PI-88 (phosphomannopentaose sulphate) – antiangiogenic heparanase inhibitor

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Abstract

PI-88 (phosphomannopentaose sulphate) is a mixture of sulphated oligosaccharides prepared by hydrolysis of the extracellular phosphomannan produced from the yeast Pichia holstii. It is the only heparanase inhibitor to date which has undergone clinical trials, both as a single agent and with chemotherapy. The development of PI-88 has been especially exciting as it shows most promise in two fields of oncology, melanoma and hepatocellular carcinoma, where treatment options are very limited indeed. It has been granted orphan drug status for the treatment of advanced melanoma and as adjuvant treatment post hepatocellular carcinoma resection. Toxicities seen to date include injection site discomfort, thrombocytopaenia which may be immune-related and thrombosis. PI-88 on the whole was well tolerated. Significant clinical bleeding has only occurred in patients with cerebral melanoma metastases. Different schedules of subcutaneous PI-88 are currently under investigation with good patient compliance as the drug is self administered at home. PI-88 has also been investigated in patients with non small cell lung cancer, prostate cancer and multiple myeloma. Analogues of PI-88 are being developed which may confer improved efficacy and pharmacokinetic profiles compared to the parent drug.

Introduction

Heparan sulphate proteoglycan is a major component of the basement membrane and the extracellular matrix. It consists of a protein core with multiple complex glycosaminoglycan heparan sulphate (HS) side chains. Heparanase is an endo-beta-D-glucuronidase which cleaves these HS side chains, thereby physically disrupting the basement membrane and assisting tumour cell invasion (1). Growth factors stored in the extracellular matrix, including vascular endothelial growth factors (VEGF) and

fibroblast growth factors (FGF), are also released which promotes angiogenesis and therefore tumour growth and metastasis. Furthermore, HS side chains regulate functions of proteins with clusters of positively charged amino acids by binding to them to alter their activities and concentrations.

Heparanase is the predominant HS-degrading enzyme found in human cancer tissues. Increased heparanase activity correlates with poor prognosis in patients with pancreatic and cervical cancer (2, 3). Various compounds have been developed targeting heparanase as a strategy for the treatment of cancer including small molecular inhibitors (4), sugar inhibitors (PI-88), protein inhibitors (5) and neutralising antibodies (6).

In addition to its anti-tumour effects, PI-88 has a wide pharmacodynamic portfolio with activity against infections and benign pathophysiological processes. PI-88 is active against herpes simplex virus type 1 (8,9), Plasmodium falciparum (10), dengue and encephalitic flaviviruses (11). PI-88 also reduced proteinuria in passive Heymann nephritis (12) and restenosis post angioplasty (13) in animal models. This review however, will concentrate on the development and data of PI-88 as an anti-cancer agent.

Synthesis

PI-88 is prepared by extensive sulphation of oligosaccharide phosphate fractions obtained from acid-catalysed hydrolysis of the extracellular phosphomannan produced by Pichia holstii NRRL Y-2448 (14). The composition and the structures of the different PI-88 fractions have been determined by capillary electrophoresis, gel

chromatography and nuclear magnetic resonance (7, 15, 16). PI-88 consists of at least 7 components and their generalised structures are shown in Figure 1. The major components are the penta- and tetrasaccharide phosphates which constitute 90% of the drug (17). Individual components of PI-88 have also been artificially synthesised (17). Analogues of PI-88 have been developed with introduction of specific lipophilic hydrophobic/aromatic group(s) at the reducing end of the oligosaccharide chain. Preclinical testing of single oligosaccharides of PI-88 analogues has shown that these may confer an improved pharmacokinetic profile and efficacy, measured as endothelial cell proliferation and of endothelial tube formation (18).

Pharmacological actions

PI-88 has multiple mechanisms of action. It inhibited heparanase and increased cell surface HS levels in pancreatic cancer cells in vitro (19). PI-88 also prevented HS side chains from binding to angiogenic growth factors, especially VEGF in a rodent model of pancreatic cancer (20) and FGF-1 as demonstrated by surface plasmon resonance (21). An endogenous antiangiogeneic protein, tissue factor pathway inhibitor (TFPI), is released after administration of PI-88 in primates (15). TFPI is a Kunitz type protease inhibitor which inhibits formation of the tissue factor/factor VIIa complex in a factor Xa-dependent manner (22). The anticoagulant properties of PI-88 are mediated by heparin cofactor II by inhibition of thrombin generation (15).

