Becaplermin and its role in healing neuropathic diabetic foot ulcers

Matthew Young

Introduction

Becaplermin, a genetically engineered form of platelet-derived growth factor, is claimed to be able to restart the healing process in chronic, previously non-healing, neuropathic foot ulcers. It is thought to act by stimulating the migration of cells to the ulcer site, encouraging the body to grow new tissue to heal the open wound. In clinical trials, becaplermin gel plus best wound healing practice healed more diabetic ulcers than placebo gel plus best wound healing practice, and was safe and well tolerated. Becaplermin 0.01% gel is marketed by Janssen-Cilag under the name Regranex.

The management of neuropathic diabetic foot ulceration is relatively simple in concept, but often infuriatingly complex in execution. Theoretically, in the presence of pure neuropathy with little or no vascular insufficiency, all ulcers should heal with pressure relief, rest, debridement and antibiotics. Unfortunately, because of late presentation, poor compliance with care or inappropriate care, there continues to be a cohort of patients with ulcers that do not follow a simple route to closure.

In these patients the wound healing mechanism appears to have stalled, and the institution of best practice care is unable to restart adequate healing. It is postulated that the difference in behaviour between diabetic wounds and non-diabetic wounds, which is due to the glycaemic burden and microcirculatory changes in diabetic patients, may account for this.

As wounds are studied in greater detail, it has become clear that the growth factors and other cytokines present in a wound are released in coordinated waves with defined roles in the formation of healing tissue. In the last 2 years a series of products which claim to be able to restart the healing process and improve the closure of chronic neuropathic ulcers have been released onto the market.

The latest of these, in Europe, is recombinant human platelet-derived growth factor BB (rhPDGF-BB) which is generically named becaplermin (Regranex, Janssen-Cilag*).

Characteristics of PDGF

PDGF is a 25 kDa dimeric protein comprising two disulphide-linked polypeptide chains. There are three different isoforms: the heterodimer PDGF-AB, consisting of an A and B chain, and two homodimers, consisting of two A and two B chains, PDGF-AA and PDGF-BB, respectively.

Although referred to as platelet derived, PDGF is also found in macrophages and fibroblasts. It has been shown to be mitogenic for vascular smooth muscle. PDGF-BB therefore promotes the formation of granulation tissue at the wound site and stimulates wound healing (Ross, 1989). There is evidence that the level of PDGF, among other growth factors, is lower in chronic wounds than in healing wounds, or at least is inappropriate for the stage of healing (Cooper et al, 1994).

Becaplermin

Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of PDGF into the yeast *Saccharomyces cerevisiae*. The biological activity of becaplermin is similar to that of naturally occurring PDGF. It has been shown in vitro and in pre-clinical animal studies to promote chemotactic recruitment and proliferation of the cells involved in wound repair and to improve healing rates (LeGrand, 1998).

* UK address: Janssen-Cilag Ltd, PO Box 79, Saunderton, High Wycombe, Bucks HP14 4HJ (Tel. 01494 567567)

ARTICLE POINTS

1 Chronic wounds are characterised by defects in growth factor activity.

2 Becaplermin is an analogue of human platelet-derived growth factor BB.

3 Clinical trials have demonstrated clear evidence of a treatment effect in neuropathic ulcers of 5cm^2 or less, over that of placebo or standard wound care.

4 No significant side-effects have been reported so far.

5 It is hoped that advanced wound healing products such as becaplermin will help to reduce the incidence of amputations in this patient group.

KEY WORDS

- **Neuropathic ulcers**
- **Wound healing**
- **Growth factors**
- **Becaplermin**

Matthew Young is Consultant Diabetologist at the Royal Infirmary of Edinburgh.

