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Palifermin

In Myelotoxic Therapy-Induced Oral Mucositis

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Contents

Abstract

▲ Palifermin, a recombinant human keratinocyte growth factor (KGF), mimics the actions of endogenous KGF and has shown efficacy in the management of myelotoxic therapy-induced oral mucositis in cancer patients.

▲ In a randomised, double-blind trial in patients with haemtaological malignancies receiving conditioning radiochemotherapy before undergoing autologous stem cell transplant, intravenous palifermin 60 μg/kg/day (two 3-day cycles, administered before myelotoxic therapy and after transplant) significantly reduced the median duration (primary endpoint) [3 vs 9 days] and incidence (63% vs 98%) of WHO grade 3 or 4 oral mucositis, compared with placebo.

▲ Patient-reported outcomes also showed significant improvement with palifermin treatment, which was associated with significant reductions in healthcare resource utilisation, compared with placebo.

▲ The drug was generally well tolerated, with skin/oral toxicities, pain/arthralgias and dysaesthesia being the most common palifermin-related adverse reactions.

Features and properties of palifermin (Kepivance™)	
Indication	
To decrease the incidence and duration (the EU indication also includes severity) of severe oral mucositis induced by myelotoxic therapy in patients with haematological malignancies requiring haematopoietic stem cell support	
Mechanism of action	
Growth factor; mimics the actions of endogenous keratinocyte growth factor in promoting proliferation, differentiation and migration of epithelial cells	
Dosage and administration	
Route of administration	Intravenous
Dosage	60 μg/kg/day in 3-day cycles
Frequency	Twice: before myelotoxic therapy and after transplant
Pharmacokinetic profile (single dose of intravenous palifermin 60 μg/kg in healthy volunteers)	
Initial plasma concentration	891 ng/mL
Area under the plasma concentration-time curve from time 0 to ∞	134 ng • h/mL
Half-life	4.5 hours
Tolerability	
Adverse events with an incidence ≥5% higher in palifermin than in placebo recipients	Rash, fever, elevated serum amylase, pruritus, erythema, oedema, mouth/tongue thickness or discolouration, taste alteration, pain, dysaesthesia, elevated serum lipase, arthralgia

Oral mucositis, which develops as a result of the damage caused to the epithelial layer lining the mouth, is one of several common adverse effects of myeloablative cancer therapy.[1,2] It is particularly frequent in certain specific patient populations, such as those receiving high-dose chemotherapy with or without total-body irradiation for haematopoietic stem cell support in whom the incidence of WHO grade 3 or 4 (severe) mucositis mostly exceeds 60%.[1] The risk of mucositis is also high in patients who frequently receive radiotherapy, fluorouracil or irinotecan, such as those with cancers of the head and neck, oesophagus or upper gastrointestinal tract.[1] Other chemotherapy regimens are associated with varying risks of mucositis, ranging from very low (1–2%, e.g. with single-agent etoposide) to very high (>20%, e.g. with combination regimens involving high-dose anthracyclines).[1]

Oral mucositis profoundly affects a patient's daily functioning and health-related quality of life, and sometimes becomes a dose-limiting toxicity, resulting in delayed, missed or reduced doses or treatment discontinuations.[1-3] Oral mucositis has been considered by patients as the most debilitating complication of a transplant.[4] In more serious scenarios, interruption of the mucosa may lead to bleeding and infections[1,2] and, in neutropenic patients, may increase the risk of septicaemia.[5] In addition, extended hospitalisation and increased need for parenteral nutrition and analgesic use not only have clinical implications for the patients, but may substantially increase treatment costs, thus imposing further economic burden.[2,3]

Until recently, no standard therapy to prevent or treat severe oral mucositis was available. Various strategies, including oral-care protocols, cryotherapy and topical anti-infective or anti-inflammatory agents, coupled with palliative treatment (e.g. analgesics), have been recommended for the management of oral mucositis.[6] In patients receiving high-dose chemotherapy, with or without total-body irradiation, and haematopoeitic stem cell support, low-level laser therapy may reduce the incidence of oral mucositis and associated pain. However, expensive equipment and specialised training are required for this therapy and there is a lack of robust clinical data on its efficacy.[6]