Pharmacokinetics and metabolism

The pharmacokinetic profile of PI-88 was investigated in healthy male volunteers by subcutaneous and intravenous administrations at doses of up to 160 mg (23). PI-88 plasma levels were measured as prolongation in activated partial thromboplastin time

(APTT), as the latter is known to reflect drug concentration. Maximum plasma concentrations (Cmax) were reached at (tmax) 2 h in a dose dependent manner. Similarly, systemic drug exposure measured as area under curve (AUC) also increased with dose. Bioavailability based on AUC values were 96% and mean elimination half life was 2.4 h after intravenous drug administration.

The pharmacokinetic profile of subcutaneous PI-88 in patients with advanced solid tumour was investigated in two different schedules and the data are summarised in Table 1. The first schedule was bimonthly with drug administration on days 1-4 and 15-19 of a 28 day cycle, whilst the second schedule was weekly with 4 consecutive days of drug administration every week in a 28 day cycle (24). The pharmacokinetic profile was a one-compartment model with first order elimination and first order absorption from an extravascular site. PI-88 plasma concentration was linear to dose as measured by AUC and Cmax. Intrapatient variability was low and interpatient variability was moderate. Patient weight but not age correlated significantly with AUC, Cmax and total body clearance (CL/F). Creatinine clearance also correlated significantly to Cmax values. There was no drug accumulation with chronic dosing. Twenty four hours after PI-88 administration, APTT levels for 92% and 74% of doses given as the bimonthly and the weekly schedules respectively returned to normal. The weekly schedule was therefore recommended for further study as it maintained a more sustained drug concentration over time.

Toxicology

The main serious clinical toxicity of PI-88 is thrombocytopaenia which maybe associated with anti-heparin platelet factor 4 (PF4) complex antibodies and

thrombosis. Thrombocytopaenia did not occur in preclinical trials of PI-88 in monkeys and rodents (15, 20, 25). Dexamethasone administered orally at 20 mg evening before and day of PI-88 injection as the bimonthly schedule prevented thrombocytopaenia in 18 patients with advanced solid malignancies (26), but 17 of these patients developed elevation in serum glucose reaching grade 3/4 toxicity in 5 courses of treatment. Dexamethasone administered at a lower dose of 10 mg orally evening before drug administration (24) did not prevent thrombocytopaenia.

A review in 2007 of 402 patients who had been administered PI-88 to date showed 17 cases (4.2%) of CTC grades 2, 3 or 4 immune mediated thrombocytopaenia, occurring most frequently in the first 8-19 days of treatment (27). In the remaining cases with later onset of immune mediated thrombocytopaenia, 4 out of 5 patients were receiving combination treatment with docetaxel. Thrombocytopaenia resulted in clinically significant bleeding only in patients with cerebral metastases.

All other toxicities of PI-88 were generally mild with the commonest being discomfort at drug administration site, but this did not influence patient compliance. PI-88 also caused gastrointestinal symptoms, fatigue, headaches and hot flushes.

Clinical studies

The clinical trials of PI-88 are summarised in Table 2. The efficacy data of PI-88 has been especially encouraging in patients with advanced melanoma and as adjuvant treatment for patients post hepatocellular carcinoma resection. PI-88 was granted orphan drug status in May 2004 for the treatment of advanced melanoma. It was granted fast track status by the US FDA (Food and Drug Administration) for adjuvant

treatment of hepatocellular carcinoma and received orphan drug status for this indication in Europe in September 2007.

PI-88 was initially administered intravenously as a 2 h infusion, increasing in dose and duration of up to 14 days continuously in a phase I study of 14 patients with advanced solid malignancies (28). Dose limiting toxicities occurred at 2.28 mg/kg/day for 14 days with grade 3 immune mediated thrombocytopaenia, as evidenced by the presence of antibodies to PF4 in 4 patients. Thrombocytopaenia did not result in clinically significant complications and resolved with cessation of PI-88. Prolongation in APTT however, was not achieved and in view of lack of pharmacodynamic effects but toxicities, PI-88 administration was changed to a subcutaneous route.

