

# 'Dermagraft'<sup>†</sup>: a New Treatment for Diabetic Foot Ulcers

Dermagraft is a bioengineered human dermis designed to replace a patient's own damaged or destroyed dermis. It consists of neonatal dermal fibroblasts cultured *in vitro* on a bioabsorbable mesh to produce a living, metabolically active tissue containing the normal dermal matrix proteins and cytokines.

Dermagraft is manufactured through the process of tissue engineering, the science of growing living human tissues for transplantation. Human fibroblast cells established from newborn foreskins are cultivated on a three dimensional polyglactin scaffold. As fibroblasts proliferate within the scaffold, they secrete human dermal collagen, fibronectin, glycosaminoglycans, growth factors and other proteins, embedding themselves in a self-produced dermal matrix. This results in a metabolically active dermal tissue with the structure of a papillary dermis of newborn skin. A single donor foreskin provides sufficient cell seed to produce 250,000 square feet of finished Dermagraft tissue. Maternal blood samples and cultured cells are tested throughout the manufacturing process to ensure that Dermagraft is free from known pathogenic agents including HIV, human T-cell lymphotropic virus (HTLV), herpes simplex virus (HSV), cytomegalovirus (CMV) and hepatitis viruses.

After manufacture, Dermagraft is stored at  $-70^{\circ}\text{C}$ . Since it is designed to function as a living tissue, remaining viable and secreting growth factors and matrix proteins into the wound bed after implantation, the metabolic activity of the product is assessed, before and after cryoprecipitation, by measurement of specific levels of collagens and other matrix proteins. Dermagraft is then shipped on dry ice to clinical sites. Prior to implantation, the product is thawed, rinsed three times with sterile saline, cut to the wound size and placed onto the wound bed. The fibroblasts, evenly dispersed throughout the tissue, remain metabolically active after implantation and deliver a variety of growth factors which are key to neovascularisation, epithelial migration and differentiation and integration of the implant into the patient's wound bed. Thus, Dermagraft rebuilds a healthy dermal base over which the patient's own epidermis can migrate and close the wound. No sutures are required but dressings are needed to ensure the dermal implant remains in place.

Clinical experience has included pilot, pivotal and supplemental studies. The pilot study evaluated healing

over a 12 week period in 50 patients with full thickness neuropathic plantar and heel ulcers, greater than  $1\text{ cm}^2$  in size<sup>1</sup>. Patients were randomised into four groups (three different dosage regimes of Dermagraft and one control group). Ulcers treated with the highest dose of Dermagraft (1 piece applied weekly for eight weeks) healed significantly more often than those treated with conventional wound closure methods; 50 % of the Dermagraft treated ulcers healed completely compared with only 8 % of the control ulcers ( $p = 0.03$ ). After a mean of 14 months of follow up, (range 11–22 months) there were no recurrences in the Dermagraft healed ulcers.

In the pivotal study, 281 patients with similar foot ulcers were enrolled into a multicentre, randomised controlled study to evaluate wound closure at 12 weeks, with follow up at 32 weeks<sup>2</sup>. At the time of a planned interim analysis, there was evidence that some patients had received product of low metabolic activity at the time of implantation and that these patients had significantly poorer healing results. A complete analysis of all *in vitro* and clinical data at the conclusion of study showed that the metabolic activity of Dermagraft must lie within a definite therapeutic range to ensure that the tissue is sufficiently active after implantation to affect wound healing. The total evaluable Dermagraft group, which included many patients who had not received metabolically active Dermagraft at their early doses, had a higher rate of healing than the control group. (38.5 % v 31.7 %), but the difference did not reach statistical significance. However, when evaluable patients who received Dermagraft with metabolic activity within the therapeutic range were analysed, 50.8 % had experienced complete wound closure compared with 31.7 % in controls ( $p = 0.006$ ). Furthermore, at week 32, Dermagraft patients still had a statistically significant higher number of healed ulcers, 58 % compared with 42 % in controls ( $p = 0.04$ ).

These data illustrate the importance of implanting Dermagraft that is within the appropriate metabolic range and the commercial manufacturing system is now designed to produce Dermagraft within the defined therapeutic range. Indeed, in a supplemental study to the pivotal trial, a further 50 patients were treated with Dermagraft and again showed an ulcer healing rate of over 50 % at 12 weeks. Preliminary studies at King's College Hospital have shown similar results; six patients with 'hard to heal' neuropathic plantar ulcers of a mean duration of 43 months have been treated. 50 % healed within 12 weeks.

Using clinical data obtained from the pivotal study and projecting costs for a cohort of 100 patients over 52 weeks in the British health care system, a cost

\* Correspondence to: Dr Michael Edmonds, Department of Diabetes, King's College Hospital, Denmark Hill, London SE5 9RS. Tel: 0171 346 3223 Fax: 0171 346 3407

<sup>†</sup> Dermagraft is manufactured by Advanced Tissue Sciences of California

effectiveness analysis developed by the York Health Economics Consortium,<sup>3</sup> has shown that Dermagraft may be cost saving to the health care system. It is estimated that the cost of healing ulcers using conventional therapy per year is £4,327. However, when Dermagraft is used, more ulcers are healed and healed significantly faster. The cost to achieve such healing is lower, at £3,475 per healed ulcer per year, resulting in an £852 saving per healed ulcer.

Dermagraft appears to be a very safe treatment and more than 1,000 pieces of Dermagraft have been implanted with no immune rejection observed. Clinical experience to date has shown no significant differences between Dermagraft-treated and control groups in incidence of infection, cellulitis or osteomyelitis. However, Dermagraft should not be used if infection is present in the wound.

Tissue engineering offers the ability to replace damaged or destroyed dermis of a patient suffering from a full thickness ulcer with a manufactured living dermal implant. Hitherto, Dermagraft has been used in indolent plantar neuropathic ulcers to kick-start persistent lesions

which are reluctant to heal. However, it may also prove to be useful in recently-formed neuropathic ulcers and also in the neuroischaemic ulcer and further studies are awaited with these types of ulcers.

In the meantime, Dermagraft presents a new and exciting treatment for the indolent plantar neuropathic ulcer that has failed to respond to conventional treatment.

**M E Edmonds\*, AV Foster, M McColgan**

*Diabetic Foot Clinic, King's College Hospital, London*

## References

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