REVIEW ARTICLE

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Benefit-Risk Assessment of Becaplermin in the Treatment of Diabetic Foot Ulcers

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Contents

Abstract

Becaplermin is a recombinant platelet-derived growth factor composed of two B chains that is approved for the treatment of neuropathic diabetic foot ulcers extending into or beyond the subcutaneous tissue in patients with adequate arterial perfusion. The aim of this review is to assess the benefits and risks associated with the use of this agent. Randomized controlled trials have provided evidence for the efficacy of becaplermin in increasing healing rates, and cost analyses have repeatedly shown a favourable cost-effectiveness ratio. However, clinical experience has not met these high expectations and becaplermin is not widely used. Moreover, this agent has not been compared with other additional treatment modalities, notably bioengineered skin substitutes and extracellular matrix proteins, and such comparisons are eagerly awaited. Of particular note, increased cancer risk has been reported in patients treated with more than three tubes of becaplermin; thus, this agent should be used only when the anticipated benefits outweigh the potential harm, and with extreme caution in patients with diagnosed malignancy. Finally, longer follow-up data are necessary to shed more light on the potential risk of malignancy in connection with becaplermin use.

Foot ulcers represent one of the major long-term complications of diabetes mellitus and are associated with significant increases in morbidity and mortality.[1,2] Ulceration results from the complex interaction between the three major aetiological pathways – neuropathy, peripheral

arterial disease and infection.[3,4] Neuropathy is often considered the principal aetiological factor, underlying approximately two-thirds of all cases.[5-7] The role of neuropathy is 3-fold: first, it leads to stocking-distribution sensory loss, so that foot injury may go unrecognized, eventually leading to continuing tissue breakdown; second, it may lead to various foot deformities (such as claw toes) that are responsible for the redistribution of foot pressures and the development of high pressures in some areas; and third, it impairs sweating, leading to dry skin with fissures, which facilitate foot injury and entry of bacteria into deep tissues.[2-4,7] The situation is aggravated by the poor blood supply to the limb in case of peripheral arterial disease, as well as by superimposed infection.[2-4,7]

The aim of this review is to assess the benefits and risks associated with the use of becaplermin gel, a treatment modality approved for neuropathic diabetic foot ulcers in patients without lower extremity ischaemia.[8,9]

1. Literature Search Strategy

Articles for this review were obtained by searches of PubMed, EMBASE and the ISI Web of Knowledge databases, to June 2009, using combinations of the following keywords: 'becaplermin', 'diabetes mellitus', 'diabetic foot', 'healing', 'neuropathy' and 'ulcer'. All types of articles (randomized controlled trials, original studies, review articles, case reports) were included. Publications were studied in full, but only the abstracts were considered for studies not written in English.

2. Becaplermin

2.1 Background

Becaplermin is a recombinant platelet-derived growth factor (PDGF) composed of two B chains that is produced by incorporation of the gene for the B-chain of human PDGF into the yeast *Saccharomyces cerevisiae*.[8] The resultant product is a homodimeric protein with a molecular weight of approximately 25 kD, composed of two identical polypeptide chains that are held together by a disulfide bond.[8,10] Becaplermin has biological activities similar to endogenous PDGF, which promotes wound healing by acting on several cell lines, mainly fibroblasts, smooth muscle cells and endothelial cells, and also induces production of fibronectin and hyaluronic acid.[8] Becaplermin is commercially available as a gel form with 100 μg/g active ingredient (Regranex® gel, Ortho-McNeil Pharmaceutical, Inc., Titusville, NJ, USA; and Janssen-Cilag International NV, Beerse, Belgium). In 1997, Regranex® was approved by the US FDA and European Medicines Agency for the treatment of diabetic neuropathic ulcers in patients with adequate arterial perfusion.[8-10]

2.2 Use and Indications

Becaplermin has been used in various clinical situations, including pressure ulcers, necrobiosis lipoidicum diabeticorum, abdominal wound separation and previously irradiated wounds.[11] It is currently indicated for the treatment of neuropathic diabetic foot ulcers that extend into the subcutaneous tissue or beyond and which have adequate arterial perfusion.[8,10,12] It is indicated for use in combination with sharp debridement, off-loading and infection control, but has not been evaluated for the treatment of ischaemic foot ulcers or neuropathic foot ulcers that do not extend through the dermis into subcutaneous tissue.[8,10,12]