Subcutaneous PI-88 was investigated in a phase I study as bimonthly or weekly schedules in 42 patients with advanced solid malignancies (24). The maximum tolerated dose (MTD) for both schedules was 250 mg with dose limiting toxicities (DLT) of thrombocytopaenia and pulmonary embolism. There were however, no episodes of clinically significant bleeding. Development of anti-PI-88/PF4 IgG antibodies in cycle 1 occurred only in the 3 patients who experienced thrombocytopaenia. Overall toxicities were mainly mild, Common Toxicity Critera (CTC) grades 1/2 only, and included thrombocytopaenia (6%), echymosis at injection sites (55% and 89% of cycles with bimonthly and weekly schedule respectively) and fatigue (13% and 39% of cycles with bimonthly and weekly schedule respectively).

VEGF and FGF were excluded as pharmacodynamic markers as plasma and urinary levels did not correlate to PI-88 administration or efficacy. Prothrombin time, fibrinogen and D-dimers also did not relate to drug levels. Although efficacy was not an end-point of this study, 26% of patients experienced stable disease or partial response for 6 treatment cycles. This included 6/17 patients with advanced melanoma with one patient achieving partial response and received study medication for >50 months. These encouraging data led to further studies of PI-88 in patients with metastatic melanoma, both as a single agent and in combination with dacarbazine.

A phase II study of PI-88 administered at 250 mg subcutaneously per day for 4 consecutive days every week in a 28 day cycle was carried out in 44 patients with advanced melanoma (27). Drug related serious adverse events (SAEs) included thrombocytopaenia (9%) with antibodies to PF4 detected in 3 of these 4 patients, haemorrhage cerebral metastases (5%), vascular thrombosis or cardiac ischemia (4%), transaminitis (2%), pancreatitis (2%), myalgia (2%) and hypoaesthesia (2%). All patients recovered from their SAEs except for one who died due to haemorrhagic cerebral metastasis. All adverse events (AEs) noted were of CTC grades 1/2 only except for one report of hot flush. The commonest AE was drug injection site reaction (64%) but there was complete patient compliance. Other AEs reported included fatigue (32%), constipation (9%), diarrhoea (7%), nausea (30%), alopecia (14%), fever/hot flush (16%) and headache (14%).

Partial response or stable disease was achieved as best response in 16% of patients. Median time to progression and overall survival was 1.7 months and 9 months

respectively. The authors concluded that efficacy of PI-88 was similar to standard chemotherapy but an alternative daily dosing regime may improve its efficacy.

Daily continuous administration of PI-88 has been investigated in a phase I study of patients with metastatic melanoma at 140 mg, 190 mg and 250 mg (29). The MTD was established at 250 mg and a second cohort of patients was recruited for administration of daily PI-88 at 140 mg or 190 mg with dacarbazine at 1000 mg/m2 every 21 days. All DLTs in both cohorts were grades 3/4 immune mediated thrombocytopaenia with one report of cerebral venous sinus thrombosis. PI-88 did not increase dacarbazine toxicity. Tissue factor pathway inhibitor levels correlated to drug administration but not to PI-88 dose. PI-88 administered alone did not result in radiological efficacy, but 3/9 patients experienced partial response in the combination treatment group. A study is now ongoing with PI-88 at 190 mg/day continuously with dacarbazine 1000 mg/m2 ever 3 weeks, versus dacarbazine alone in patients with metastatic melanoma (29).

PI-88 administered for 4 consecutive days every week in a 28 day cycle was investigated as adjuvant treatment in patients post hepatocellular carcinoma resection. In this phase II study, 172 patients were randomised to no treatment to one of three arms: no treatment, PI-88 160 mg or PI-88 250 mg per day for 9 treatment cycles and follow up of 12 weeks. At study completion, 63% of patients in the 160 mg dose group were disease free compared to 50% of controls and 41% of patients in the 250 mg dose group. The disease free survival for patients in the 160 mg group was 48 weeks compared to 22 weeks in the control group with a trend for significance ($p=0.09$, HR 1.7, 30).

