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Becaplermin

Prop INN; BAN; USAN

Platelet-Derived Growth Factor
Wound Healing Agent

rhPDGF-BB
RWJ-60235
Regranex®

Recombinant human platelet-derived growth factor B (rhPDGF-BB) homodimer produced from genetically engineered *Saccharomyces cerevisiae* cells into which the gene for the B-chain of PDGF has been inserted and with a molecular weight of approximately 25 kD

CAS: 165101-51-9

EN: 198489

Introduction

Through the process of wound healing, the body of a living organism attempts to restore the original structure and function to an injured organ or tissue. The objective of this fundamental process is to reestablish the optimal environment required for said organism to survive and remain active. Medical science has for many centuries attempted to assist in and facilitate this process, as evidenced by the existence of poultices, dressings, *etc.*, long before the processes of wound healing began to be understood. Modern science has succeeded in achieving a broader understanding of the wound healing process and the many factors that influence it, and the treatment of wounds has improved vastly as a result. Nonetheless, there is still a wide range of wounds that are considered difficult to heal, or that do not remain closed after healing occurs. Diabetic foot ulcers, a major and serious complication of diabetes mellitus, represent perhaps the most difficult class of chronic wounds in terms of efficient and permanent healing (1).

Three classic phases of a normal wound healing response have been identified: inflammation, fibroplasia and epithelialization. Various cell types are involved in this process, as well as structural proteins, growth factors and proteinases, and the interactions between them are complex and intricate (2).

Given the essential role played by growth factors in the healing process, recombinant growth factors have been studied for more than a decade as a method of accelerating wound healing. In general, the results obtained with these products have been discouraging, although some successes have also been reported. This variability has been attributed to the essential differences between different types of wounds. Each wound is unique and is affected by unique circumstances, and therefore could presumably be treated most effectively by identifying the particular growth factor, cytokine or other biologic agent involved and providing the appropriate targeted treatment (3).

To date, only one growth factor has been successfully developed for the indication of wound healing: Chiron's recombinant platelet-derived growth factor BB (rhPDGF-BB, becaplermin).

Platelet-derived growth factor is an endogenous growth-promoting protein that is released from cells involved in the healing process. The core protein of PDGF is a dimer of two polypeptides: A and/or B. All three forms of PDGF (PDGF-AA, PDGF-AB and PDGF-BB) are biologically active, but fibroblasts respond particularly well to the latter form. Becaplermin is a recombinant form of PDGF-BB which retains the biological activity of the native protein (17).

Pharmacological Actions

The mitogenic, chemotactic and synthetic responses to becaplermin were evaluated *in vitro* in rat periodontal ligament (PDL) fibroblastic cells obtained from the coagulum of healing tooth sockets and were compared to those seen with other growth factors. The mitogenic effects of becaplermin were similar to those of PDGF-AB and insulin-like growth factor-I (IGF-I), with maximum mitogenic activity at the concentration of 10 ng/ml for both becaplermin and PDGF-AB. Potent chemotactic responses were also observed in PDL cells, with only IGF-I producing more potent effects than becaplermin. The study compound had no effect on collagen synthesis or other protein syntheses. The potent mitogenic and chemotactic activities observed with becaplermin in this study indicate its potential utility in the promotion of PDL healing. Furthermore, its effects may be enhanced through combination with IGF-I (4).

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Becaplermin also demonstrated wound healing activity in animal models, primarily by enhancing the formation of granulation tissue. The compound was evaluated in various models, including guinea pig and pig models of partial and full thickness skin excision wounds, in rats, mice and guinea pigs with subcutaneous sponge implants and in normal and healing-impaired rats and mice with incision wounds. Overall, topical treatment with becaplermin was extremely effective in terms of enhancing the formation of granulation tissue, although it had highly variable effects on epithelialization and wound contraction and did not consistently improve the strength of incisional wounds (5).

Becaplermin was also effective in stimulating bone formation in a rabbit model of calvarial defects. A single dose of the compound (50 mg/ml in 4.4% methylcellulose gel) was applied topically to critical-size defects in the calvarial bone; methylcellulose gel alone was used as control. Healed bone in becaplermin-treated rabbits analyzed at 8 weeks had a trabecular structure, whereas that in control rabbits was more compact. Furthermore, the porosity of newly formed bone in the drug-treated group was 84% greater than in the control group. Mineralized tissue increased by 112% and bone marrow increased by 75% in becaplermin-treated animals (6).