Although becaplermin has been on the market for more than 10 years, it has never achieved wide routine use in specialized foot clinics.[8,13] The situation was summarized in the 2007 consensus statement of the International Working Group on the Diabetic Foot, which suggested that widespread use of becaplermin could not yet be justified by the available evidence.[13] In published clinical trials, becaplermin has been used in at least 3675 patients for treatment periods of between 1 and 3 months.[14-20] In actual clinical practice, the number of patients who have received this agent is certainly larger, but there are no data to quantify patient exposure more precisely.[8,13]

2.3 Benefit Evaluation

The benefit conferred by becaplermin in terms of healing rates for the diabetic foot has to be

evaluated in the context of the vast burden incurred by this ominous complication of diabetes.[1-3,21] Indeed, more than 5% of diabetic patients have a history of foot ulceration, and the lifetime risk of developing this condition in patients with diabetes has been estimated at 25%.[2,6] Diabetic foot ulcers are characterized by very poor healing and high recurrence rates.[1-4] This holds true for neuropathic ulcers in particular.[22-24] Despite progress achieved to date, almost half of the latter (49%) may still fail to heal,[24] indicating the need for further improvement in treatment options.[1,3,21] Failure to achieve wound healing in the diabetic foot has very important consequences since the majority of lower limb amputations are the result of prior ulceration.[1,2]

Becaplermin is the only FDA- and European Medicines Agency-approved growth factor for use in the management of diabetic foot lesions.[8,9,11] The rationale for its use lies in the major role that endogenous growth factors play in normal healing by mutually interacting chemoattractive and mitotic effects on various cells.[8,9,11] Importantly, there is evidence of reduced or abnormal expression of growth factors in chronic diabetic wounds.[25,26] Diminished action due to glycation of growth factors,[27] as well as resistance to their action,[28,29] has been reported. These perturbations have already been emphasized as being of clinical significance to impaired healing in diabetes.[29-31] While growth factors act via complex mutual interactions and no single growth factor could be truly identified as the most important one, PDGF has been documented to play a key role in wound healing. The pivotal role of endogenous PDGF creates expectations for a favourable effect of recombinant platelet-derived growth factor in the advancement of healing.[8] Consequently, becaplermin treatment aims to improve healing rates and reduce time to wound closure in diabetic neuropathic foot ulcers compared with standard medical practice alone.[8] Its beneficial effect can be evaluated by examining the evidence available both from randomized controlled trials and results obtained in actual clinical practice.

A number of randomized controlled trials, reviewed in more detail elsewhere,[8] testify to the beneficial effect of becaplermin. Steed[14] recruited 118 patients with lower extremity diabetic ulcers who were randomly assigned becaplermin 30 μg/g or placebo. In the becaplermin group, 48% (29/61) of ulcers healed compared with 25% (14/57) in the placebo group ($p = 0.01$). There was also a slightly greater ($p = 0.09$) reduction in wound area in the former group (98.8%) than the latter group (82.1%).[14]

Wieman et al.[15] recruited 382 patients with chronic neuropathic diabetic ulcers who were randomized to becaplermin gel 30 μg/g, becaplermin gel 100 μg/g or placebo added to standard wound care. Becaplermin 100 μg/g significantly increased healing rates and decreased time to complete healing ($p = 0.007$). Healing rates were 49.5% (61/123), 36.3% (48/132) and 34.6% (44/127) with becaplermin 100 μg/g, becaplermin 30 μg/g and placebo, respectively.[15]

In a trial of 172 patients with non-healing lower extremity diabetic ulcers, D'Hemercourt et al.[16] compared good wound care alone with add-on topical carboxymethylcellulose (carmellose) gel or add-on becaplermin gel 100 μg/g. A slightly higher (p = non-significant) healing rate was attained in becaplermin-treated patients (44.1%) than carboxymethylcellulose-treated patients (35.7%) and in those receiving standard wound care alone (22%).[16]

Smiell et al.[32] published a combined analysis including patients recruited in the three aforementioned studies,[14-16] as well as 250 patients from a fourth study that was never published separately. This combined analysis demonstrated a significant beneficial effect of becaplermin on healing.[32] Use of becaplermin 100 μg/g significantly ($p = 0.0007$) increased healing rates compared with placebo by 39% (50% vs 36%, respectively). Time to complete healing also decreased significantly (mean 14.1 weeks vs 20.1 weeks, respectively; $p = 0.01$).[32]