Four SAEs were reported as possibly related to PI-88 and included intracerebral haemorrhage, gum bleeding, tumour recurrence and subsequent rupture. In the 250 mg group, 24% of patients did not complete study treatment and although this may have affected drug efficacy assessment, it was felt that the 160 mg dose level should be carried through alone into the phase III trial. This phase III study will aim to commence recruitment of 600 patients at the end of 2007.

PI-88 was investigated in combination with docetaxel in a phase I study in patients with advanced solid malignancies (31), and then in a phase II trial with non-small cell lung carcinoma patients who had failed first line platinum chemotherapy. Results of the lung cancer study were disappointing with no improvement in progression free rate, time to progression, response rate, overall survival or quality of life compared to docetaxel alone (32). PI-88 has also been investigated in patients with advanced multiple myeloma and a phase II study of PI-88 in combination with docetaxel and prednisolone is ongoing in patients with androgen-independent prostate cancer.

Manufacturer

Progens Pharmaceuticals Limited, Brisbane, Australia.

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Figure 1. Structure of the oligophosphosulfomannan components of PI-88

Legend

R = SO_3^- Na^+ or H

n = 0-4

Table 1. Day 1 pharmacokinetic profile of PI-88 in patients with advanced solid tumours (24), mean ± SD

PI-88 dose	AUC (µg/h/mL)	Cmax (µg/mL)	t1/2 (h)	Vd/F (L)	CL/F (L/h)	Tmax (h)
80 mg n=3	27.8 ± 18.0	4.1 ± 3.3	3.65 ± 1.12	20.9 ± 13.2	4.41± 3.74	1.6 ± 0.6
106 mg n=6	34.0 ± 6.4	5.6 ± 2.9	3.67 ± 1.94	17.2 ± 10.0	3.22 ± 0.62	1.6 ± 0.7
140 mg n=3	46.0 ± 13.2	6.7 ± 4.1	3.92 ± 0.85	18.8 ± 8.6	3.20 ± 0.85	1.7 ± 0.8
190 mg n=3	80.4 ± 20.7	8.5 ± 1.9	5.09 ± 0.53	18.0 ± 3.7	2.46 ± 0.57	1.9 ± 0.4
250 mg n=10	127.2 ± 50.6	9.4 ± 4.0	7.59 ± 4.45	19.4 ± 9.4	1.7 ± 0.71	2.0 ± 1.0
315 mg n=5	127.0 ± 22.8	12.5 ± 3.3	4.28 ± 0.74	15.8 ± 4.6	2.55 ± 0.46	3.1 ± 1.2

Legend

SD standard deviation

AUC area under concentration versus time curve

Cmax maximal plasma concentration

t1/2 half life

Vd/F apparent volume of distribution

CL/F apparent total body clearance

Tmax median time of maximal plasma concentration

Table 2. Summary of clinical trials of PI-88

Ref	PI-88 schedule	Patients	End point	Toxicities
28	iv 0.57 mg/kg for 2 h escalating to 2.28 mg/kg/day for 14 days	Advanced solid malignancies, n=14	MTD and DLT, MTD was 2.28 mg/kg/day for 14 days	DLT was CTC grade 3 thrombocytopaenia but no clinical complications from this
26	sc 80-250 mg/day on days 1-4 and 15-19 in a 28 day cycle	Advanced solid malignancies, n=18	Pharmacokinetics, MTD, DLT and toxicities. MTD not reached.	No DLT. Dexmaethasone 20mg day before and day of treatment caused hyperglycaemia at grades 1/2 in 31 courses, and grades 3/4 in 5 courses.
34	Not specified	Multiple myeloma refractory to standard treatment	39% clinical response defined as stable or decrease in paraprotein levels	Not specified
23	sc 80-160 mg or iv 160 mg over 2 h as single doses	Healthy male volunteers n=9	Pharmacokinetics profile	Not specified
30	sc 106-315 mg/day on days 1-4, 8-11 and 15-19 of a 28 day cycle, with docetaxel 30mg/m2 on days 1, 8 and 15 in a 28 day cycle	Advanced solid malignancies n=3	Pharmacokinetics, MTD, DLT and toxicities	No DLT to date and recruitment on-going. No significant drug toxicity seen.
24	sc 80-315 mg/day on days 1-4 and 15-18 of 28 day cycle, or sc 190-250 mg/day on days 1-4 every week in a 28 day cycle	Advanced solid malignancies n= 42	Pharmacokinetics, MTD, DLT, pharmacodynamic markers and toxicities. MTD 250 mg/day for both schedules.	DLTs thrombocytopaenia and pulmonary embolism. Common mild toxicities include fatigue, bruising at injection site.
27	sc 250 mg/day on days 1-4 every week in a 28 day cycle	Advanced melanoma n=44	Progression free survival, overall survival, response rate and time to progression	SAEs thrombocytopaenia, bleeding and thrombosis. Common AEs include fatigue, bruising at injection site, fever and gastrointestinal events.
29	sc 140-250 mg/day continuously alone or with dacarbazine 1000 mg/m2 every 3 weeks	Metastatic melanoma n=19	MTD, DLT, pharmacodynamic markers, efficacy and toxicities. MTD PI-88 sc 190 mg/day continuously with dacarbazine 1000 mg/m2 every 3 weeks	DLT CTC grade 3/4 immune mediated thrombocytopaenia and thrombosis. 3/9 patients in combination arm had partial response.