In-depth understanding of the pathophysiological mechanisms underlying mucositis[1] and the recognition of the keratinocyte growth factor (KGF) as a potent and specific mitogen for epithelial cells[7] led to the investigation of the therapeutic potential of KGF in this indication. A more stable, *N*-terminal truncated version of KGF was produced using recombinant DNA technology in *Escherichia coli*; the 16.3 kDa recombinant human KGF, palifermin (Kepivance™)[1], has a biological activity similar to that of endogenous KGF.[8,9]

Palifermin has been investigated for efficacy in the management of mucosal epithelial damage in cancer patients[9-11] (section 3). In a randomised, placebo-controlled, phase II trial in 64 patients with advanced colorectal cancer, intravenous palifermin 40 μg/kg/day showed preliminary evidence of efficacy in reducing the incidence and duration of oral mucositis over two chemotherapy (fluorouracil/leucovorin) cycles.[11] Nevertheless, palifermin has been evaluated more comprehensively for use in the management of oral mucositis in patients undergoing haematopoeitic stem cell transplant, which is the focus of this review.

1. Pharmacodynamic Properties

- Palifermin mimics the actions of endogenous KGF,[8] a member of the fibroblast growth factor family that binds to its receptors and causes proliferation, differentiation and migration of epithelial cells.[7] Thus, it plays an important role in the repair

1 The use of trade names is for product identification purposes only and does not imply endorsement.

of damaged epithelial tissues.[7] The KGF receptor is found on epithelial cells in the entire gastrointestinal tract and several other organs, including lungs, liver, pancreas, kidney and skin,[7,8] but not on haematopoietic cells.[8]

• Palifermin markedly increased the oral mucosal tolerance to radiation and chemotherapy in murine models of oral mucositis.[12,13] The test radiation dose effective in inducing tongue ulceration in 50% of the mice (ED_{50}) was decreased from 10.9 to 5.6Gy after fractionated irradiation treatment (five daily fractions of 3Gy).[12] Subcutaneous palifermin 5 mg/kg/day (3–5 doses) prevented this effect when given before (days −3 to −1), during (days 0–4) or after (days 4–6) fractionated irradiation, increasing the ED_{50} values to 7.8, 11.9 and 13.5Gy, respectively (all $p \leq 0.01$ vs control).[12] Similar protective effects of palifermin were also seen when chemotherapy (cisplatin and/or fluorouracil) was added before irradiation.[13]

• In healthy volunteers, buccal epithelial cell proliferation increased with increasing single intravenous doses of palifermin in the range 60–160 μg/kg, with the response being greater at 48 than at 72 hours; a plateau was apparent at doses ≥160 μg/kg.[14] This was a randomised, double-blind, placebo-controlled study that used Ki67 immunohistochemical staining for pharmacodynamic assessments (available as an abstract).[14]

• *In vitro* and *in vivo* studies have shown that palifermin augmented the growth of some human epithelial cancer cells, albeit generally at several-fold higher exposures than those expected in a clinical setting.[8] The *in vitro* proliferative effect on epithelial tumour cell lines was seen at palifermin concentrations (≥10 μg/mL) that were over 15-fold higher than mean therapeutic concentrations in humans.[8] A published study reported proliferation of KGF receptor-positive human carcinoma cell lines when incubated for ≥7 days with palifermin 0–1000 ng/mL in a dose-dependent manner; however, the proliferative effect of palifermin was significantly ($p < 0.001$) less pronounced in carcinoma cells than in Balb/MK normal keratinocytes.[15] After treatment with intravenous palifermin, one of seven KGF receptor-expressing human tumour cell lines in nude mouse xenograft models showed, in a dose-dependent manner, an increase in the growth rate.[8] In these studies, palifermin 1500 and 4000 μg/kg/day (25- and 67-fold higher than the recommended human dose) was given as three consecutive daily treatments and repeated weekly for 4–6 weeks.[8]

