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Velafermin

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Treatment of Mucositis
Cytoprotectant
Radioprotectant

rhFGF-20
CG-53135
CG-53135-05

Recombinant human fibroblast growth factor-20

Fibroblast growth factor-20 (human recombinant CG53135)

CAS: 697766-75-9

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Abstract

Oral mucositis is an inflammation of the oral and esophageal mucosa that commonly follows high-dose chemotherapy and radiotherapy in patients with head and neck cancer, and in those undergoing bone marrow transplant. The condition is associated with painful ulcers that can have a significant impact on the health of the patients and on the cost of cancer treatment. Velafermin (rhFGF-20, CG-53135), a recombinant human fibroblast growth factor, promotes epithelial and fibroblast cell proliferation *in vitro* and speeds the repair of damaged mucosa in animal models of mucositis. A phase II study indicated efficacy and good tolerability in cancer patients.

Background

Mucositis is an acute inflammation of the oral or intestinal mucosa resulting from high-dose chemotherapy or radiotherapy. The symptoms can range from mild inflammation to extremely painful ulcers that can prevent the patient from being able to swallow or speak, greatly affecting their quality of life and response to cancer therapy. In addition, severe mucositis may necessitate the use of analgesics, parenteral nutrition and dose reductions or delays in cancer treatment, with an impact on patient outcome and healthcare resources. Mucositis is estimated to affect 40% of those receiving radiation or chemotherapy, rising to 70-80% of patients receiving myelotoxic conditioning regimens prior to hematopoietic stem cell transplant, and over 80% of those receiving radiation therapy whose fields include the oral cavity, for example in head and neck cancer (1).

The oral and intestinal cavities are lined with rapidly dividing epithelial cells that have a finite life due to mechanical and chemical wear. Although rapid cell division is essential for maintaining the mucosa, this property also renders it vulnerable to the cytotoxic effects of radiotherapy and chemotherapy. The condition begins with radio/chemical damage to the DNA of basal epithelial cells, endothelial cells and submucosal fibroblasts, and with the generation of reactive oxygen species (ROS) that cause further cellular damage. Inflammation follows, along with apoptosis to cause breaks in the mucosa. Painful ulcers follow (usually 2-10 days after initiation of the therapy) and persist for 2-3 weeks after therapy ceases. The ulcers also provide a port of entry for commensal microbes that can amplify the ulceration, and in some cases, pathogens such as α-hemolytic streptococci gain entry to cause sepsis. Healing involves proliferation, differentiation and migration of epithelial cells to restore the integrity of the mucosa (2).

The fibroblast growth factor (FGF) family, comprising over 20 members, regulates various cellular functions, including growth, survival, apoptosis, motility and differentiation (3). CuraGen scientists identified and cloned a human gene encoding FGF-20, a new member of the FGF family. Velafermin (rhFGF-20, CG-53135) is a recombinant human fibroblast growth factor that stimulates epithelial and fibroblast cell growth and has a general cytoprotective effect via activation of the ROS-scavenging cascade. Velafermin is in phase II clinical trials for radiotherapy/chemotherapy-induced oral mucositis (4, 5).

Preclinical Pharmacology

The protective effect of velafermin was first evaluated in a mouse model of inflammatory bowel disease. During daily 5% dextran sulfate sodium administration, velafermin (5 mg/kg/day i.p. for 7 days) significantly decreased hemorrhagic diarrhea by 93%, colon submucosal edema by 76%, colon mucosal inflammation by 55%, colon glandular epithelial loss by 57% and colon surface epithelial loss by 84%. Velafermin also inhibited decreases in colon

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length and enhanced survival rates in the treated mice (6, 7).

In a rat model of indomethacin-induced small intestinal ulceration and inflammation, velafermin reduced small intestinal weight gain by 52%, necrosis by 53%, inflammation by 38% and weight loss by 36% relative to vehicle controls (7).

In a murine total-body irradiation (5.3-6.1 Gy) experiment, velafermin administered at a dose of 4 mg/kg i.p. 1 day prior to radiation led to significant gains (30-50%) in survival rates in the subsequent 30 days compared to controls (8). In a similar study, the odds of survival in animals treated with 12 mg/kg i.p. velafermin at day –1 were calculated to be 4.8-fold greater than for untreated irradiated animals (9). Velafermin was also associated with a decrease in ROS in irradiated animals, suggesting that upregulation of of free radical-scavenging pathways may be involved in its radioprotective effects (8, 9).

