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Palifermin

Keratinocyte Growth Factor
Treatment of Mucositis

Recombinant Human Keratinocyte Growth Factor
rhKGF
rHuKGF
Kepivance™

Human fibroblast growth factor-(24-163)-peptide
24-163 Fibroblast growth factor 7 (human)

CAS: 162394-19-6
EN: 198476

Abstract

Mucositis is an inflammation of the oral and gastrointestinal mucosa, often associated with the administration of high-dose chemotherapy and radiotherapy regimens for cancer. It can be very debilitating, and in its most severe form can result in patients being unable to drink or swallow. It is particularly common following bone marrow transplantation in patients with hematological cancers. Palifermin is a recombinant human keratinocyte growth factor (rhKGF, rHuKGF), a novel compound that selectively stimulates epithelial cell growth and affords protection from the damaging effects of chemotherapy and radiotherapy. In normal human nasal epithelial cells, incubation with palifermin resulted in a significant increase in the number of cell doublings, whereas no significant effect was seen in human epithelial tumor cells. Palifermin also increased the dose required to induce ulceration of the tongue mucosa in mice receiving single-dose and fractionated radiotherapy with or without chemotherapy. Phase I studies in healthy subjects demonstrated a dose-dependent proliferation of buccal mucosal cell epithelium, and clinical studies in patients with head and neck cancer and advanced colorectal cancer showed reductions in the incidence and duration of mucositis. A pivotal phase III study in patients undergoing high-dose chemotherapy and radiotherapy regimens prior to bone marrow transplantation demonstrated a clinically meaningful reduction in the incidence of grade 3 and 4 mucositis, associated with significant reductions in opioid analgesia use and total parenteral nutrition. Palifermin was recently launched in the U.S. for the prevention and treatment of mucositis in this group of patients.

Introduction

Patients receiving high-dose chemotherapy and radiotherapy regimens for the treatment of cancer often experience mucositis, an inflammation of the oral and gastrointestinal mucosa. The condition may be associated with considerable pain and discomfort, leading to dose reductions or delays in chemotherapy regimens. In its most severe form, it can result in patients requiring liquid food, or even total parenteral nutrition (TPN) (1). Mucositis is a particularly common complication in patients receiving conditioning regimens prior to hematopoietic progenitor cell transplantation, with one prospective analysis reporting 99% of patients with oral mucositis and 67% with grade 3 or 4 mucositis (2, 3). In a similar group of patients, mouth sores were reported as the single most debilitating side effect of treatment, making it difficult or impossible to eat, swallow, drink or talk (4). In addition to its direct effects upon patients' well-being and quality of life, mucositis may also result in serious clinical consequences, with a subsequent impact upon healthcare resources. It can result in bleeding and infection, with increases in hospital stays and increased requirements for TPN and narcotics (5, 6).

Understanding the pathobiology of mucositis has resulted in the identification of potential therapeutic targets and the development of novel agents to treat the condition. One of these is palifermin (rhKGF, rHuKGF, Kepivance™), a recombinant human keratinocyte growth factor, a member of the heparin-binding family of fibroblast growth factors (FGFs). The compound stimulates epithelial cell growth, leading to increased thickening of the oral epithelium, and thus protection from the damaging effects of chemotherapy and radiotherapy. Palifermin

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was recently approved and launched in the U.S. following a priority review by the FDA (7, 8).

Pharmacological Actions

The *in vitro* effect of palifermin on the proliferation, clonogenic capacity and the response to radiation was investigated in low-passage human epithelial cells. Normal nasal epithelial cells incubated with palifermin showed a significant 2-3-fold increase in the number of cell doublings, whereas in tumor cells proliferation only occurred in 2 of 8 samples and was not significant. Addition of palifermin to the medium did not influence radiation-induced impairment of proliferation nor clonogenic cell survival of tumor cells. The results of this study indicated the potential of palifermin to selectively protect normal epithelia during clinical radiotherapy (9).

