Drugs of the Future 2009, 34(10): 789-792

CCC: 0377-8282/2009
DOI: 10.1358/dof.2009.34.10.1426671

PRO-140

Humanized Anti-CCR5 Monoclonal Antibody
Anti-HIV Agent

EN: 271997

ABSTRACT

PRO-140 is a humanized anti-CCR5 monoclonal antibody currently in phase II clinical development for the treatment of HIV. It has exhibited potent in vitro antiviral activity against a broad range of HIV-1 isolates. This antiviral activity has been confirmed in a number of clinical studies involving HIV-infected patients, with no drug-related serious adverse events reported.

BACKGROUND

There is currently intense investigation of viral entry into host cells as a target for therapeutic and preventive intervention in HIV infection. Viral entry occurs in a number of sequential steps (1). In the first step, the HIV glycoprotein gp120 attaches to the host cell CD4 receptor. However, this step by itself is not sufficient for entry of the virus into the cell; a coreceptor for entry into target cells is required. The chemokine receptors CXCR4 and CCR5 have been identified as the principal coreceptors for entry of HIV into its target cells (2, 3). When gp120 binds to the CD4 receptor it undergoes a conformational change that exposes a structural coreceptor binding site. Coreceptor binding leads to additional conformational changes in the envelope proteins, ultimately resulting in the "fusion" of viral envelope and host cytoplasmic membranes. This creates a pore through which the viral capsid enters the cell.

CCR5 and CXCR4 have become targets for antiretroviral drug development. The CCR5 antagonist maraviroc has already received FDA approval, while other agents are in various stages of development. PRO-140 is a humanized anti-CCR5 monoclonal antibody that has demonstrated potent antiviral activity and is currently in clinical development as an antiretroviral drug. This review presents available data on the preclinical and clinical safety and efficacy of PRO-140.

PRECLINICAL PHARMACOLOGY

PRO-140 is a humanized monoclonal antibody that binds CCR5, thereby inhibiting the process of HIV and coreceptor binding. Unlike small-molecule CCR5 antagonists such as maraviroc, which bind to a hydrophobic cavity and inhibit CCR5 through allosteric mechanisms, PRO-140 is thought to exert its anti-HIV-1 effect through competitive mechanisms by binding to hydrophilic extracellular regions on CCR5. The concentration of PRO-140 required to inhibit HIV-1 entry is approximately 25 nM and is believed to be too low to affect the natural chemokine receptor activity of CCR5 (4).

PRO-140 blocked the replication of a broad range of genotypically and geographically diverse primary HIV-1 isolates in primary T cells and macrophages (5). The median IC_{90} values were 17 nM (2.5 µg/mL) for subtype B HIV-1 virus and 15 nM (2.2 µg/mL) for a panel of subtype A, C, E and F viruses (5). In a study of the susceptibility of patient-derived HIV-1 isolates to various entry inhibitors during acute and chronic HIV infection, the PRO-140 IC_{90} value was 1.3 µg/mL (6). PRO 140 exhibited broad activity in blocking CCR5-mediated HIV-1 entry in both the PhenoSense™ entry assay and the traditional whole-virus assays, with a median IC_{50} value of approximately 1 µg/mL (7). Although CCR5 inhibitors are in general thought to be only effective against R5 HIV-1, PRO-140 has exhibited in vitro activity against dual-tropic HIV-1 in at least two studies (5, 6, 8).

PRO-140 retained its antiviral activity when tested against viral isolates with resistance mutations to protease inhibitors, nucleoside analogue reverse transcriptase inhibitors and the fusion inhibitor enfuvirtide (9). The EC_{50} value was 0.50 ± 0.27 µg/mL and the fold-change value compared to the well-characterized reference virus HIV-$1_{92HT594}$ was 1.5 ± 0.8.

An interesting aspect of the antiretroviral potential of PRO-140 is its activity relative to small-molecule CCR5 antagonists. PRO-140 retained antiviral activity against maraviroc-resistant HIV-1 isolates. Viruses that were selected for resistance to maraviroc through serial passage and displayed reduced maximal inhibition (48%) by maraviroc remained susceptible to inhibition by PRO-140, with a maximal inhibition of 98% and essentially no change in IC_{50} compared to the parental isolate (10).

PRO-140 also exhibited synergy with enfuvirtide and the small-molecule CCR5 antagonists ancriviroc, vicriviroc and TAK-779 that enabled 5- to 10-fold dose reductions (11, 12).

PHARMACOKINETICS AND METABOLISM

A clinical trial of single-dose PRO-140 (0.1, 0.5, 2 or 5 mg/kg i.v.) demonstrated that serum concentrations increased dose-proportionally, with a serum half-life of approximately 2 weeks (13).