In a multicentre, open-label study, Embil et al.[17] assessed the efficacy of becaplermin gel 100 μg/g in 134 patients with chronic lower extremity diabetic ulcers. Treatment was associated with healing rates as high as 57.5%, with a mean healing time of 63 days and a 21% recurrence rate at 6 months.[17]

A more recent small trial compared the efficacy of add-on becaplermin to wound care only in 20 patients with large neuropathic plantar ulcers off-loaded by a modified total contact cast.[19] Use of becaplermin reduced time to complete healing by 41.8% (mean ± SD 50.10 ± 23.38 days vs 68.10 ± 32.35 days with wound care only; $p = 0.02$).[19]

In another double-blind trial, 113 patients with neuropathic foot ulcers were randomized to becaplermin gel 100 μg/g ($n = 55$) or placebo gel ($n = 58$) for 20 weeks.[20] Complete ulcer healing was significantly ($p < 0.05$) more common in the becaplermin-treated group (58%) than in the placebo group (26%). Mean healing time was also significantly ($p < 0.001$) shorter with becaplermin (57 days) than with placebo (96 days).[20]

Despite the positive results obtained in randomized controlled trials, clinical experience with becaplermin has not matched these results.[8,13] This incongruity is explicable on the basis that randomized trials are performed in the ideal world of tightly controlled conditions, whereas clinicians encounter patients in the real world.[8] Consequently, the excellent efficacy of a drug in controlled trials does not equate to its effectiveness in actual clinical practice. Therefore, Margolis et al.[18] set out to examine the effectiveness of becaplermin in 'real-world' situations. They included 24 898 patients with neuropathic foot ulcers, of whom 2394 (9.6%) received becaplermin. Becaplermin increased healing rates by 32% versus the control group (33.5% vs 25.8%, respectively; absolute difference 7.7%; $p < 0.0001$). Similarly, becaplermin was linked to a significant reduction in amputations (4.9% vs 6.4% in the control group; absolute difference 1.5%; $p < 0.0001$).[18] Despite the significant differences achieved, this study may be criticized for its retrospective design and the very small absolute differences between becaplermin and control. Further limitations, as acknowledged by the authors themselves, include the reliance on a propensity score model and the absence of information on dose of PDGF and compliance with treatment. The propensity score model aimed to control for co-variates but could not guarantee absolute control of all confounders. Thus, one may argue that this model does not provide robust evidence for the effectiveness of becaplermin in ordinary situations.

All in all, the effectiveness of becaplermin reported in randomized trials has not been adequately confirmed in everyday clinics, and the drug is consequently still not widely used.[8] In a recent consensus statement, the International Working Group on the Diabetic Foot has, accordingly, suggested that evidence justifying the use of becaplermin remains to be confirmed.[13]

2.4 Cost Effectiveness

Several analyses have shown the cost effectiveness of becaplermin.[33-39] The favourable cost-effectiveness ratio holds true for Sweden,[33,35] Switzerland,[35] UK,[34,35] France,[35] Canada[38] and USA.[36,37,39] In the USA, add-on becaplermin is, initially, linked with higher cost but the effectiveness of the drug succeeds in reducing expenses arising from long-term treatment, including office visits, dressings and recurrence rates.[37] In Canada, add-on becaplermin treatment for 20 weeks over a 12-month period has been reported to reduce ulcer-days per patient by 26.[38] Thus, the health system may save $Can6 per ulcer-day avoided.[38] More recently, a cost analysis from a US tertiary-care referral wound centre showed that the average becaplermin use was 1.54 tubes per patient over 12 months, amounting to only $US42 per course of therapy.[39] This cost could easily be afforded by the insured patient in this setting.[39]

It is also important to note, however, that studies to date have failed to examine the cost effectiveness of becaplermin in other parts of the world, including the developing countries. Given the high cost of becaplermin and the financial constraints in such countries, the cost effectiveness data reported in Western countries is not directly generalizable worldwide.[8] Moreover, the effectiveness of becaplermin has not been adequately confirmed in 'real-world' clinical situations.[13] Hence, it is rather unclear whether the cost effectiveness calculated in the above-mentioned analyses holds true in everyday practice.