The protective efficacy of palifermin was evaluated in mouse tongue mucosa. During combined single-dose or fractionated radiotherapy protocols, palifermin (5 mg/kg/injection) increased the ED_{50} (the dose after which ulcer induction was expected in 50% of the mice) from 11.5 Gy for single-dose irradiation to approximately 19 Gy. In daily fractionated irradiation protocols, treatment with palifermin increased the ED_{50} for test irradiation from 5.7 to 12-15 Gy. Similar responses were seen when chemotherapy with platinum regimens and/or 5-fluorouracil (5-FU) was added to radiotherapy (10).

The effect of palifermin on tumor growth and small intestinal mucositis was investigated in rats bearing breast cancer implants and treated with methotrexate. In this study, palifermin did not protect the gut from mucositis, as indicated by the similarity in villus area between control and palifermin-treated groups. Palifermin synergized with methotrexate to increase apoptosis in both intestinal crypts and the implanted tumor (11).

In a murine model of massive small bowel resection, palifermin (5 mg/kg/day for 7 days) improved epithelial absorptive function and stimulated intestinal proliferation. Treatment with palifermin resulted in increases in mucosal villus height, crypt cell proliferation, mucosal DNA and protein content, and basic ion transport activity (12, 13).

The protective effect of palifermin was also studied in a murine model of graft-*versus*-host disease (GVHD) following experimental allogeneic bone marrow transplantation. Subcutaneous injection of palifermin (5 mg/kg/day) for 10 days significantly improved the survival of allogeneic bone marrow transplant recipients from 10% to 80%. In bone marrow transplantation, gastrointestinal tract injury results in translocation of lipopolysaccharides across the damaged mucosa, with subsequent systemic inflammatory cytokine production. Treatment with palifermin significantly reduced serum lipopolysaccharide levels at day 5 following transplantation, and also significantly reduced serum tumor necrosis factor-α (TNF-α) levels. It had a significant protective effect on both small and large bowel. The severity of GVHD, as measured by clinical score, was significantly reduced in palifermin-treated animals (14).

Palifermin (3 mg/kg/day for 3 days) improved the glutathione redox state of the colonic mucosa in fasted rats (15).

Studies have also been performed to determine the protective effects of palifermin in radiation-induced lung injury. Lung damage was induced in rats by fractionated irradiation and palifermin (5 or 15 mg/kg) was administered as a single i.v. injection immediately following the last fraction of irradiation. Late lung damage was assessed over a 6-month period. The average breathing frequencies, which increased at 6 weeks and reached a peak at 14 weeks after irradiation in the control group, were significantly lower in the palifermin-treated group. The severity of lung fibrosis and the level of immunoreactivity expressed by the components of the transforming growth factor-β (TGF-β) pathway were also significantly reduced, although only in the high-dose palifermin group, suggesting a dose-response effect (16).

Another study in rats evaluated the protective effect of intratracheal palifermin prior to bilateral thoracic irradiation or combined irradiation and bleomycin treatment. Although survival rates at 75 days in the radiation alone group were not significantly different between palifermin- and saline-treated rats, histological examination showed significantly greater pneumonitis and pulmonary fibrosis in the latter group. In rats receiving combined radiation and bleomycin treatment, all saline-pretreated rats died following treatment, with a mean survival of 16 days. In contrast, 9 of 18 palifermin-pretreated rats survived for more than 70 days. These rats also showed normal lung histology at 7 days, whereas rats in the control group showed severe pneumonitis and pulmonary fibrosis (17).