The protective effects of velafermin were investigated in two hamster models of oral mucositis. In the first study, velafermin (0.6 or 1.2 mg/kg/day i.p.) was administered on days 3-15 after irradiation and significantly reduced the days spent with severe mucositis from 68% in controls to 41% and 31%, respectively, at 0.6 and 1.2 mg/kg/day. When 5-fluorouracil (5-FU), a stomatotoxic agent associated with a high incidence of oral mucositis in humans, was added to the radiotherapy, optimal responses were obtained when velafermin was administered immediately after the chemo/radiotherapy combination treatment. Coincident with protection against mucositis, velafermin induced proliferation of cheek pouch and jejunal epithelial cells in the hamsters (10).

In vitro mechanistic studies showed that velafermin enhances the growth and migration of a variety of mesenchymal and epithelial cells. In one set of experiments, velafermin induced DNA synthesis in murine fibroblasts, normal human skin fibroblasts, human keratinocytes and human renal carcinoma, osteosarcoma and breast epithelial cells with half-maximal concentrations of approximately 10 ng/ml. It also stimulated cell proliferation, as demonstrated in murine fibroblasts, and these effects could be inhibited by soluble FGF receptors (6). Other studies confirmed its ability to induce DNA synthesis in murine fibroblasts and epithelial cells, as well as its ability to stimulate the growth of normal human colonic fibroblasts and intestinal epithelial cells. Moreover, concentration-dependent stimulation of wound repair was observed using human colonic epithelial cancer cells, as was concentration-dependent stimulation of normal human intestinal epithelial cell migration. Velafermin was shown to stimulate COX-2 and ITF genes in human colonic epithelial cancer cells and it also significantly and concentration-dependently increased PGE_2 levels in these cells (7). Velafermin also enhanced the survival of irradiated mesenchymal and epithelial cells, suggesting that it is a cytoprotectant as well as a stimulant of cell proliferation. Specifically, velafermin enhanced the expression of the transcription factor Nrf2 and MnSOD, and it also activated the Akt and ERK (extracellular signal-regulated kinase) pathways, which may be involved in its radioprotective effect. Treatment of irradiated cells with velafermin also reduced intracellular ROS levels (8).

Pharmacokinetics and Metabolism

In a single-dose study in hamsters, velafermin (6 mg/kg i.p.) reached peak plasma concentrations of 290 ng/ml in 1 h, which declined steadily with a $t_{1/2}$ of 20 h. The AUC was 1.2 μg.h/ml (10).

In the first phase I study in humans, the safety, tolerability, pharmacokinetics and biological activity of velafermin were investigated. Ten patients with advanced cancer received velafermin at 0.03 (n=4) or 0.1 (n=6) mg/kg as a single i.v. infusion 3 days after completion of chemotherapy. Peak plasma levels of velafermin were reached within 1 h, with an elimination half-life of 49 min (11).

Safety

Velafermin was well tolerated in the above study, with no serious drug-related adverse events, and no study discontinuations due to adverse events. Three patients had grade 2 mucositis and none had grade 3 or 4 oral mucositis (11).

In another phase I study in patients developing oral mucositis following high-dose chemotherapy, no adverse events were reported in 3 patients who received daily i.v. doses of 0.03 mg/kg velafermin for 3 consecutive days starting within 24 h of the development of oral mucositis. Dosing continues with 0.1 and 0.2 mg/kg/day (12).

Clinical Studies

Single escalating i.v. doses of velafermin (0.03, 0.1, 0.2 and 0.33 mg/kg) were administered to 30 patients with multiple myeloma (n=16), non-Hodgkin's lymphoma (n=12), acute myelogenous leukemia or desmoplasmic round cell tumor (n=1 each) undergoing high-dose chemotherapy and autologous peripheral blood stem cell transplantation in a phase I study. Velafermin was well tolerated at up to 0.33 mg/kg, but 2 patients experienced dose-limiting infusion reactions at this dose. Plasma exposure was dose-dependent. Twenty-three patients did not experience severe (grade 3-4) mucositis. No anti-velafermin antibodies were detected 30 days after treatment and tolerance was generally good (13-16).

A double-blind, placebo-controlled, dose-ranging phase II study was performed to determine the safety and efficacy of velafermin in 212 patients receiving high-dose chemotherapy with or without total-body irradiation as a conditioning regimen for autologous hematopoietic stem cell transplant. Patients were equally randomized to receive velafermin 0.03, 0.1 or 0.2 mg/kg or placebo as a single i.v. dose 24 h after completion of the stem cell transplant. Velafermin was well tolerated. A statistically significant reduction in grade 3 or 4 oral mucositis was observed in the lowest dose group (18% *vs.* 37% for

placebo). The duration of grade 3-4 oral mucositis was also significantly reduced. Most adverse events were mild to moderate, the most common serious events being neutropenia, fever and pneumonia (17, 18). A second phase II study is ongoing to confirm the activity of velafermin in preventing oral mucositis (19).

Source

CuraGen Corporation (US).

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