2.5 Risk Evaluation

In the clinical trials mentioned earlier, the safety of becaplermin has been reported as excellent and not inferior to placebo.[8] One of the earliest publications specifically evaluating the safety of becaplermin reached positive conclusions.[40] Indeed, rash occurred in 2% of becaplermin-treated patients and in 1% of those receiving placebo, while all other adverse reactions (cardiovascular, respiratory, musculoskeletal and central or peripheral nervous system disorders) were comparable between becaplermin and placebo. Of note, becaplermin administration was not associated with the development of neutralizing antibodies. The safety of becaplermin has been re-affirmed in a more recent report.[41]

However, more recently, data from longer patient follow-up became available to regulatory authorities.[12] Data for 651 patients from two randomized controlled trials followed up for 20 months to ascertain any malignancy diagnosed after completion of the trials revealed increased risk with becaplermin. In the becaplermin group, the frequency of new cancer was 3% (8 of 291 patients) compared with 1% (2 of 200) in the control group (odds ratio 2.7; $p < 0.005$). There was no association with any particular type of malignancy, and all cancers were remote from the application site.[12]

Subsequently, a larger patient database was examined for the incidence of cancer. The analysis comprised 1622 patients using becaplermin and 2809 controls.[12] The incidence of cancer was not increased with becaplermin (10.2 per 1000 patient-years) compared with the control group (9.1 per 1000 patient-years; p = non-significant). Mortality from cancer was also comparable in the becaplermin (1.6 per 1000 patient-years) and control (0.8 per 1000 patient-years; p = non-significant) groups. However, patients who had been treated with more than three tubes of becaplermin had increased cancer risk (3.9 per 1000 patient-years vs 0.9 per 1000 patient-years; odds ratio 5.2; $p < 0.05$).[12]

This new information prompted the FDA to issue a drug warning in July 2009 about the increased risk of cancer associated with the administration of more than three becaplermin tubes.[42] The drug should only be used when clinicians estimate that the anticipated benefits outweigh the potential harm, and extreme caution is certainly warranted in patients with known malignancy.[42]

2.6 Comparison with Other Therapies

Becaplermin is a therapeutic adjunct in the overall management of diabetic foot ulcers. It may be added to standard wound care but is still secondary to the application of established therapeutic measures.[8] Such measures include adequate off-loading to relieve high-pressure plantar areas, aggressive debridement to remove callus and necrotic debris, and prompt infection control.[1,3,4] Other additional treatment modalities comprise miscellaneous bioengineered skin substitutes and extracellular matrix proteins.[8,43] However, there is no head-to-head comparison of becaplermin with other therapeutic adjuncts;[8] thus, becaplermin can be compared with standard treatment only.

Compared with standard treatment, becaplermin may increase healing rates and reduce the time needed to heal.[8] A recent meta-analysis published in abstract form re-affirmed that application of becaplermin 100 μg/g gel in patients with diabetic neuropathic foot ulcers resulted in a significant ($p < 0.05$) increase in healing rates by 36% and a significant reduction in time to wound closure compared with standard treatment.[41] However, serious reservations apply to the assumption that the superiority of becaplermin demonstrated in small studies may be achieved in clinical practice.[8,13]

2.7 Benefit-Risk Evaluation

Becaplermin is one of a group of agents making up the therapeutic arsenal for the diabetic foot. According to available evidence, becaplermin may increase healing rates and decrease time to successful healing.[14-17,19,20] This efficacy notwithstanding, the drug has never been widely used and there are reservations as to whether such excellent results are actually achieved in everyday practice.[13] More importantly, increased

cancer risk has been reported among becaplermin-treated patients but this increase appears to be significant only in patients treated with more than three tubes of becaplermin.[12]

Based on this knowledge, wide routine use of becaplermin must be discouraged. Instead, clinicians should make the best use of validated therapeutic measures in the management of neuropathic ulceration.[3,4,8,43] Only after such an approach has failed should patients receive becaplermin. Until longer safety data become available, it is also advisable to restrict prescriptions to three tubes of becaplermin.[42,44] However, extreme caution is suggested in patients with a history of cancer.[42,44]

3. Conclusions

Longer follow-up data are necessary to shed more light on the potential risk of malignancy in connection with becaplermin use. For this reason, use of becaplermin should now be reserved only for difficult-to-heal neuropathic foot ulcers that do not respond to established treatment. In patients with a history of malignancy, becaplermin should be used only with the utmost caution. Finally, under no circumstances should established treatment modalities be neglected in patients receiving becaplermin.

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