Idiopathic pneumonia syndrome (IPS) is a significant complication following bone marrow transplantation. The effect of palifermin given prior to conditioning and transplantation was investigated in a mouse model of IPS. Mice treated with palifermin showed alveolar type II cell hyperplasia and increased lung weights 3 and 7 days posttransplant, respectively. Serum levels of the T helper-2 (Th2) cytokines IL-4, IL-6 and IL-13 were increased 4 days after stopping palifermin treatment, and 7 days post-transplant serum TNF-α and bronchoalveolar lavage fluid (BALF) interferon gamma levels were reduced. The role of the Th2 response was confirmed by significantly increased levels of monocyte chemoattractant protein-1 (MCP-1) in BALF on the day of transplantation, and markedly increased (28-fold) chemokine CCR_4 expression. The studies indicated that palifermin reduced the injury caused by IPS by stimulating alveolar epithelialization and inducing Th2 cytokines (18, 19).

In another study, however, intratracheal instillation of 5 mg/kg palifermin prior to hemithoracic irradiation in rats failed to prevent terminal fibrosis, although there was a minor delay in the onset of fibrosis (8 weeks *vs.* 6 weeks postradiation) (20).

The therapeutic potential of palifermin in certain forms of diabetes has also been suggested by its ability to normalize blood glucose levels in rats with streptozotocin-induced diabetes (21).

Pharmacokinetics and Metabolism

The pharmacokinetics of palifermin were evaluated in a series of single- and multiple-dose studies in rats. In single-dose studies, palifermin was administered at 6 dose levels ranging from 10 μg/kg to 3000 μg/kg i.v. or s.c. Following i.v. dosing, the pharmacokinetics of palifermin were linear across the dose range tested. Subcutaneous absorption of palifermin was rapid, with a mean t_{max} of 1 h for all doses. The terminal half-life was approximately 3 h following both i.v. and s.c. administration. There was an apparent dose-dependent increase in s.c. bioavailability, from 1% at the lowest dose to 20% at the two higher doses. No accumulation of palifermin was observed following multiple s.c. doses. Studies in nephrectomized rats indicated that palifermin was at least partially cleared by the kidney (22).

In experiments in rhesus monkeys, a single dose of palifermin of 30 or 300 μg/kg was administered i.v. or s.c., followed 3 days later by multiple doses using the alternative route of administration. The pharmacokinetics of palifermin appeared to be linear after i.v. dosing, and the terminal half-life was approximately 3 h following both routes. Serum concentrations following the low s.c. dose were mostly below the limit of quantification, but with the higher dose palifermin was rapidly absorbed, reaching peak concentrations at 10 min. No accumulation was observed following administration for 7 days (23).

In the first phase I study in humans, the safety, tolerability, pharmacokinetics and biological activity of palifermin were investigated. In this double-blind, randomized, placebo-controlled study, palifermin was administered as a single i.v. dose or as daily i.v. doses for 3 days, in 5 sequential dose cohorts of 0.2, 1.0, 5.0, 10 and 20 μg/kg/day. A total of 61 healthy volunteers participated in the study. Serum concentration-time profiles were triphasic, with an elimination half-life of 4 h. No accumulation was observed, and pharmacokinetic parameters were linear to dose over the range studied. Palifermin was well tolerated, with no clinically significant effects on routine safety parameters. Biological activity was demonstrated by a statistically significant increase in epithelial proliferative activity of the buccal mucosa after 3 days of treatment with 10 and 20 μg/kg (24).

In another double-blind, randomized, placebo-controlled phase I study, single escalating i.v. doses of palifermin (60-250 μg/kg) were administered to 79 healthy subjects. Exposure to palifermin increased approximately proportionally to dose. The pharmacodynamic response assessing the proliferation of buccal mucosal cell epithelium was also dose-dependent, reaching a maximum at 160 μg/kg. The response at 48 h was greater than that at 72 h (25).

Clinical Studies

A double-blind, randomized, placebo-controlled, dose-ranging phase I/II study was performed to determine the safety of palifermin in 60 patients with advanced head and neck cancer (HNC) receiving high-dose radiotherapy with concurrent chemotherapy. Patients with previously untreated, nonmetastatic HNC received hyperfractionated radiotherapy with 5-FU and bolus cisplatin. Patients received palifermin 20, 40, 60 or 80 μg/kg/day prior to the initiation of therapy, and then weekly for a total of 10 doses. Palifermin was well tolerated at the doses tested, with the only adverse events reported being skin flushing and excess salivation. Grade 3 or 4 mucositis related to radiotherapy and chemotherapy had a median duration of 6.5 days in the palifermin-treated patients compared with 11.0 days in placebo-treated patients. The duration of other toxicities (dysphagia and acute xerostomia) was also reduced by approximately 50% (26). The results from this study and most of those that follow are summarized in Table I.

