

Dermagraft in the treatment of diabetic foot ulcers

Maureen McColgan, Ali Foster and Mike Edmonds

Introduction

Dermagraft is a metabolically active, living dermal tissue manufactured from neonatal dermal fibroblasts by tissue engineering. It is an exciting new treatment that provides health professionals with a means of replacing damaged or destroyed dermis in a full-thickness ulcer by a living dermal implant. At present, it is indicated mainly for the longstanding neuropathic ulcer that has not responded to conventional wound closure methods. In clinical trials, Dermagraft-treated ulcers have healed significantly better and faster than ulcers treated by conventional therapy.

Dermagraft is a bioengineered human dermis that is designed to replace a patient's own damaged or destroyed dermis (Langer et al, 1995). 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.

Manufacture of Dermagraft

Dermagraft is produced by tissue engineering — the science of growing living human tissues for transplantation. Tissue engineering involves seeding mammalian cells onto special scaffolds, growing the cells on these scaffolds in vitro, and then implanting the cell polymer constructs in vivo as the transplanted tissue (Figure 1). The use of this approach to produce cartilage, tendon and bone is also being

explored. However, the most advanced area of tissue engineering at present is the manufacture of skin.

In this process, human fibroblast cells established from neonatal foreskins are cultivated on a three-dimensional polyglactin scaffold (Figure 2). 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 (Figure 3).

A single donor foreskin provides sufficient cell seed to produce 250,000 ft² of finished Dermagraft tissue.

Maternal blood samples and cultured cells are tested throughout the manufacturing process to ensure that Dermagraft is free from known pathogens, including human immunodeficiency virus, human T-cell lymphotropic virus, herpes simplex virus, cytomegalovirus and hepatitis viruses.

Storage and method of use

After manufacture, Dermagraft is stored at -70°C. Since it is designed to be a living tissue, remaining viable and delivering growth factors and matrix proteins into the wound bed after implantation, the metabolic activity of Dermagraft is assessed pre- and post-cryoprecipitation by measurement of

ARTICLE POINTS

1 Dermagraft is a bioengineered, metabolically active human dermal tissue.

2 It is designed to replace a patient's own damaged or destroyed dermis.

3 Constant testing during manufacture ensures that it is pathogen free.

4 It is indicated for the longstanding neuropathic ulcer that does not respond to conventional therapy.

5 Ulcers have been shown to heal more frequently and faster with Dermagraft.

6 The use of Dermagraft has the potential to produce considerable cost savings for the health service.

KEY WORDS

- Dermagraft
- Living dermal implant
- Tissue engineering
- Neuropathic

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Figure 1. Basic principles of tissue engineering.

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PAGE POINTS

1 The fibroblasts in Dermagraft remain metabolically active and deliver growth factors and matrix proteins to the wound bed.

2 Growth factors are key to successful integration of the implant into the wound bed.

3 The metabolic activity of Dermagraft must lie within a definite therapeutic range to effect wound healing.

specific levels of collagens and other matrix proteins.

Dermagraft is then shipped on dry ice to clinical sites. Before implantation, the product is thawed, rinsed three times with sterile saline, cut to the appropriate wound size and placed in the wound bed.

The fibroblasts, evenly dispersed throughout the tissue, remain metabolically active after implantation and deliver a variety of growth factors to the wound bed. These are the key to neovascularisation, epithelial migration and differentiation and integration of the implant into the wound bed. Thus, Dermagraft builds a healthy dermal base over which the patient's epidermis can migrate and close the wound. No sutures are required, but dressings are needed to ensure that the dermal implant remains in place.

Clinical studies

Clinical experience has included pilot, pivotal and supplemental studies, carried out in the USA. The pilot study evaluated healing over a 12-week period in 50 patients with full-thickness neuropathic plantar and heel ulcers greater than 1 cm² in size (Gentzkow et al, 1996). Patients were randomised into four groups (three different dosage regimens of Dermagraft and one control group). All patients received standard care comprising wound debridement and pressure relief with custom-fitted footwear.

Ulcers treated with the highest dose of Dermagraft (one piece applied weekly for 8 weeks) healed significantly more frequently than those treated with conventional wound closure methods: 50% of the Dermagraft-treated ulcers healed completely compared with only 8% of the control ulcers ($P=0.03$). Also, after a mean follow-up of 14 months (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 (Naughton et al, 1997). However, at the time of a planned interim analysis, there was evidence that some patients had received a product with low metabolic activity at the time of implantation and that these patients had significantly poorer healing results.

