing the results of all 14 in each group), or per protocol (results just from those who completed the study). This distinction is important because five of the 14 participants in the placebo group withdrew.

The results section refers only to reduction in surface area within groups and this was said to be significant in the PDGF gel treated group, but not in the controls (even though *Figure 1*, and the data in *Table 2*, suggest that the fall in area in controls – from 33.75 ± 2.48 cm^2 to 5.03 ± 0.21 cm^2 – was also highly significant). *Table 2* also seems to

indicate that there were significant differences in area between groups, but this is not mentioned in the text and the comparisons that form the basis of the *P*-values in *Table 2* are not clear. The meaning of *Figure 2* is opaque. For all of these reasons, we do not feel that the data presented by Agrawal and colleagues have any impact on the question of whether PDGF gels should be considered for the treatment of diabetic foot ulcers in clinical practice.

We would also urge readers to consider the article's opening sentence: "To improve the outcomes for those with diabetic foot ulcers and, ultimately, to reduce the rate of lower-limb amputation, new treatment modalities are urgently needed". We disagree. The first priority is to ensure that all people with active diabetic foot disease are rapidly assessed by specialists (or expert multidisciplinary teams). The key to improving outcomes for people with diabetic foot disease is the close integration of professionals with the necessary clinical skills, and the prompt deployment of existing, and generally simple, remedies: regular cleansing and re-dressing, debridement and off-loading, and the appropriate use of antibiotics. So-called "advanced wound therapies" may yet find a role, but their use must be substantiated by robust evidence (Jeffcoate et al, 2008).

Yours sincerely,

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