SAFETY

Single i.v. doses of PRO-140 were well tolerated with no significant changes in electrocardiogram (ECG) in healthy volunteers (14). The adverse events reported following administration of two single i.v.

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doses of PRO-140 (5 or 10 mg/kg) to HIV-infected individuals included headache, diarrhea, arthralgia, nasal congestion, pharyngolaryngeal pain and sunburn. However, there were no serious drug-related adverse events or infusion-related or dose-limiting toxicities in this study (15). In a third trial in which HIV-infected individuals were administered three different s.c. doses, adverse events that were reported included injection-site reactions, headache, fatigue, diarrhea, constipation, lymphadenopathy, high blood pressure and upper respiratory tract infection. However, there were no dose-related adverse events or drug-related serious adverse events. In addition, injection-site reactions were minimal to mild and self-limited (16).

CLINICAL STUDIES

A number of studies have examined the safety and antiviral activity of PRO-140 in humans. The first clinical study of PRO-140 was conducted in healthy male subjects as a randomized, double-blind, placebo-controlled phase I trial to examine the safety, pharmacokinetics and immunological effects of single doses of PRO-140 (14). Participants (N = 20) received PRO-140 at doses of 0.1, 0.5, 2 and 5 mg/kg i.v. or placebo (n = 5 per group) and were evaluated for 60 days post-treatment. PRO-140 exhibited dose-dependent binding to CCR5-expressing cells. Cellular CCR5 receptors remained coated with PRO-140 for over 60 days at the dose of 5 mg/kg, which has been demonstrated in prior laboratory studies to block HIV infection. Plasma RANTES levels were not affected by treatment and anti-PRO-140 antibodies were not observed (13).

The activity of PRO-140 in 39 HIV-infected individuals was investigated in study 1302, a proof-of-concept, ascending-dose phase Ib trial. Study participants were only infected with R5 virus, had HIV-1 RNA > 5000 copies/mL, a CD4 count of > 250 cells/mm^3 and had no antiretroviral therapy in the preceding 3 months. Individuals were randomized to receive a single i.v. infusion of placebo or one of three different doses of PRO-140 (0.5, 2 or 5 mg/kg). The study follow-up period was 58 days. Antiviral responses are shown in Table I. Significant, dose-dependent reductions in HIV-1 RNA were noted. All study participants receiving 5 mg/kg had viral load reductions of 1 $\log_{10}$ copies/mL or greater. The duration of response was also dose-dependent, with the four participants receiving 5 mg/kg experiencing viral load reductions of 1 $\log_{10}$ copies/mL or greater through day 22. There was no significant change from baseline in viral load for participants in the placebo arm of the study. Viral loads returned to baseline by day 29 in all patients. No drug-related serious adverse events or dose-limiting toxicities were reported (17).

Following the two studies above that provided preliminary safety and efficacy data for PRO-140 administered as a single i.v. infusion, the optimal administration route and dose of PRO-140 were further explored in two phase IIa trials (15, 16). Study 2301 explored higher doses of PRO-140 administered i.v., while study 2101 examined the safety and efficacy of PRO-140 administered s.c.

Study 2301 enrolled 31 HIV-infected individuals with no antiretroviral therapy in the preceding 12 weeks and examined the tolerability, antiviral activity and pharmacokinetics of two single i.v. doses (5 or 10 mg/kg) of PRO-140 compared with placebo (15). To be eligible, study participants were required to have only R5 virus, HIV-1 RNA > 5000 copies/mL, a CD4 count of > 300 cells/mm^3 (nadir > 250 cells/mm^3) and no AIDS-defining illness. The follow-up period was 58 days. Both doses of PRO-140 showed high-level antiviral activity compared with placebo. With the exception of one individual who was subsequently found to have dual/mixed-tropic HIV-1, all study participants treated with PRO-140 achieved a decrease in HIV-1 RNA of > 1 $\log_{10}$ copies/mL. Over half of the individuals who had received 10 mg/kg of PRO-140 achieved a decrease in HIV-1 RNA of > 2 $\log_{10}$ copies/mL. The duration of antiviral effect was also increased with PRO-140 (10 mg/kg), showing a mean viral load reduction of 1.3 $\log_{10}$ copies/mL through day 22 (15) (Table II).

Study 2101 had identical design, objectives and eligibility criteria as study 2301 but evaluated three different s.c. doses and dosing schedules (16). Individuals (N = 44) were randomized to receive three weekly doses of PRO-140 162 mg, two biweekly doses of 324 mg, three weekly doses of 324 mg or placebo and were followed for a total of 58 days for safety and antiviral effects. The antiviral effects of s.c. PRO-140 were dose-dependent and significantly better than placebo for all PRO-140 arms (Table III). Based on these data, Progenics selected the s.c. form of PRO-140 for further development for the treatment of HIV infection (18).

