Lower limb complications

Back to the future

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As I write this editorial, the 25th anniversary re-release of the film *Back to the Future* sees a DeLorean time machine return to cinemas. DeLoreans were meant to be the future of sports cars, but they never took off (outside of the films). The same could be said of advanced biological wound therapies – principally growth factors and skin replacements – in the management of diabetic foot ulceration. They were seen as the future of wound healing and yet, after initial enthusiasm, they have largely fallen into disuse, particularly in the UK. But could they be due for a revival too?

The two articles summarised here reflect, respectively, on series of USA clinics' experience with these therapies (Kirsner et al, 2010; summarised alongside) and a wider world view of experience with becaplermin (Papanas and Maltezos, 2010; summarised below).

Kirsner et al appear to use such therapies regularly. As with any diabetic foot ulcer, the key factors that influence healing in this study appear to be delay in referral, ulcer grade and size. Infection also significantly impacts on ulcer healing, but did not really come out in this analysis. Centres reported on by Kirsner at al appear to have achieved 30–40% better healing rates than other studies using biological therapies (see, for example, Steed, 1995; Wieman et al, 1998), which were widely criticised at the time of their publication (particularly in the UK). However, the advanced therapy results that Kirsner et al report probably only approach the results seen in the better UK published series (Jeffcoate et al, 2006; Krishnan et al, 2008) and are not, in themselves, controlled or spectacular.

The systematic review of all the published evidence on becaplermin by Papanas and Maltezos demonstrates that the actual "real-world" clinical results with becaplermin may not be as good as the effect demonstrated in trials. In addition, when taken with the recently highlighted possible increase in cancers associated with the use of more than three tubes of becaplermin, they suggest that the case for regular use of becaplermin is not proven. Centres using this product – and, I would suggest, by extension, similar products – need to be very selective in whom they use it.

Overall, comprehensive and convincing clinical and economic cases for these products remain to be made. I suspect that future products in this area will need to produce significantly better results if they are to succeed.

Jeffcoate WJ, Chipchase SY, Ince P, Game FL (2006) Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. *Diabetes Care* **29**: 1784–7

Krishnan S, Nash F, Baker N et al (2008) Reduction in diabetic amputations over 11 years in a defined U.K. population: benefits of multidisciplinary team work and continuous prospective audit. *Diabetes Care* **31**: 99–101

Steed DL (1995) Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers: Diabetic Ulcer Study Group. *J Vasc Surg* **21**: 71–8

Wieman TJ, Smiell JM, Su Y (1998) Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. *Diabetes Care* **21**: 822–7

DRUG SAFETY

Routine use of becaplermin not recommended

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 The recombinant platelet-derived growth factor becaplermin is for the treatment of neuropathic diabetic foot ulcers. The authors assessed the benefits and risks associated with the use of this agent from the published literature.

2 While randomised controlled trials show evidence for the efficacy of becaplermin, clinical experience has not reflected this and it is not widely used.

3 Increased cancer risk with becaplermin therapy (>three tubes) is of concern. The authors call for long-term follow-up data to shed light on the potential risk of malignancy.

Papanas N, Maltezos E (2010) Benefit-risk assessment of becaplermin in the treatment of diabetic foot ulcers. *Drug Saf* **33**: 455–61

ARCHIVES OF DERMATOLOGY

Advanced biological therapies improve ulcer healing time

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 To assess the clinical use of advanced biological therapies (i.e. engineered skin, growth factor therapy and platelet releasate) in treating diabetic foot ulcers the authors designed a retrospective cohort study base in the USA.

2 Between 1 January 2001 and 31 December 2004, validated wound care database records of 2517 people with neuropathic diabetic foot ulcers who received an advanced biological therapy were assessed for their time to healing after initial use of an advanced biological therapy.

3 On average, an advanced biological therapy was used within 28 days of the first clinic visit in this cohort. Median time to healing was 100 days.

4 Larger wound area, increasing wound severity (grade), longer wound duration prior to first clinic visit and prolonged time to treatment with an advanced biological therapy were all significantly associated with longer time to healing (all $P<0.05$).

5 Wounds treated with engineered skin as the first advanced biological therapy were 31.2% more likely to heal than wounds first treated with topical recombinant growth factor ($P<0.001$), and 40.0% more likely to heal than those first treated with platelet releasate ($P=0.01$).

6 The authors concluded that advanced biological therapies improved healing time in diabetic foot ulcers, with engineered skin therapy showing better healing rates than other advanced biological modalities.

Kirsner RS, Warriner R, Michela M et al (2010) Advanced biological therapies for diabetic foot ulcers. *Arch Dermatol* **146**: 857–62

"The authors concluded that people with diabetes receiving dialysis therapy require intensive foot care."

EMERGENCY MEDICINE J

Monitor low-energy foot injuries for Charcot arthropathy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 The authors report the case of a 46-year-old woman with diabetes who presented to an emergency department following a low-energy mid-foot sprain. X-ray was normal, treatment was conservative but Charcot rapidly developed.

2 Clinicians should be more aware of the risk of Charcot following low-energy foot injuries among people with diabetes, and the need for specialist follow-up, said the authors.

Obolensky L, Trimble K (2010) Importance of close surveillance for Charcot arthropathy in diabetic patients presenting to the emergency department with low-energy foot injuries. *Emerg Med J* **27**: 484–5

DIABETIC MEDICINE

Offloading critical following surgery for osteomyelitis

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The authors report a person who underwent surgery for osteomyelitis without X-ray signs of Charcot.

2 Twenty-five days post-surgery the foot was swollen, erythematous and 2ºC warmer than the contralateral foot. X-ray was taken and acute Charcot diagnosed.

3 The authors believe that being weight-bearing precipitated the Charcot and stress that post-surgical immobilisation of the foot is critical.

Aragón-Sánchez J, Lázaro-Martínez JL, Hernández-Herrero MJ (2010) Triggering mechanisms of neuroarthropathy following conservative surgery for osteomyelitis. *Diabet Med* **27**: 844–7

DIABETES CARE

Dialysis independently associated with foot ulceration

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 People (n=326) with diabetes and stage 4 or 5 chronic kidney disease were classified as either receiving dialysis therapy or not. Cohort foot ulceration risk factors were assessed.

2 Compared with no dialysis, people on dialysis had higher prevalences of prior amputations, prior foot ulceration and current foot ulceration (all P<0.05).

3 The authors concluded that people with diabetes receiving dialysis therapy require intensive foot care.

Ndip A, Rutter MK, Vileikyte L et al (2010) Dialysis treatment is an independent risk factor for foot ulceration in patients with diabetes and stage 4 or 5 chronic kidney disease. *Diabetes Care* **33**: 1811–6