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Iseganan Hydrochloride

Prop INNM

Treatment of Mucositis
Treatment of Cystic Fibrosis
Antibiotic

Protegrin IB-367
IB-367

H-Arg-Gly-Gly-Leu-Cys-Tyr-Cys-Arg-Gly-Arg-Phe-Cys-Val-Cys-Val-Gly-Arg-NH_2 cyclic (S-3.5-S-3.14:S-3.7-S-3.12)-bis(disulfide) hydrochloride

$C_{78}H_{126}N_{30}O_{18}S_4HCl$
Mol wt: 1936.77
CAS: 257277-05-7
EN: 238060

Abstract

Oral mucositis is a side effect often found in cancer patients treated with high doses of chemotherapy and radiotherapy. Its painful lesions may be exacerbated by colonization by endogenous microflora and pathogens, which in turn may cause systemic infections. Iseganan hydrochloride is a protegrin analog that binds to components of the bacterial cell surface, such as LPS and LTA, damaging the cell membranes and killing the bacteria through swelling and bursting. *In vitro* studies have shown iseganan to be effective against Gram-positive and Gram-negative bacteria, and experimental studies in hamsters demonstrated that the compound decreased the severity and duration of oral mucositis and improved the survival rate of animals. Iseganan was found to decrease the pain and severity of oral mucositis in patients undergoing myeloablative chemotherapy, and was also effective against other conditions such as ventilator-associated pneumonia.

Synthesis

Iseganan can be synthesized by general solid-phase peptide synthesis methodology using either acid-labile Boc (*tert*-butyloxycarbonyl) or base-labile Fmoc (9-fluorenylmethoxycarbonyl) as α-amino protecting groups. The synthesis can be carried out on an automatic synthesizer.

For Boc synthesis, the amino acids' side chain functional groups are protected as follows: tosyl for Arg, 2-bromobenzyloxycarbonyl for Tyr and 4-methoxybenzyl for Cys. The peptide chain is assembled by coupling the first C-terminal amino acid to 4-methylbenzhydrylamine resin, then the Boc group is removed using trifluoroacetic acid and the next protected amino acid is coupled using dicyclohexylcarbodiimide (DCCI). Repetition of the cycle with the protected amino acids in the desired sequence results in the fully protected iseganan peptide chain. Cleavage of the peptide from resin is achieved with hydrogen fluoride and ethyl methyl sulfide/anisole as scavengers.

For Fmoc synthesis, the amino acids' side chain functional groups are protected as follows: 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonyl for Arg, *tert*-butyl for tyrosine and trityl for Cys. The peptide chain is assembled by coupling the first C-terminal amino acid to Rink amine resin, then the Fmoc group is removed using piperidine and the next protected amino acid derivative is coupled using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU). Repetition of the cycle with the protected amino acids in the desired sequence results in the fully protected iseganan peptide chain. The peptide is cleaved from the resin by treatment with TFA and ethanedithiol/thioanisole as scavengers.

Finally, the iseganan peptide chain is cyclized by air oxidation in 10% DMSO in Tris buffer (1, 2).

Introduction

Oral mucositis is a debilitating side effect occurring in 75-80% of cancer patients receiving high doses of chemotherapy and radiotherapy. Nonspecific cytotoxic therapy decreases the cell renewal rate of basal epithelial

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Table I: Compounds in development for the treatment of oral mucositis (Prous Science Integrity®).

Drug	Source	Phase
Amoxanox*	Acces	II
Sargramostim*	Immunex	III
rHKGF	Amgen	III
Iseganan Hydrochoride	IntraBiotics	III
Repifermin	Human Genome Sciences	II
RK-0202	Elan/RxKinetix	I
P-113L	Demegen	I/II
OC-1012	OraPharma	I
ATL-104	Alizyme	I
Gelclair™	Sinclair	L-2001
Epicept MS Spray	Epicept	IND
PV-701	Gropep	I
AES-14	Aesgen	III
Amifostine*	MedImmune Oncology	II

*Available for another indication

cells of the oral mucosa, thus resulting in atrophic epithelium that is especially susceptible to spontaneous or traumatic ulceration. The pain associated with this condition may limit oral intake and often requires treatment with narcotic analgesics. Furthermore, mouth lesions may be exacerbated by colonization of endogenous microflora and pathogens, which may also lead to potentially life-threatening systemic infections. These observations have suggested the use of antibiotics for the treatment of oral mucositis.