CONCLUSIONS

Despite the dramatic improvements in HIV-related illness and death as a result of combination antiretroviral therapy, treatment failures, drug-related toxicities and adherence continue to present significant challenges to the HIV clinician. Therefore, the development of new drugs with improved tolerability and nonoverlapping resistance profiles is critical for the continued long-term success of antiretroviral therapy. PRO-140 is a candidate antiretroviral drug in clinical development with a number of characteristics that hold promise for its

Table I. *Results from study 1302.*

	Placebo (n = 9)	PRO-140		
		0.5 mg/kg (n = 10)	2 mg/kg (n = 10)	5 mg/kg (n = 10)
Baseline median HIV-1 RNA ($\log_{10}$ copies/mL)	4.44	4.45	4.62	4.37
Baseline median CD4 count (mm^3)	439	493	438	535
Mean nadir change in HIV RNA from baseline ($\log_{10}$ copies/mL)	−0.39 ± 0.20	−0.58 ± 0.30	−1.20 ± 0.63	−1.83 ± 0.41
Proportion of participants with < 400 HIV-1 RNA copies/mL	0	0	10%	40%
Mean change in CD4 cell count on day 8 from baseline	19 ± 85	−6 ± 82	22 ± 144	129 ± 150

Table II. *Results from study 2301.*

	Placebo (n = 11)	PRO-140	
		5 mg/kg (n = 10)	10 mg/kg (n = 9)
Baseline median HIV-1 RNA (log_{10} copies/mL)	4.52	4.58	4.63
Baseline median CD4 count (mm^3)	414.5	389	368
Mean maximum HIV-1 RNA reductions (log_{10} copies/mL)	0.32	1.83	1.83
Median maximum HIV-1 RNA reductions (log_{10} copies/mL)	0.23	1.84	2.09
Mean change from baseline in HIV RNA at day 12 (log_{10} copies/mL)	+0.02	–1.69	–1.73
Mean change from baseline in HIV RNA at day 22 (log_{10} copies/mL)	–0.01	–0.92	–1.30
Proportion of patients with HIV-1 RNA reduction > 1 log_{10} copies/mL	0	100	100
Proportion of patients with HIV-1 RNA reduction > 2 log_{10} copies/mL	0	20	55

Table III. *Results from study 2101.*

	Placebo (n = 10)	PRO-140		
		162 mg once weekly (n = 11)	324 mg biweekly (n = 12)	324 mg once weekly (n = 11)
Baseline median HIV-1 RNA (log_{10} copies/mL)	4.09	4.43	4.60	4.19
Baseline median CD4 count (mm^3)	409	352	493	389
Mean maximum reductions in HIV-1 RNA (log_{10} copies/mL)	0.23	0.99 ($P = 0.0093$)	1.37 ($P < 0.0001$)	1.65 ($P < 0.0001$)
Mean changes in HIV-1 RNA at day 22 (log_{10} copies/mL)	+0.15	–0.75 ($P = 0.0072$)	–1.2 ($P < 0.0001$)	–1.51 ($P < 0.0001$)

potential future use. Although it exerts its antiviral effect by inhibiting the CCR5 coreceptor, it appears to do so at concentrations that do not affect the natural activity of CCR5. While this may provide some reassurance that the therapeutic use of PRO-140 will not result in serious unforeseen adverse events, the long-term safety of CCR5 inhibition remains to be proven. Preliminary clinical trial data indicate that PRO-140 is well tolerated without significant drug-related adverse events. However, this will need to be confirmed in phase III studies enrolling a larger number of patients followed for a longer period of time. Preliminary data also suggest that it may act synergistically with other entry inhibitors and retain antiviral activity against HIV-1 isolates resistant to other small-molecule CCR5 inhibitors; however, the effectiveness of PRO-140 in combination with other antiretrovirals has not been evaluated. PRO-140 has two additional potential shortcomings that may limit its clinical utility. Firstly, similar to all current CCR5 inhibitors, it is only active against R5 virus, thus significantly limiting its use in a significant proportion of HIV-infected patients. Secondly, it requires parenteral administration. However, this last shortcoming may be offset by its long half-life and the potential for s.c. self-administration.

SOURCE

Progenics Pharmaceuticals, Inc. (US).

DISCLOSURE

The author has received research grant funding from Pfizer and grant funding from Tibotec and Gilead.

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