PAGE POINTS

1 Research on becaplermin to date has concentrated on diabetic foot ulcers.

2 There have been four major trials of the use of becaplermin in its preserved formulation in neuropathic ulcers.

3 All but one trial were double blind or placebo controlled.

4 The best efficacy was seen with becaplermin 100 μg/ml and this is the concentration that was finally licensed.

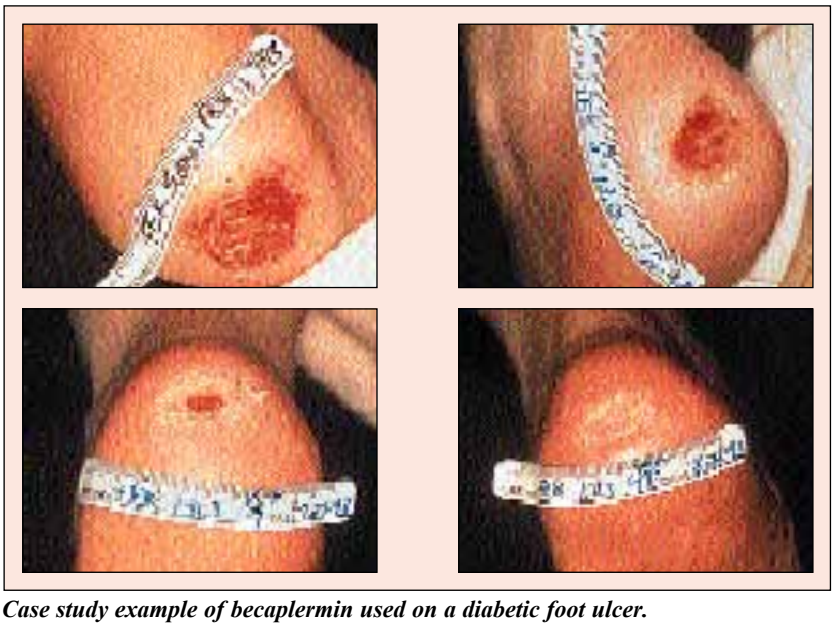
The safety data from these animal studies and the early phase I and II trials demonstrated that becaplermin gel has negligible systemic absorption and is well tolerated. In-vitro and in-vivo studies of fluid from diabetic foot ulcers have also shown that becaplermin is active in the wound environment for more than 12 hours (Castronuovo et al, 1998).

Becaplermin is formulated in a preserved, sodium carboxymethylcellulose-based gel for topical administration. This formulation was granted a licence for use in the USA in December 1997 and in Europe in March 1999. The aqueous gel provides the additional benefit of a moist wound healing environment, which is now the favoured mode of wound healing (d'Hemecourt et al, 1998). The use of becaplermin might be expected to promote wound healing by replacing any actual or relative deficiency with a pharmacological excess of PDGF.

Research to date has concentrated on diabetic foot ulcers as the most common example of chronic wounds, but ultimately is likely to embrace leg ulcers and pressure sores.

There have been four major trials of the use of becaplermin in its preserved formulation in neuropathic ulcers which have reported so far (Steed, 1995; d'Hemecourt et al, 1998; Wieman, 1998; Wieman et al, 1998). All but one was double blind or placebo controlled. Although the trials used different concentrations of rhPDGF, the best efficacy was seen with 100 μg/ml and this is the concentration that was finally licensed.

Publisher's note: Full resolution images are not available in the online version.



Case study example of becaplermin used on a diabetic foot ulcer.

Trial data

The study designs were all different and not all were powered for a treatment effect. Therefore, in a recent overview of efficacy there has been some pooling of data to compare like subjects.

The entry criteria for all the studies were similar. Patients had to have a chronic diabetic neuropathic foot ulcer of at least 8 weeks duration. The sizes of ulcer varied between the trials; consequently patients with ulcers of >10 cm^2 area were excluded from the analyses. This left 95% of patients from the four trials eligible for pooled analysis.

The primary end-point was the total number of patients healed, with a secondary endpoint of the time to healing. Improvement was not used as an endpoint and is therefore not reported, potentially reducing the impact of the effectiveness of becaplermin in the results that were reported.

The patients in the studies had a median age of 58 years and 70% were male. All patients had to have a peri-ulcer transcutaneous oxygen tension of >30 mmHg.

The ulcers were predominantly forefoot ulcers with a median area of 3 cm^2. This is typical of the general ulcer population. However, the median time to entry in the studies, from the onset of ulceration, was 30 weeks. This is far in excess of the median healing time for most ulcers in routine practice and demonstrates what a difficult to heal group becaplermin was being used on.