Protegrins are antibiotics that were originally isolated from porcine neutrophils. They are produced from antimicrobial peptide precursors called cathelicidins, which are synthesized as the C-terminal portion of a cathelin-containing proregion. When activated, the porcine neutrophils release pro-protegrins that have no antimicrobial activity until cleaved by the extracellular enzyme elastase to form the active protegrin. Five native protegrin molecules have been identified (1); each of them is a chain of 16-18 amino acids with four cysteines at positions 6, 8, 13 and 15. These cysteines establish disulfide bonds that maintain the secondary structure of the molecule, which constitutes the basis of its antimicrobial activity. Data demonstrating that protegrins were active against many Gram-positive and Gram-negative bacteria, that their effects were already detected shortly after administration and that bacteria developed little or no resistance to protegrins led to structure-activity relationship studies designed to find a protegrin analog that would be a suitable candidate for clinical development. These SAR studies culminated in the discovery of iseganan hydrochloride (IB-367), a 17 amino acid-long protegrin analog that is effective against oral microflora. Because of its good antimicrobial profile, IntraBiotics selected the compound for further evaluation in the prevention of oral mucositis, ventilator-associated pneumonia (hospital-acquired bacterial pneumonia occurring in patients receiving mechanical ventilation) and respiratory infections associated with cystic fibrosis.

Table I lists compounds under development for the treatment of oral mucositis.

Pharmacological Actions

The mechanism of action of iseganan against bacteria has been determined by transmission and scanning electron microscopy. It binds to bacterial cell surface components, such as lipopolysaccharide (LPS) and lipoteichoic acid (LTA) (3, 4). This binding permeabilizes the outer and inner membranes of bacteria such as *Escherichia coli*, which allows the influx of water and the release of intrabacterial fluid (5). This leads to bacterial swelling, which increases the effective diameter of iseganan-induced channels and causes protrusion of some parts of the inner membrane; these protrusions eventually rupture and release bacterial cytoplasmic contents. Similar extrusions and ruptures have been found with staphylococci treated with iseganan (6). The damage to the outer bacterial membrane caused by iseganan induces the expression of outer membrane proteins and stress response genes such as cspA, in the latter case an effect usually associated with ribosome inhibitors (*e.g.*, chloramphenicol and tetracycline) that is indicative of termination of bacterial DNA and protein synthesis (7, 8).

Iseganan exhibited a broad spectrum of activity against Gram-positive and Gram-negative bacteria and a low potential for resistance (Table II). MIC values ranged from 0.13-64 μg/ml for Gram-positive bacteria and from 0.06-8 μg/ml for Gram-negative bacteria associated with oral mucositis (9, 10). Bacterial metabolism ceased rapidly within 5 min after the addition of iseganan at a concentration equal to twice the MIC (11). At concentrations near the MIC, iseganan decreased the viability of *Staphylococcus aureus* and *Pseudomonas aeruginosa* by more than 3 logs in less than 16 min. A higher concentration of

Table II: Antibacterial activity of iseganan against a variety of clinical isolates (Prous Science Integrity®).

Organism	MIC
Acinetobacter calcoaceticus	0.06-2.0
Corynebacterium spp.	0.13-0.25
Escherichia coli	0.25-1.0
Haemophilus spp.	1.0-8.0
Klebsiella pneumoniae	1.0-5.0
Moraxella spp.	0.2-0.8
Neisseria spp.	8.0
Pseudomonas aeruginosa	1.0-8.0
Serratia marcescens	16->256
Staphylococcus spp.	0.13-4.0
Streptococcus spp.	1.3-16.0
Streptococcus group D	0.25-4.0
Streptococcus mitis	2.0-43.0
Streptococcus mutans	0.7-1.3
Streptococcus salivarius	0.2-5.0
Streptococcus sanguis	4.0-64.0

MIC (μg/ml) determined by broth dilution method (from ref. 10).

Table III: Antibacterial and antifungal activity (MIC, μg/ml) of iseganan and reference compounds against drug-sensitive and drug-resistant bacteria (Prous Science Integrity®).

	Iseganan	Gentamicin	Norfloxacin	Polymyxin B
Bacteria				
MRSA	4.0 (10)	1.0 (10)	0.50 (10)	1.0 (10)
P. aeruginosa	2.0 (10)	0.5 (10)	0.25 (10)	0.5 (10)
Fungi				
Candida albicans	4.0-16.0 (10, 13)	>128 (20)	128 (20)	64.0 (20)
Candida albicans[a]	16.0 (13)	–	–	–
Aspergillus terreus[b]	8.0 (13)	–	–	–

[a]Fluconazole-resistant. [b]Amphotericin-resistant. MICs determined by broth dilution method. References in parentheses.

iseganan (250 μg/ml) was needed to achieve a 4-log decrease of endogenous microflora in human saliva within 2 min, probably due to the presence of negatively charged glycoproteins that bind to the positively charged iseganan. Nevertheless, this higher concentration was easily obtained by local administration of the drug (9).