Metabolic activity refers to the activity of the viable fibroblasts that remain after the cryopreservation/storage/thaw process: a low metabolic activity indicates that fewer fibroblasts in the product have survived cryopreservation (Naughton et al, 1997). Metabolic activity is measured by a specific assay which reflects the mitochondrial activity of the fibroblasts.

A complete analysis of all in vitro and clinical data at the conclusion of the pivotal study (Naughton et al, 1997) 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 effect wound healing. The total evaluable Dermagraft group, which included many patients who had received

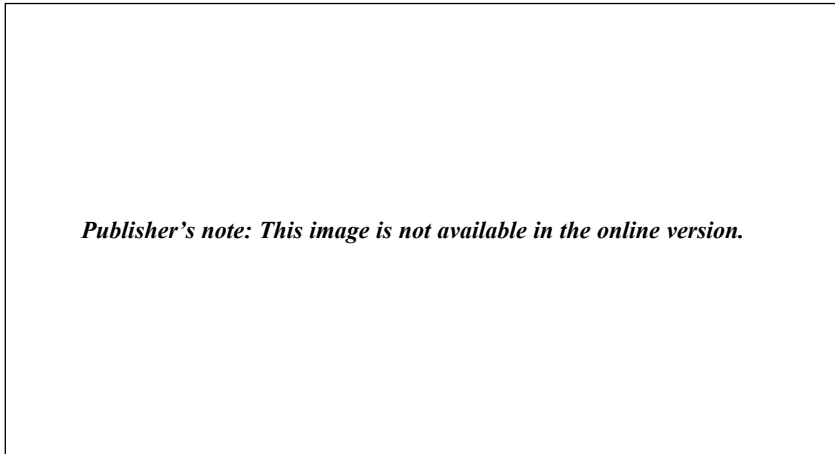


Figure 2. The tissue engineering process to produce Dermagraft.

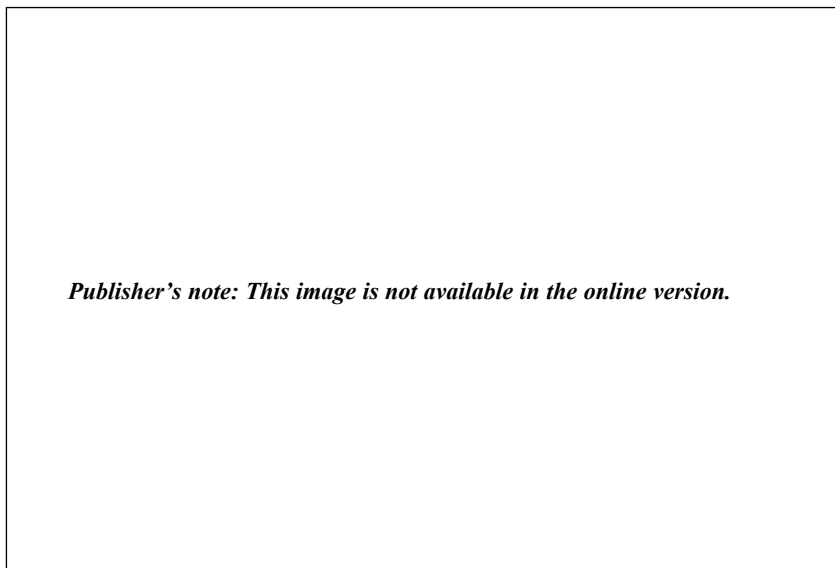


Figure 3. Histological cross-section of Dermagraft.

Dermagraft with low metabolic activity at their early doses, had a higher rate of healing than the control group (38.5% vs 31.7%) but the difference was not significant.

However, when evaluable patients who received Dermagraft with metabolic activity within the therapeutic range were analysed, 50.8% of this population experienced complete wound closure compared with 31.7% of controls (P = 0.006). At week 32, Dermagraft patients still had a significantly higher number of healed ulcers than controls (58% vs 42% respectively; P = 0.04).

These data illustrate the importance of using Dermagraft with a metabolic activity within the appropriate range. The commercial manufacturing system is now designed to produce Dermagraft within this 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 above 50% at 12 weeks.