2. Pharmacokinetic Properties

• The pharmacokinetic properties of intravenous palifermin have been investigated in healthy volunteers (dose range 20–250 μg/kg) and in patients with haematological malignancies (60 μg/kg).[8,14] The pharmacokinetics are linear and show a triphasic profile with a rapid decline (>95%) in palifermin concentrations (first 30 minutes), followed by an increase or plateau (~1–4 hours) and then a terminal decline.[8] This is consistent with initial distribution, redistribution and a log-linear elimination, respectively.[16]

• Following administration of single-dose palifermin 60 μg/kg in healthy volunteers, the initial plasma concentration was 891 ng/mL and the area under the plasma concentration-time curve from time 0 to infinity was 134 ng • h/mL.[14] At this dose, an increase was apparent in the total body clearance (2- to 4-fold) and the volume of distribution at steady state (2-fold) in cancer patients compared with the values in healthy volunteers.[8]

• The elimination half-life of palifermin ranged from 3.3 to 5.7 hours (average 4.5 hours) and was similar between healthy volunteers and cancer patients.[8]

• Palifermin did not show accumulation after three consecutive daily doses in healthy volunteers (doses 20 and 40 μg/kg) or cancer patients (60 μg/kg).[8]

3. Therapeutic Efficacy

The therapeutic efficacy of intravenous palifermin in the management of oral mucositis induced by myelotoxic cancer therapy has been evaluated in a randomised, double-blind, placebo-controlled, multicentre, phase III trial in patients with haematological malignancies undergoing autologous stem cell transplant.[9] The malignancies were non-Hodgkin's lymphoma, Hodgkin's disease, acute myelogenous leukaemia, acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and multiple myeloma.[9]

The trial included 212 patients with a Karnofsky performance score of ≥70 and at least 1.5×10^6 cryopreserved CD34+ cells per kilogram available for transplantation, who were scheduled to undergo autologous stem cell transplant following a conditioning regimen of fractionated total-body irradiation and high-intensity chemotherapy (figure 1). Patients received two 3-day cycles of treatment with palifermin or placebo. All patients also received intravenous filgrastim 5 μg/kg/day to accelerate neutrophil recovery.[9]

The five-grade WHO oral-toxicity scale was the primary scale used to evaluate oral mucositis.[9] The severity of oral mucositis on this scale is rated as follows: grade 0, no oral mucositis; grade 1, soreness or erythema; grade 2, erythema and ulcers; grade 3, extensive erythema, ulcers and inability to swallow solid food; and grade 4, mucositis that makes alimentation, including swallowing of liquids, impossible. Patients were assessed daily from 8 days before to 28 days after transplantation or until resolution of severe oral mucositis (i.e. return to mucositis of grade 0–2).[9]

Patients completed daily questionnaires for reporting soreness of the mouth and throat and ability to participate in the activities of daily living.[9] In addition, the Functional Assessment of Cancer Therapy (FACT) general questionnaire was administered daily from 12 days before to 28 days after transplantation. A beneficial response was indicated by a decrease in mouth/throat soreness and swallowing limitations scores and an increase in FACT questionnaire score. The scores on a 0–4 scale were plotted against time and the areas under the score-time curves were compared between treatments.[9]

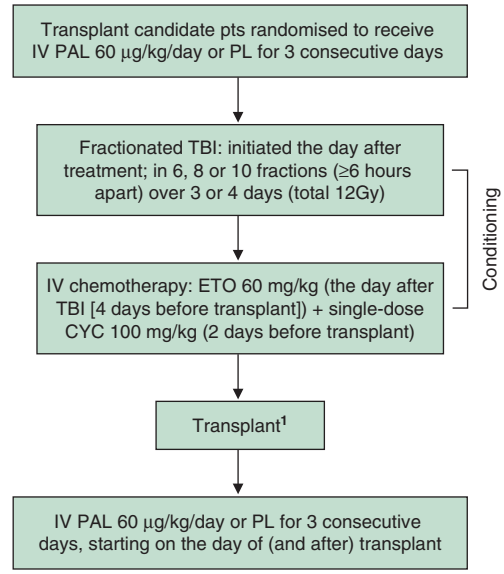

Fig. 1. Treatment schedule in a double-blind, placebo (PL)-controlled, phase III trial of intravenous (IV) palifermin (PAL) in the management of oral mucositis.[9] **1** Peripheral-blood haematopoietic stem cells collected after mobilisation using either cytokines or chemotherapy with cytokines (without cytokines in one patient). **CYC** = cyclophosphamide; **ETO** = etoposide; **pts** = patients; **TBI** = total-body irradiation.