Iseganan is also effective against bacterial isolates from the lungs of cystic fibrosis patients. A multicenter, placebo-controlled clinical trial analyzed 250 such isolates and reported MIC values of 8 μg/ml against *P. aeruginosa* and 4 μg/ml against *S. aureus*. No cross-resistance between iseganan and other antibiotics (*i.e.*, ceftazidime, ciprofloxacin, colistin, tobramycin, vancomycin and andoxacillin) was found and the MIC values for iseganan were similar for isolates obtained before therapy as compared to those obtained after treatment with either iseganan or placebo (12).

Regarding the antifungal activity of iseganan, the MIC values against 67 fungal strains representing 9 genera and 18 species ranged from 1-64 μg/ml. Iseganan was effective against both fluconazole-sensitive and -resistant *Candida albicans* isolates (MIC = 8 μg/ml) and moderately effective against an amphotericin-resistant *Aspergillus terreus* strain (MIC = 16 μg/ml) (13). The results of these and other studies confirm that iseganan has a broad spectrum of activity against bacteria and fungi.

Iseganan has shown superior bactericidal activity to conventional antimicrobial agents at concentrations near their respective MICs. The addition of iseganan to stationary-phase cultures of methicillin-resistant *S. aureus* and *P. aeruginosa* decreased the numbers of viable colony-forming units 8 (CFU) of both species by 3 log units within 8 min. Polymyxin B produced a similar, rapid reduction in the numbers of stationary-phase *P. aeruginosa* CFU, whereas gentamicin and norfloxacin required more than 2 h to produce the same effect. Vancomycin, gentamicin and norfloxacin had no bactericidal effects against stationary-phase *S. aureus* (10). Iseganan was also more effective on log-phase cultures of *S. aureus* and *P. aeruginosa* than gentamycin, norfloxacin and vancomycin (10) (Table III).

The effects of iseganan on oral mucositis have been confirmed *in vivo* in animal studies. One such study evaluated the drug in a hamster cheek pouch model of oral mucositis induced by intraperitoneal administration of 5-fluorouracil followed by mechanical irritation of buccal mucosa. The animals were treated 5-6 times daily for 7 days with either placebo or iseganan (0.12, 0.5 or 2.0 mg/ml). Oral microflora densities were reduced on day 4 and day 7 in hamsters treated with 0.12 and 0.5 mg/ml of iseganan, respectively; results in hamsters administered 2.0 mg/ml were similar to those in the 0.5 mg/ml group. Treatment with iseganan resulted in a concentration-dependent decrease in the severity and duration of oral mucositis, and the maximum incidence rate of ulcerative mucositis was 39% with placebo and 22, 16 and 6% with 0.12, 0.5 and 2.0 mg/ml of iseganan, respectively. Survival rates in iseganan-treated hamsters were 89-95% as compared to 74% for placebo-treated animals. Bacteria colonized the lesions in the mucosa of hamsters that received no treatment or were treated with placebo, whereas the lesions of hamsters treated with iseganan were free of bacteria. Iseganan, however, was not effective in altering the course of mucositis if the endogenous microflora colonized the mucosa for more than 2 days, indicating that the compound would be most useful as a prophylactic treatment in patients at risk for developing oral mucositis (14).

Clinical Studies

The results from animal studies led to clinical trials evaluating the efficacy and safety of iseganan in humans. A randomized, placebo-controlled, double-blind phase II study conducted in patients undergoing myeloablative chemotherapy and bone marrow transplantation showed that treatment with iseganan (9 mg every 4 h) as an oral rinse decreased the average oral mucositis severity by 22% in the 134 evaluable patients and by 40% in 76 patients who began iseganan treatment more than 3 days before transplantation (15) (Box 1).

The effects of iseganan oral solution on the severity of pain were assessed in a phase III randomized, placebo-controlled, double-blind study in patients receiving myeloablative chemotherapy. Only patients who received high-dose chemotherapy, expected to cause Grade II or higher stomatitis in at least 50% of patients, were included in the study. The patients had to be free of stomatitis at the time of inclusion and were evaluated 3 times weekly for 3 weeks. Both stomatitis and dysphagia were assessed using NCI-CTC scales. Patients also

Box 1: Effect of iseganan on reducing the incidence of oral mucositis (15) [Prous Science Integrity®].