Additional clinical experience with Dermagraft has recently been acquired in the UK and Canada, and preliminary studies have shown similar results. At King's College Hospital, London, 10 patients with 'hard to heal' neuropathic plantar ulcers of a mean of 41 months' duration have been treated: seven of these ulcers have healed, three of which showed complete wound closure within 12 weeks.

At the Royal Alexandra Hospital in Edmonton, Alberta, Canada, seven patients have completed 12 weeks of follow-up since their initial Dermagraft application. Five of these patients have had complete wound closure within this period (Bowering, 1998). These are early studies and a further randomised controlled study is planned.

Potential cost savings

Using clinical data from the USA pivotal study and projecting the costs for treating a cohort of 100 patients over 52 weeks to the British healthcare system, a cost-effective analysis developed by the York Health Economics Consortium (1997) has shown that Dermagraft is cost saving to the health service.

The cost of healing ulcers using conventional therapy is estimated at £4,327 per ulcer per year. However, when Dermagraft is used, more ulcers are healed and they heal significantly faster. Moreover, the cost to achieve such healing is lower at £3,475 per healed ulcer per year, resulting in an £852 saving per healed ulcer using Dermagraft.

Dermagraft is a very safe treatment and more than 1,000 pieces of Dermagraft have been implanted with no immune rejection observed (Naughton and Tolbert, 1996/1997). The reason for this is probably that, unlike other skin cells, neonatal fibroblasts, lack HLA-DR surface antigens, which generate the classic allograft rejection (Cuono et al, 1987).

Clinical experience has shown no significant difference between Dermagraft and control groups with respect to incidence of infection, cellulitis or osteomyelitis. However, Dermagraft should not be used if the ulcer is infected (Figure 4).

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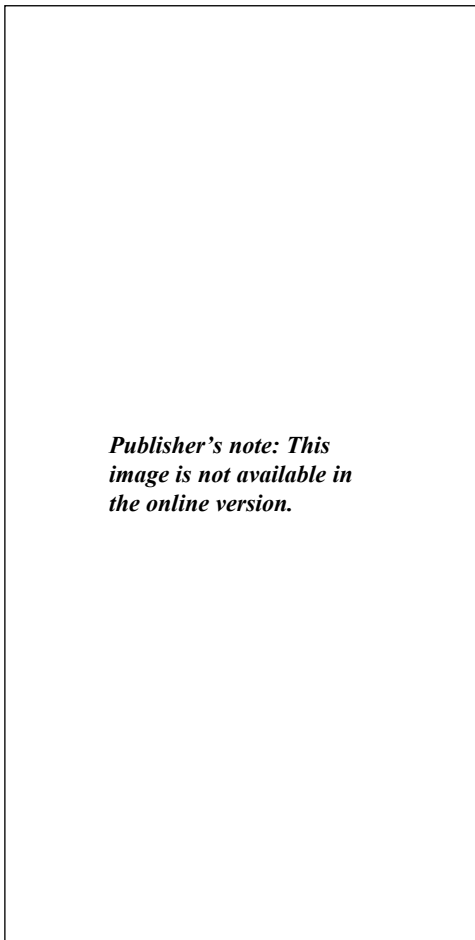
1 It is estimated that Dermagraft treatment would result in an annual saving of £852 per healed ulcer, compared with conventional treatment.

2 No immune reaction has been observed in more than 1,000 applications of Dermagraft tissue.

3 The lack of HLA-DR surface antigens on neonatal fibroblasts probably accounts for the absence of an immune reaction.

4 Incidence of infection, osteomyelitis and cellulitis did not differ between Dermagraft-treated patients and controls in clinical studies.

5 Dermagraft should not be used if the ulcer is infected.



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Figure 4. Dermagraft should not be used in an ulcer which is infected.

Indications

Dermagraft enables the damaged or destroyed dermis of a patient with a full-thickness ulcer to be replaced by a manufactured living dermal implant. The main indication at present is a long-standing neuropathic ulcer that has not responded to conventional therapy, i.e. standard wound healing treatment, aggressive debridement and implementation of non-weight-bearing techniques. However, before Dermagraft is applied to an indolent ulcer, the wound should be thoroughly debrided and be free from slough and purulent discharge.

Dermagraft may also be useful in a recently formed neuropathic ulcer and in a neuroischaemic ulcer; further studies with these types of ulcer are awaited in the UK.

At present, Dermagraft is a new and exciting treatment for the indolent plantar

neuropathic ulcer that has failed to respond to conventional treatment. ■

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