Efficacy assessments included all randomised patients who received at least one dose of study medication.[9] The duration of grade 3 or 4 oral mucositis was the primary endpoint, with the duration considered to be 0 days in patients with no oral mucositis.[9]

The palifermin treatment regimen was based on the results of randomised, early-phase trials in patients with haematological malignancies.[17,18] In a double-blind, placebo-controlled, phase II trial in 129 patients,[18] the duration of WHO grade 3 or 4 oral mucositis was significantly reduced by two 3-day cycles of treatment with intravenous palifermin

60 μg/kg/day (administered before conditioning radiochemotherapy and after transplant) compared with placebo (4 vs 7.7 days; p = 0.001). Another regimen used in this trial, involving palifermin administration only before transplant, produced less impressive, but significant, results (5 days; p = 0.04 vs placebo).[18]

Physician-Assessed Outcomes

● Intravenous palifermin 60 μg/kg/day was significantly more effective than placebo in reducing the duration and incidence of oral mucositis in patients with haematological malignancies receiving radiochemotherapy and autologous stem cell transplant.[9] The median duration of grade 3 or 4 oral mucositis was significantly decreased in patients receiving palifermin compared with those receiving placebo in all patients (primary endpoint) and in patients with this adverse effect (figure 2). In addition, the median proportion of patients who developed grade 3 or 4 mucositis or grade 4 mucositis was significantly lower in palifermin than in placebo recipients (figure 2).[9]

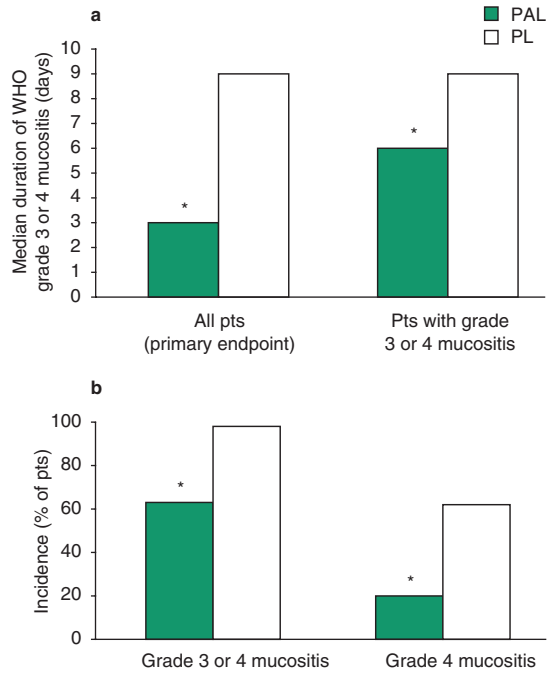

Fig. 2. Efficacy of palifermin (PAL) in reducing the duration (**a**) and incidence (**b**) of oral mucositis. Results of a randomised, double-blind, placebo (PL)-controlled, multicentre, phase III trial in patients (pts) with haematological malignancies undergoing autologous stem cell transplant.[9] Pts received two cycles of PAL 60 μg/kg/day or PL intravenously daily for 3 consecutive days before conditioning regimen (radiotherapy plus high-dose chemotherapy) and after transplant (see figure 1). * p < 0.001 vs PL.