The efficacy of palifermin (60 μg/kg) was further evaluated in patients with HNC in a double-blind, randomized, placebo-controlled phase II study. Patients were treated with standard or hyperfractionated irradiation, with concurrent cisplatin and 5-FU chemotherapy. Palifermin was administered i.v. 3 days prior to the start of radiation, and then weekly for a total of 10 doses. A total of 99 patients were enrolled in the study. In patients receiving hyperfractionated radiation (n=33), the median duration of mucositis was significantly shorter in palifermin-treated patients compared with placebo (34 days *vs.* 57 days). The AUCs for all grades of mucositis and for pharyngeal toxicity were also significantly reduced in patients who received palifermin compared to those who received placebo. However, no therapeutic effect was observed in patients administered a standard radiation schedule, indicating that these patients may require a different palifermin dose schedule. Palifermin was well tolerated in both groups (27).

The safety of palifermin was evaluated in a double-blind, randomized, placebo-controlled, dose-ranging phase I study in 81 patients with metastatic colorectal cancer. Patients received palifermin at doses of 1.0, 10, 20, 40, 60 or 80 μg/kg/day i.v. for 3 days prior to treatment with 5-FU and leucovorin. Skin and oral adverse events occurred, principally at the two higher doses. Asymptomatic increases in serum amylase and lipase were also observed. As a preliminary indicator of efficacy, there were decreases in grade 2-4 mucositis in all cohorts receiving at least 10 μg/kg/day palifermin, with the overall frequency being 43% on palifermin compared to 67% on placebo (28).

The efficacy of palifermin was further evaluated in 64 patients with advanced colorectal cancer in a randomized, placebo-controlled phase II study. Patients received a dose of palifermin of 40 μg/kg/day i.v. for 3 days prior to 5-FU and leucovorin chemotherapy over two 28-day cycles. There was a significant reduction in grade 2, 3 and 4 mucositis in both cycles combined in palifermin-treated patients (32% *vs.* 78%). The duration of mucositis was also significantly reduced from 10.2 days with placebo to 3.4 days with palifermin. The most frequently