The bone formation-regenerating effects of becaplermin were studied in rats with craniotomy defects administered 0, 20, 60 or 200 μg of the drug via an implant, with or without the addition of bovine osteogenin. Eleven days after implantation, the becaplermin-treated rats presented subcutaneous masses comprised of serosanguinous fluid encapsulated by fibrous connective tissue; these masses were larger than the defect size and were of greatest volume in the 200-μg dose group. No such masses were observed in rats that did not receive the growth factor. Twenty-eight days after surgery, all masses were resorbed. Calcified tissue within the defect site was regenerated significantly and dose-dependently in treated rats. Furthermore, bone regeneration stimulated by osteogenin was inhibited by 17-53% in the study group. Thus, becaplermin stimulated soft tissue wound repair and inhibited osteogenin-induced bone regeneration in this animal model (7).

Becaplermin, used in combination with dexamethasone and a collagen matrix, was also shown to enhance periodontal regeneration in a monkey model (8).

A study was conducted in rabbits with dermal ulcers of the ear in order to evaluate the characteristics of the wound matrix components induced by becaplermin and other growth factors, as well as to define the molecular mechanisms involved in accelerated repair and wound maturation. Immunohistochemical stains and image analysis techniques were employed for purposes of analyzing the wounds at various stages of the healing process. Application of a single optimal dose of becaplermin accelerated healing by 30%, mainly via an accelerated deposition of provisional wound matrix. As compared to untreated wounds, drug application significantly increased the early deposition of glycosaminoglycan and fibronectin and increased collagen levels at a later stage in the healing process (9).

Toxicity

Becaplermin demonstrated a favorable safety profile in studies evaluating its systemic toxicity, local irritation, sensitization and genotoxic potential. No notable drug-related systemic or local toxicities were seen in monkeys following administration of single and multiple i.v. or s.c. doses of up to 3 mg/kg. Rapidly reversible vasodilation and CNS depression occurred in mice receiving single large i.v. doses (up to 100 mg/kg) or multiple smaller doses (1 or 3 mg/kg) of becaplermin. Histomorphological changes indicative of accelerated bone remodeling were reported in a bone toxicity study but appeared to be potentially reversible; this effect has not been reproduced in human studies, however. Some skin-sensitizing activity was observed in animals treated with becaplermin, but the agent was not considered to be a dermal or ocular irritant. No genotoxicity was observed *in vitro* or *in vivo*. In conclusion, becaplermin did not appear to have the potential to cause significant adverse clinical reactions following its topical application to open wounds (10).

Clinical Studies

In spite of the extensive preclinical evaluation conducted with this agent, the lack of animal models that accurately represent chronic human wounds meant that the progression to clinical testing of becaplermin in human subjects required a certain “leap of faith” (5).

A small study was conducted in 12 patients with chronic diabetic ulcers (at least 8 weeks duration) or pressure ulcers (at least 4 weeks duration) in order to determine the effects of wound fluid on the structure and biological activity of becaplermin. Wound fluid was collected from the patients and cultured, with or without the addition of becaplermin, both before and after incubation for 12 h at 37 °C (*in vitro* analysis) and after 12 h of topical treatment with becaplermin gel or vehicle (*in vivo* analysis). No mitogenic or becaplermin activity was detected in chronic wound fluid alone; however, mitogenic activity was present in posttreatment samples from becaplermin-treated subjects. No such activity was present in samples from vehicle-treated control subjects. The amount, binding pattern and mitogenic activity of becaplermin remained unchanged after 12 h of exposure to chronic wound fluid, and biologically active becaplermin was still present in the wound fluid 12 h after its topical application (11).

An early randomized, double-blind, placebo-controlled phase I/II study evaluated the effects of becaplermin on the healing of chronic pressure ulcers in a small group of patients. Twenty subjects with chronic pressure ulcers were randomized to treatment with 1, 10 or 100 μg/ml/day becaplermin (0.01, 0.1 or 1.0 μg/cm^2 of ulcer

area) for 28 days. Patients in the highest dose group had a faster rate of ulcer healing than patients treated with placebo; the difference was not significant with the lower doses of becaplermin. At the end of the treatment period, wounds that had been treated with high-dose becaplermin were smaller than those treated with placebo. No drug-related toxic effects were described, and topical becaplermin was considered to be a potent and safe wound healing agent in soft tissue wounds (12).

Fifty-two elderly inpatients with stage III or IV pressure ulcers were enrolled in a multicenter, prospective, randomized, double-blind phase II trial. Subjects were randomized to treatment with placebo or becaplermin (100 or 300 μg/ml), administered as a topical spray for 28 days; gauze dressings and frequent turning were also practiced. Forty-one patients were available for analysis on day 29. At the end of the treatment period, median ulcer volume (as measured using alginate molds) had decreased to 83%, 29% and 40% of their baseline volume in the placebo, low-dose and high-dose becaplermin groups, respectively. Healing was still significantly better in the becaplermin groups when data were adjusted for initial wound volume. Using a linear contrast procedure, ulcers in the two active treatment groups were shown to be significantly smaller than those in the placebo group. The investigators suggested that complete healing could conceivably be attained with longer treatment periods (13).