Patient-Reported Outcomes

● Similarly, patient-reported outcomes showed significant improvement with palifermin treatment.[9] There was a 38% reduction in the median area under the score-time curve for mouth/throat soreness in the palifermin group compared with that in the placebo group (29 vs 47; p < 0.001).[9] Swallowing limitations were also significantly improved with palifermin compared with placebo (area under the curve 23 vs 38; p < 0.001), as were the other mucositis-related activities of daily living, including drinking, eating, talking and sleeping (data not reported).[9]

● Physical and functional well-being significantly improved in patients receiving palifermin compared with that in placebo recipients as demonstrated by the FACT general questionnaire results (median area under the curve values 737 vs 712 [p = 0.003] and 546 vs 543 [p = 0.036]).[9]

Healthcare Resource Use

● Compared with placebo, palifermin use was associated with significant reductions in healthcare resource utilisation,[9,19] which may translate into cost savings in this setting.[20]

● The duration of in-patient hospitalisation (15.3 vs 17.3 days; p = 0.008) was reduced by a mean of 2 days with palifermin compared with that with placebo (data available as an abstract).[19] The use of parenteral or transdermal opioid analgesics was also significantly less frequent in palifermin than in pla-

cebo recipients, as indicated by significantly ($p < 0.001$) smaller median cumulative dose (morphine equivalents 212 vs 535mg) and median duration of administration (7.0 vs 11.0 days). In addition, 31% of palifermin recipients required parenteral nutrition compared with 55% of placebo recipients ($p < 0.001$).[9]

- The incidence of febrile neutropenia was also sigificantly lower in palifermin than in placebo recipients (75% vs 92%; $p < 0.001$).[9]
- A preliminary pharmacoeconomic analysis (available as an abstract)[20] using data from the phase III trial[9] estimated the impact of differences between palifermin and placebo in hospital stays related to one or more of four downstream outcomes (bacteraemia, febrile neutropenia, total parenteral nutrition and intubation). The national mean costs per hospital day, estimated using the US National Inpatient Sample for an equivalent patient population, were applied to the clinical trial population. The mean costs per patient (2003 values) with palifermin or placebo were $US61 160 and $US76 104, resulting in mean cost savings of $US14 943 (95% CI $US12 043, $US17 845) with palifermin use. However, these cost savings may be lower when costs of outpatient transplant and palifermin (not included in this analysis)[20] are taken into account.

4. Tolerability

The discussion in this section is based mainly on the tolerability data for palifermin available from the US prescribing information that includes data from four studies (three randomised, placebo-controlled clinical studies and a pharmacokinetic study) in a total of 650 (palifermin 409, placebo 241) patients with haematological malignancies.[8] The palifermin regimen was administered before and/or after myelotoxic chemotherapy (with or without total-body irradiation) followed by stem cell transplantation. Figure 3 summarises adverse events that occurred with an incidence ≥5% higher in palifermin than in placebo recipients.[8]

- Skin/oral toxicities, pain/arthralgias and dysaesthesia were the most common palifermin-related adverse reactions.[8] Skin toxicity appeared 6 days (median) after the first dose of the 3-day cycle of palifermin and persisted for a median of 5 days. Dysaesthesia affected mainly the perioral region in patients receiving palifermin, whereas extremities were more likely to be affected in placebo recipients.[8]
- Skin rash (<1%) was the most common treatment-related serious adverse event in palifermin recipients and, serious or not, led to discontinuation of treatment in 1.2% and 0.8% of palifermin- or placebo-treated patients.[8] The incidence of other serious adverse reactions was similar between palifermin and placebo recipients (20% vs 21%), with fever, gastrointestinal events and respiratory events being most frequently reported.[8]
- Transient hypertension, which did not require treatment discontinuation, was seen in 13% (2/15) or 9% (2/14) of patients treated with two 3-day cycles of palifermin 60 μg/kg/day or placebo in a phase I study in patients undergoing haematopoietic transplantation.[8] When analysed for all palifermin studies in this setting, the incidence of hypertensive events was 7% (30/409) and 5% (13/241) in palifermin or placebo recipients.[8]
- Transient, asymptomatic elevations in serum lipase and amylase levels have also been seen with palifermin treatment, with maximum increases during chemotherapy, returning to baseline by the day of transplant.[8]
- Antibodies to palifermin were found in 2% of 645 patients treated with the drug in clinical studies. However, there was no evidence of neutralising activity and the clinical significance of antibodies to palifermin remains unknown.[8]