32	sc 250 mg/day on days 1-4, 8-11 and 15-19 of a 28 day cycle with docetaxel 30mg/m2 on days 1, 8 and 15 of a 28 day cycle, versus docetaxel alone	Advanced non-small cell lung cancer as 2nd line treatment	Progression free survival, time to progression, overall survival, response rate and quality of life. PI-88 did not improve any of these paramaeters compared to docetaxel alone.	SAEs related to PI-88 included hrombocytopaenia and thrombosis.
30	sc 160 mg or 250 mg/day on days 1-4 every week in a 28 day cycle	Adjuvant treatment for hepatocellular carcinoma	Efficacy and toxicity. 160 mg dose improved disease free survival with trend for significance.	SAEs bleeding, tumour recurrence and tumour rupture.
33	Variable sc dose on days 1-4 every week or daily, with docetaxel 75 mg/m2 every 21 days and prednisolone 5 mg twice daily	Androgen-independent prostate cancer, recruiting	Prostate specific antigen response rate, radiological response rate, progression free survival, overall survival, toxicity, quality of life, pharmacodynaimc markers	Study on-going
30	sc 160 mg/day on days 1-4 every week in a 28 day cycle	Adjuvant treatment for hepatocellular carcinoma	Primary end point disease free survival	Recruitment due to commence end of 2007
29	sc 190 mg/day continuously with dacarbazine 1000 mg/m2 every 21 days	Advanced melanoma, recruiting	Efficacy	Study on-going

Legend

DLT dose limiting toxicities

MTD maximum tolerated dose

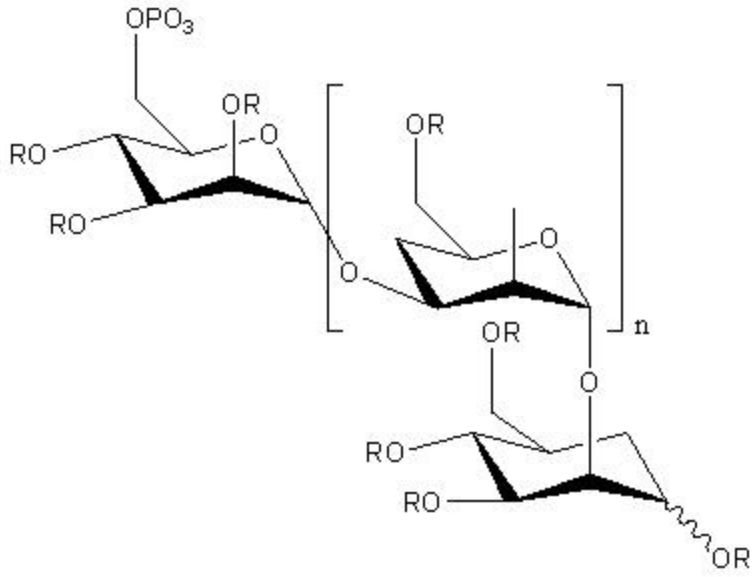
iv intravenous route of drug administration

sc subcutaneous route of drug administration

CTC Common Toxicity Criteria

SAE Serious Adverse Events

AE Adverse Events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