A double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of becaplermin was performed in 118 patients with chronic (at least 8 weeks duration) full-thickness diabetic neurotrophic ulcers of the lower extremities. Patients were treated once daily with topical becaplermin (2.2 μg/cm^2 of ulcer area) or placebo until complete resurfacing of the ulcer or for a maximum of 20 weeks, whichever occurred first. Complete wound healing was observed in 29/61 patients (48%) randomized to treatment with becaplermin, as compared to only 14/57 (25%) in the control group. The frequency and severity of adverse events were similar in the active treatment and placebo groups (14).

In another multicenter phase III trial in 382 patients with type 1 or type 2 diabetes and chronic (at least 8 weeks duration) neuropathic ulcers, becaplermin (30 or 100 μg/g) or placebo gel was administered in combination with good wound care. Again, treatment lasted for a maximum of 20 weeks or until complete wound closure, whichever came first. The incidence of complete wound closure was 43% greater and time to complete wound closure was 32% shorter in the high-dose becaplermin gel group as compared to placebo. Adverse events during treatment and over a 3-month follow-up period were similar in frequency and type in all three groups. High-dose becaplermin (100 μg/g) gel, in combination with good wound care, was considered to be very effective and safe in the treatment of chronic diabetic neuropathic ulcers. Furthermore, the gel formulation of becaplermin employed in this study was easy to use in an outpatient setting (15).

The efficacy of ulcer treatment using becaplermin gel (100 μg/g) was compared with that of good ulcer care alone in a study in 250 patients. Eighty-eight percent of the study participants completed the study, and the incidence of complete ulcer healing was statistically equivalent in the becaplermin group (36%) and in the good ulcer care group (32%) (16).

A meta-analysis has been performed on data from the above four studies (13-16), in which becaplermin gel was provided as active therapy in a trial actually designed to evaluate the safety of a placebo gel. The results of this meta-efficacy analysis showed that becaplermin gel at the optimum dosage of 100 μg/g increases the incidence of ulcer healing, thereby improving the management of lower extremity diabetic neuropathic ulcers (16).

A related review article has concluded, on the basis of a meta-analysis of the safety data on becaplermin gel generated in six well-controlled clinical studies, that the agent possesses an excellent safety profile. The incidence of ulcer-related adverse events (*i.e.*, infections, cellulitis or osteomyelitis) was similar among patients treated with becaplermin or good ulcer care alone, and erythematous rash occurred in 2% and 1% of patients treated with becaplermin or placebo gel, respectively. Systemic adverse events affecting the cardiovascular, respiratory, musculoskeletal, central and peripheral nervous systems and treatment-related mortality occurred with a similar frequency across all treatment groups. Furthermore, no neutralizing antibodies against becaplermin developed in patients treated with the agent (17).

A phase I/II trial has further evaluated the wound-healing activity of becaplermin in combination with IGF-I in the setting of periodontal disease. Thirty-eight patients with bilateral osseous periodontal lesions were enrolled in the double-blind study. All subjects underwent full-thickness flap reflection, after which the experimental growth factors were applied at two dose levels (50 or 150 μg/ml each) in a gel vehicle directly to periodontal osseous defects according to a split-mouth design. Control treatment consisted in conventional periodontal flap surgery alone or surgery plus vehicle. The primary therapeutic endpoint was bone fill as analyzed by surgical reentry 6-9 months posttreatment. Patients in the high-dose becaplermin/IGF-I treatment group, but not those in the low-dose group, showed significantly increased alveolar bone formation 9 months after application of the growth factors. New vertical bone height increased by 2.08 mm in the high-dose growth factor group compared to an increase of only 0.75 mm in the control group. In a similar fashion, osseous defect fill increased by 42.3% and 18.5% in the high-dose treatment group and control group, respectively. Furcation lesions showed the most favorable response to the experimental treatment. Safety was also evaluated thoroughly, and no local or systemic toxicity was reported. Further evaluation of this combination growth factor therapy in patients with periodontal disease was considered to be warranted (18).

Regranex®, a topical formulation of becaplermin (0.01%) in an aqueous-based sodium carboxymethylcel-

lulose (NaCMC) gel, was approved in December 1997 by the Food and Drug Administration and was launched last year in the U.S. as an adjunct to good ulcer care of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and that have an adequate blood supply. Becaplermin is the first recombinant growth factor to be approved for the treatment of a chronic wound condition. Becaplermin continues to be studied for other wound-healing indications including pressure and venous ulcers (16, 19, 20).

Sources

Becaplermin concentrate is provided by Chiron Corp. (US); Regranex® Gel is manufactured by OMJ Pharmaceuticals, Inc. (US) and distributed by Ortho-McNeil Pharmaceutical, Inc. (US).

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