The median ulcer area was 1.5 cm^2. The becaplermin gel 100 μg/g treatment group demonstrated a 39% increase in complete healing compared with the placebo gel treatment group (50% vs 36%, respectively, $P = 0.007$). Becaplermin gel 100 μg/g significantly decreased ($P = 0.01$) the time to complete healing compared with placebo gel, with a 30% reduction in the 35th centile for time to complete healing (99 vs 141 days).

In ulcers of ±5 cm^2 area at baseline, becaplermin gel 100 μg/g significantly increased the incidence of complete healing (46.7% vs 30.4%, $P = 0.009$), with a similar decrease in the time to healing (35th centile for healing 92 vs 112 days, $P = 0.008$, respectively).

Summary of preclinical studies

- Chronic wounds are characterised by defects in growth factor activity
- Becaplermin is an analogue of human platelet derived growth factor activity
- Topical application of becaplermin was not associated with significant systemic toxicity
- Becaplermin is still active in wounds more than 12 hours from application

Summary of clinical studies

- In ulcers of 5cm^2 area or less, becaplermin 0.01% gel increases the number of chronic neuropathic ulcers which heal completely within 20 weeks
- The median healing time is reduced for those ulcers that do heal
- There have been no significant side-effects in the trials reported so far

Practice points

- Becaplermin is only licensed for use on chronic ulcers of ±5cm^2 area
- Becaplermin should only be used in conjunction with best wound healing practices, i.e. pressure relief, debridement and treatment of infection
- The total lifetime exposure of any individual patient to becaplermin gel must not exceed 20 weeks at present

Adverse events reported during treatment or during a 3-month follow-up period were not unexpected for this patient population and were similar in nature and incidence across all treatment groups.

The treatment effects seem small, but it should be remembered that only patients who achieved complete healing were considered to have demonstrated a treatment effect — not those in whom healing improved or in whom healing took place after the 20-week treatment period.

Three of the trials followed patients for 3 months after complete healing. In these follow-up periods no standardised regimen of footcare was prescribed and the recurrence rate in all treatment arms was around 30%. This aspect of treatment probably requires further study.

Clinical usage

There is, overall, clear evidence for a treatment effect above that of placebo or standard wound care. In clinical use, Regranex (becaplermin 0.01% gel) is presented as a 15 g single patient, multidose tube. The commercial cost of Regranex is not yet known, but is likely to be lower than tissue-engineered equivalents for a full course of treatment.

There is unlikely to be any head-to-head trial of these products, and patient selection is therefore vital. As in the trials, Regranex must be used only in the context of a complete wound healing regimen comprising pressure relief, appropriate debridement, and antibiotics.

A smear of Regranex gel is spread over the ulcer each day and covered with a secondary dressing. The tube must be used within 6 weeks of opening and stored in a refrigerator at all times when not in immediate use. Repeated evaluation of the wound should be performed to ensure that progress is being made. As the trial evidence is limited to 20 weeks use, this is the current maximum lifetime exposure for one patient.

It is hoped that the development of growth factors and other advanced wound healing products will have a significant impact on the continuing toll of amputations in chronic, previously non-healing, neuropathic ulcers. ■

Castronuovo JJ, Ghobrial I, Giuisti AM, Rudolph S, Smiwll JM (1998) Effects of chronic wound fluid on the structure and biological activity of becaplermin (rhPDGF-BB) and becaplermin gel. *Am J Surg* **176**(Suppl 2A): 61S-67S

Cooper DM, Yu EZ, Hennesey P et al (1994) Determination of endogenous cytokines in chronic wounds. *Ann Surg* **219**: 688-92

d'Hemecourt PA, Smiell JM, Karim MR (1998) Sodium carboxymethylcellulose aqueous-based gel *vs* becaplermin gel in patients with nonhealing lower extremity diabetic ulcers. *Wounds* **10**: 69-75

LeGrand EK (1998) Preclinical promise of becaplermin (rhPDGF-BB) in wound healing. *Am J Surg* **176** (Suppl 2A): 48S-54S

Ross R (1989) Platelet-derived growth factor. *Lancet* **331**: 1179-82

Steed DL, the Diabetic Ulcer Study Group (1995) Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. *J Vasc Surg* **21**: 71-81

Wieman TJ (1998) Clinical efficacy of becaplermin (rhPDGF-BB) gel. *Am J Surg* **176**(Suppl 2A): 74S-79S.

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