Table I: Clinical studies of palifermin (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Mucositis, Cancer, head and neck	Dose-finding Double-blind Multicenter Randomized	Palifermin, 20 μg/kg i.v. → 20 μg/kg i.v. 1x/wk x 10 wks Palifermin, 20 μg/kg i.v. o.d. x 3 d → 20 μg/kg i.v. 1x/wk x 10 wks Palifermin, 40 μg/kg i.v. → 40 μg/kg i.v. 1x/wk x 10 wks Palifermin, 40 μg/kg i.v. o.d. x 3 d → 40 μg/kg i.v. 1x/wk x 10 wks Palifermin, 60 μg/kg i.v. → 60 μg/kg i.v. 1x/wk x 10 wks Palifermin, 60 μg/kg i.v. o.d. x 3 d → 60 μg/kg i.v. 1x/wk x 10 wks Palifermin, 80 μg/kg i.v. → 80 μg/kg i.v. 1x/wk x 10 wks Palifermin, 80 μg/kg i.v. o.d. x 3 d → 80 μg/kg i.v. 1x/wk x 10 wks Placebo	60	Palifermin was well tolerated and effective in reducing the duration and incidence of severe mucositis, acute pharyngitis and salivary gland toxicity associated with radiotherapy and chemotherapy in patients with advanced head and neck cancer	26
Mucositis, Cancer, head and neck	Double-blind Multicenter Placebo-controlled Randomized	Palifermin, 60 μg/kg i.v. x 10 + Cisplatin, 20 mg/m^2 i.v. o.d. + Fluorouracil, 1000 mg/m^2 i.v. o.d. + Standard radiation therapy Palifermin, 60 μg/kg i.v. x 10 + Cisplatin, 20 mg/m^2 i.v. o.d. + Fluorouracil, 1000 mg/m^2 i.v. o.d. + Hyperfractionated radiation therapy Placebo + Cisplatin/fluorouracil chemotherapy + Standard radiation therapy Placebo + Cisplatin/fluorouracil chemotherapy + Hyperfractionated radiation therapy	99	Palifermin was well tolerated and reduced the duration of mucositis in patients with head and neck cancer who were treated with chemotherapy and hyperfractionated radiotherapy. The drug had no effect in patients receiving standard radiotherapy	27
Mucositis, Cancer, colorectal	Dose-finding Double-blind Placebo-controlled Randomized	Palifermin, 1 μg/kg/d i.v. bolus x 3 d → Fluorouracil, 425 mg/m^2/d i.v. bolus + Leucovorin, 20 mg/m^2/d i.v. bolus x 5 d Palifermin, 10 μg/kg/d i.v. bolus x 3 → Fluorouracil, 425 mg/m^2/d i.v. bolus + Leucovorin, 20 mg/m^2/d i.v. bolus x 5 d Palifermin, 20 μg/kg/d i.v. bolus x 3 → Fluorouracil, 425 mg/m^2/d i.v. bolus + Leucovorin, 20 mg/m^2/d i.v. bolus x 5 d Palifermin, 40 μg/kg/d i.v. bolus x 3 → Fluorouracil, 425 mg/m^2/d i.v. bolus + Leucovorin, 20 mg/m^2/d i.v. bolus x 5 d Palifermin, 60 μg/kg/d i.v. bolus x 3 → Fluorouracil, 425 mg/m^2/d i.v. bolus x 5 d + Leucovorin, 20 mg/m^2/d i.v. bolus x 5 d Palifermin, 80 μg/kg/d i.v. bolus x 3 → Fluorouracil, 425 mg/m^2/d i.v. bolus x 5 d + Leucovorin, 20 g/m^2/d i.v. bolus x 5 d Placebo + Fluorouracil, 425 mg/m^2/d i.v. bolus + Leucovorin, 20 mg/m^2/d i.v. bolus x 5 d	81	Palifermin was well tolerated and at doses of at least 10 μg/kg/d was significantly more effective than placebo in reducing the incidence of grade 2-4 mucositis in colorectal cancer patients receiving fluorouracil/ folinate chemotherapy	28
Mucositis, Cancer, colorectal	Double-blind Placebo-controlled Randomized	Palifermin, 40 μg/kg/d i.v. bolus x 3 d → Fluorouracil, 425 mg/m^2/d i.v. bolus + Leucovorin, 20 mg/m^2/d i.v. bolus x 5 d 1x/28 d x 2 cycles Placebo + Fluorouracil, 425 mg/m^2/d i.v. bolus x 2 cycles + Leucovorin, 20 mg/m^2/d i.v. bolus x 5 d 1x/28 d x 2 cycles	64	Compared with placebo, palifermin reduced the incidence of grade 2-4 mucositis in patients with advanced colorectal cancer receiving chemotherapy. Palifermin also reduced the duration of chemotherapy-induced mucositis, but had no effect on median survival of the patients	29
Mucositis, Cancer, hematological	Double-blind Placebo-controlled Randomized	Palifermin, 60 μg/kg/d x 3 d Palifermin, 60 μg/kg/d x 6 d Placebo	129	Palifermin decreased the incidence of severe mucositis and improved the quality of life in patients with hematological malignancies who received total-body irradiation, chemotherapy conditioning and autologous peripheral blood stem cell transplantation	31

