PRO 140

Drug Class: **Entry and Fusion Inhibitors**

Drug Description

PRO 140 is a humanized monoclonal antibody against CCR5 and is designed to block the ability of HIV to enter and infect cells. [1]

HIV/AIDS-Related Uses

PRO 140 is an investigational entry inhibitor being studied for the treatment of HIV infection. PRO 140 has potential utility in both treatment-experienced and treatment-naive HIV infected individuals.[2] To date, two Phase I studies of the safety and pharmacokinetics (PK) of PRO 140 given intravenously have been completed, one in HIV uninfected males and another in HIV-1 infected individuals of both sexes.[3] [4] PRO 140 was granted fast-track status by the FDA in February 2006.[5]

Pharmacology

The CCR5 receptor is found on certain human inflammatory cells; HIV uses this receptor as a portal to enter and infect healthy cells.[6] PRO 140 inhibits entry of HIV into cells by preventing virus-cell binding at a distinct site on the CCR5 coreceptor without interfering with the natural activity of CCR5. It binds an extracellular (not a transmembrane) site, inhibiting HIV via a competitive (rather allosteric) mechanism.[7] PRO 140 exhibits dose-dependent binding to CCR5-expressing cells, significantly coating and protecting such cells for up to 60 days.[8] PRO 140 broadly and potently inhibits wild-type and drug-resistant, R5-tropic HIV in vitro. It is also synergistic with small-molecule CCR5 antagonists.[9] This synergistic effect seen when combining PRO 140 with other investigational CCR5 inhibitors suggests that PRO 140 may represent a distinct subclass of CCR5 inhibitors.[10]

A Phase I, randomized, double-blind, placebo-controlled study was conducted to examine the safety, PK, and pharmacodynamics of single-dose PRO 140 in 20 healthy males. Participants received intravenous PRO 140 doses of 0.1, 0.5, 2, and 5 mg/kg in sequential, dose-rising cohorts of 5 (4 active, 1 placebo) each and were evaluated for 60 days post-treatment. Serum concentrations of PRO 140 increased proportionally with dose; the serum half-life was approximately 2 weeks. Cellular CCR5 receptors remained coated with PRO 140 for greater than 60 days at the 5 mg/kg dose. No anti-PRO 140 antibodies were observed in preliminary bioanalytical testing.[11] [12]

In another Phase I, randomized, double-blind, placebo-controlled study, the safety, tolerability, antiviral activity, and PK of single-dose PRO 140 administered intravenously were studied in 39 HIV infected participants. Doses of PRO 140 of 0.5, 2, or 5 mg/kg were administered. A 10-fold (90%) reduction in viral load from baseline was observed as early as Day 5; the average viral load reduction by Day 10 was approximately 99%. All participants who received 5 mg/kg PRO 140 experienced at least a 10-fold reduction in viral load from baseline. The 2.0 mg/kg dose reduced viral load by an average of 90%; the 0.5 mg/kg dose reduced viral load by an average of 50%. A 29% ($p=0.055$) average increase in CD4 cells by Day 8 was also observed, suggesting a trend of increased CD4 count with PRO 140 use. Potent, rapid, prolonged, dose-dependent significant antiviral activity was observed across all dose groups. PK studies indicated that peak and total exposure increased proportionally or better with dose. Peak levels of PRO 140 were achieved within 3 to 60 minutes, and the terminal half-life of PRO 140 was determined to be about 4 days. Low titer anti-PRO 140 antibodies developed in one participant who received the 5.0 mg/kg dose; no obvious effect on PK or antiviral response could be discerned. Ex vivo fluorescently-labeled lymphocytes analyzed by flow cytometry indicated obvious coating of CCR5 lymphocytes by PRO 140, with a duration of coating of 1 to 2 weeks consistent with the compound's antiviral effects.[13]

In vitro antiviral activity of PR0 140 was independent of HIV-1 subtype and resistance to existing antiretroviral treatment classes.[14] PRO 140 exhibited potent, broad-spectrum activity in laboratory studies of more than 40 genetically diverse HIV strains. The strains failed to develop

PRO 140

Pharmacology (cont.)

resistance to PRO 140, even after 40 weeks of continued exposure in vitro.[15]

Adverse Events/Toxicity

PRO 140 was generally well tolerated in two, Phase I safety and pharmacokinetics studies conducted in healthy volunteers.[16] [17] No obvious, infusion-related, or dose-limiting toxicities, drug-related adverse effects[18] [19] , or electrocardiogram changes occurred with single doses ranging from 0.1 to 5 mg/kg.[20]

Drug and Food Interactions

PRO 140 exhibits potent and reproducible synergy in vitro with the entry inhibitors enfuvirtide[21] and maraviroc[22] and with investigational small-molecule CCR5 antagonists, such as SCH-D (vicriviroc).[23] [24]

Clinical Trials

For information on clinical trials that involve PRO 140, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: PRO 140 AND HIV Infections.