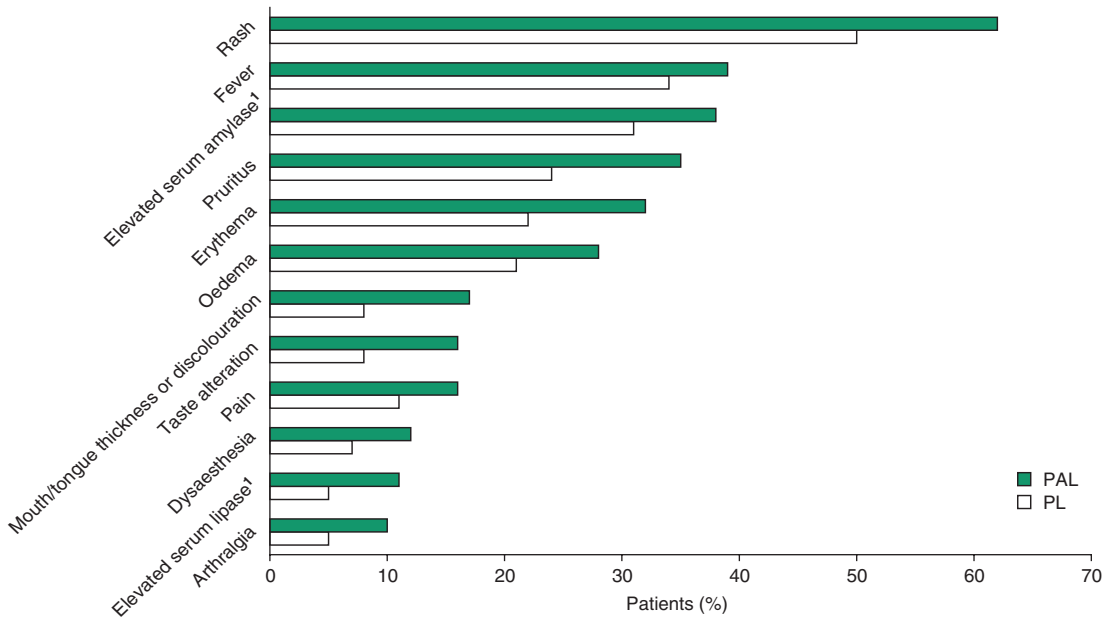

Fig. 3. Tolerability profile of palifermin (PAL). Adverse events occurring with an incidence ≥5% higher in patients with haematological malignancies treated with PAL (n = 409) than in those treated with placebo (PL) [n = 241] in four studies (three randomised, PL-controlled clinical studies and a pharmacokinetic study).[8] PAL was administered before and/or after myelotoxic chemotherapy (with or without total-body irradiation) followed by stem cell transplantation. Statistical analyses were not reported. **1** Grade 3 or 4.

5. Dosage and Administration

For the management of severe oral mucositis in patients with haematological malignancies undergoing stem cell transplant, intravenous bolus palifermin is recommended at a dosage of 60 μg/kg/day, given in two 3-consecutive-day cycles before and after myelotoxic therapy (total of six doses).[8]

For comprehensive dosage and administration guidelines, the local manufacturer's prescribing information should be consulted.

6. Palifermin: Current Status in Myelotoxic Therapy-Induced Oral Mucositis

Palifermin is approved in the US for decreasing the incidence and duration (the EU approvable indication also includes severity) of severe oral mucositis associated with myelotoxic therapy in patients with haemtaological malignancies undergoing stem cell transplant. In a randomised, double-blind trial, intravenous palifermin 60 μg/kg/day (two 3-day cycles, administered before myelotoxic therapy and after transplant) significantly reduced the duration and incidence of WHO grade 3 or 4 oral mucositis in the above group of patients, and was generally well tolerated. Furthermore, palifermin is currently in late phase clinical development for use in the management of oral mucositis induced by chemo- and/or radiotherapy in patients with solid tumours in the multicycle therapy setting.

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