Continuation

Table I Cont.: Clinical studies of palifermin (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Mucositis, Cancer, hematological	Double-blind Multicenter Placebo-controlled Randomized	Palifermin, 60 μg/kg o.d. x 6 d [for 3 days before total-body irradiation and 3 days after autologous peripheral blood progenitor cell transplantation] + Total-body irradiation, 12 Gy + Etoposide, 60 mg/kg s.d. + Cyclophosphamide, 100 mg/kg s.d. Placebo + Total body-irradiation, 12 Gy + Etoposide, 60 mg/kg s.d. + Cyclophosphamide, 100 mg/kg s.d.	212	Compared to placebo, patients subjected to autologous peripheral blood progenitor cell transplantation and intensive chemo- and radiotherapy and treated with palifermin reported fewer days with grade 3-4 severe oral mucositis and a lower incidence of grade 3-4 severe oral mucositis. Palifermin was well tolerated and was also associated with a lower requirement for opioids and parenteral nutrition. Palifermin was significantly more effective than placebo in improving the physical and functional well-being of the patients and also improved functions such as swallowing, eating, drinking, talking and sleeping, and these improvements were associated with clinically relevant reductions in mouth and throat soreness	32-36

reported treatment-related adverse events were mild to moderate skin rash, flushing and edema (29).

A dose-escalating phase I study evaluated palifermin plus standard prophylaxis in patients with high-risk hematological malignancies at risk of acute GVHD. Preliminary data indicated that administration of palifermin through the time of engraftment afforded a possible survival benefit in these patients (30).

A double-blind, placebo-controlled phase II study was performed in 129 patients with hematological malignancies undergoing total-body irradiation (TBI), chemotherapy conditioning and autologous peripheral blood progenitor cell transplantation (auto-PBPCT). Patients received palifermin 60 μg/kg/day for 3 days prior to TBI, or for 3 days prior to TBI and 3 days after PBPCT. The duration of severe (WHO grade 3 or 4) oral mucositis was significantly reduced in both groups compared with placebo. Health-related quality-of-life assessments were also improved, and mucositis-related sequelae, such as number of days of i.v. opioid analgesic use and TPN, were also reduced (31).

A pivotal, double-blind, randomized, placebo-controlled phase III study was conducted in 212 patients undergoing conditioning therapy (TBI plus high-dose chemotherapy) and auto-PBPCT for hematological cancers. Patients received placebo or palifermin 60 μg/kg/day i.v. for 3 consecutive days prior to TBI. A further 3 doses were administered on days 0, 1 and 2 after transplantation. Patients were assessed for oral mucositis from 8 days before and continuing for 28 days after transplantation, using 3 independent oral mucositis scales. The incidence of WHO grade 3 or 4 oral mucositis was significantly reduced in the palifermin group compared with the placebo group (63% *vs.* 98%). The median duration of oral mucositis was also significantly reduced in this group (6.0 days *vs.* 9.0 days), as was the median duration of grade 3 or 4 mucositis among all patients (3.0 days *vs.* 9.0 days). Palifermin was also associated with significant reductions in the incidence of grade 4 oral mucositis, patient-reported soreness of the mouth and throat, the use of opioid analgesics and TPN use. Palifermin was well tolerated, the most frequently reported adverse events being transient skin reactions. Transient and asymptomatic increases in serum amylase and lipase concentrations were also observed in both groups, but were more pronounced in the palifermin group. This phase III study provided evidence of a clinically relevant effect of palifermin in reducing the duration and incidence of severe oral mucositis following intensive chemotherapy and radiotherapy and autologous hematopoietic stem cell transplantation (32-36).

The U.S. FDA approved palifermin in December 2004 following priority review of the pivotal phase III data. It is the first therapy to be approved that has been shown to decrease the incidence and duration of severe oral mucositis in patients with hematological cancers undergoing high-dose chemotherapy, with or without radiation, followed by a bone marrow transplant. The drug is now available in the U.S. as Kepivance™ (7, 8).

Source

Amgen, Inc. (US).

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