Design	Randomized, placebo-controlled, multicenter, double-blind clinical study
Population	Patients undergoing myeloablative chemotherapy and bone marrow transplantation or somatotoxic chemotherapy (n = 526)
Treatments	Study I: Iseganan, 9 mg oral rinse 1x/4 h Placebo Study II: Iseganan, 9 mg oral rinse Placebo
Results	Study I: Oral Mucositis Assessment Scale score, % change: I (–22) -if treatment >3 d prior to transplantation: I (–40) Study II: I reduced the incidence of ulcerative oral mucositis, its clinical sequelae, pain, difficulty in swallowing, fever and systemic infections
Conclusions	Iseganan was safe and effective in reducing the incidence of ulcerative oral mucositis

Box 2: Iseganan in the treatment of oral mucositis (16) [Prous Science Integrity®].

Design	Multicenter, double-blind, placebo-controlled, randomized clinical study
Population	Patients undergoing myeloablative chemotherapy developing stomatitis, oral pain and difficulty in swallowing (n = 323)
Treatments	Iseganan, topical oral solution x 3 wks Placebo
Results	Pain remission (Likert scale score) rate (%): I (95) > P (85) Correlation between oral pain and difficulty in swallowing, stomatitis and dysphagia
Conclusions	Iseganan was effective in reducing pain, difficulty in swallowing, dysphagia and stomatitis in patients with oral mucositis

Box 3: Iseganan the prevention of ventilator-associated pneumonia (17) [Prous Science Integrity®].

Design	Multicenter, placebo-controlled, randomized, double-blind clinical study
Population	Intubated patients on mechanical ventilation (n = 16)
Treatments	Iseganan, 9 mg oral topical 1x/4 h x 5 d (n = 6) Iseganan, 9 mg oral topical 1x/6 h x 5 d (n = 6) Placebo oral topical 1x/4 h x 5 d (n = 2) Placebo oral topical 1x/6 h x 5 d (n = 2)
Results	Oral microbial burden (log cfu), intubation day change: I (–1.0) > P (–0.1) [$p = 0.01$] -@ 5 d: I/4h (–3.2) ≥ P (–0.9)
Conclusions	Iseganan oral-topical administration was a safe, well tolerated and effective treatment for decreasing oral microbial burden. It is a promising candidate for the prevention of ventilator-associated pneumonia

completed an 11-point Likert scale to describe their symptoms. Of the 323 evaluable patients, 15% on placebo and 5% on iseganan reported pain scores of 9 or 10 (*i.e.*, worst imaginable symptoms). Peak oral pain correlated with other subjective and objective evidence of oral disease, such as peak stomatitis and dysphagia, peak pain when swallowing and peak difficulty in swallowing (16) (Box 2).

The PROMPT-CT trial is a phase III, randomized, placebo-controlled, double-blind, multinational study that is currently evaluating the effects of iseganan on the incidence of ulcerative oral mucositis and its clinical sequelae. A total of 316 patients from 25 centers will be randomized to receive iseganan oral rinse (9 mg) or placebo (15).

The efficacy of iseganan in the treatment of other conditions is also being investigated. A phase IIa, multicenter, placebo-controlled study evaluated the safety and pharmacokinetics of iseganan in the prevention of ventilator-associated pneumonia. Sixteen orally intubated patients were randomized to receive iseganan oral solution (9 mg every 4 or 6 h for up to 5 days) or placebo. Oral secretion samples were collected from patients before and after drug administration for analysis every 24 h. Immediate decreases in oral microbial burden were detected after every daily dose with both dosing regimens compared to placebo, and a cumulative decrease was seen after 5 days of administration of iseganan every 4 h, thus confirming that orally administered iseganan is an effective treatment for preventing ventilator-associated pneumonia (17) (Box 3).

Iseganan hydrochloride oral solution is currently in phase III clinical trials for the prevention of oral mucositis in cancer patients undergoing chemotherapy and radiotherapy. A phase IIa clinical trial evaluating the antibiotic's activity in patients with ventilator-associated pneumonia has been completed, and a phase I trial evaluating the safety of iseganan solution for inhalation in cystic fibrosis patients with chronic respiratory infections has also been completed (18).

Source

IntraBiotics Pharmaceuticals, Inc. (US).

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