Dosing Information

Mode of Delivery: Intravenous infusion.[25]

Dosage Form: Intravenous infusions of 0.1, 0.5, 2, and 5 mg/kg doses of PRO 140 have been administered to both HIV infected and uninfected individuals in clinical trials.[26] [27] [28]

Future studies of PRO 140 administered by subcutaneous injection are planned.[29]

Chemistry

CAS Number: 674782-26-4[30]

Molecular formula: Unspecified[31]

Other Names

PRO-140[32]

Further Reading

Biswas P, Tambussi G, Lazzarin. A. Access denied? The status of co-receptor inhibition to counter HIV entry. Expert Opin Pharmacother. 2007 May;8(7):923-33.

Murga JD, Franti M, Pevear DC, Maddon PJ, Olson WC. Potent antiviral synergy between monoclonal antibody and small-molecule CCR5 inhibitors of human immunodeficiency virus type 1. Antimicrob Agents Chemother - 2006 Oct;50(10):3289-96.

Ketas TJ, DiPippo VA, Lam E, Maddon PJ, Olson WC. PRO 140, a Humanized CCR5 Monoclonal Antibody, is Active Against Genotypically Diverse and Enfuvirtide-Resistant Strains of HIV-1. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, Sydney, Australia, Abstract WEPEA093, 2007.

Saag MS, Jacobson JM, Thompson M, Fischl M, Liporace R, Reichman RC, Redfield RR, Fichtenbaum CJ, Zingman BS, Patel MC, D'Ambrosio P, Michael M, Kroger H, Ly H, Rotshteyn Y, Stavola JJ, Maddon PG, Kremer AB, Olson WC. Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, Sydney, Australia, Abstract WESS201, 2007.

Manufacturer Information

PRO 140
Progenics Pharmaceuticals, Inc.
777 Old Saw Mill Road
Tarrytown, NY 10591

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

For More Information (cont.)

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. Progenics Pharmaceuticals - Progenics Reports Positive Results From Phase I Clinical Trial of PRO 140, a Novel Monoclonal Antibody That Blocks HIV Entry [Press Release], September 9, 2005. Available at: http://www.progenics.com/releases.cfm. Accessed 10/16/07.

2. IAS Conf on HIV Pathogenesis and Treatment - 4th, 2007. Abstract WEPEA093.

3. Progenics Pharmaceuticals - Progenics Reports Positive Results From Phase I Clinical Trial of PRO 140, a Novel Monoclonal Antibody That Blocks HIV Entry [Press Release], September 9, 2005. Available at: http://www.progenics.com/releases.cfm. Accessed 10/16/07.

4. IAS Conf on HIV Pathogenesis and Treatment - 4th, 2007. Abstract WESS201.

5. Progenics Pharmaceuticals - Progenics Pharmaceuticals' HIV Drug, PRO 140, Receives FDA Fast-Track Designation [Press Release], February 22, 2006. Available at: http://www.progenics.com/releases.cfm. Accessed 10/16/07.

6. Progenics Pharmaceuticals - Progenics Pharmaceuticals' HIV Drug, PRO 140, Receives FDA Fast-Track Designation [Press Release], February 22, 2006. Available at: http://www.progenics.com/releases.cfm. Accessed 10/16/07.

7. Natap.org - Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. Available at: http://www.natap.org/2007/ICAAC/ICAAC_21.htm. Accessed 10/16/07.

8. Progenics Pharmaceuticals - Progenics Pharmaceuticals' HIV Drug, PRO 140, Receives FDA Fast-Track Designation [Press Release], February 22, 2006. Available at: http://www.progenics.com/releases.cfm. Accessed 10/16/07.

9. Natap.org - Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. Available at: http://www.natap.org/2007/ICAAC/ICAAC_21.htm. Accessed 10/16/07.

10. IAS Conf on HIV Pathogenesis and Treatment - 3rd, 2005. Abstract TuOa0206.

11. Conf Retroviruses Opportunistic Infect - 13th, 2006. Abstract 515.

12. Progenics Pharmaceuticals - Progenics Reports Positive Results From Phase I Clinical Trial of PRO 140, a Novel Monoclonal Antibody That Blocks HIV Entry [Press Release], September 9, 2005. Available at: http://www.progenics.com/releases.cfm. Accessed 10/16/07.

13. Natap.org - Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. Available at: http://www.natap.org/2007/ICAAC/ICAAC_21.htm. Accessed 10/16/07.

14. IAS Conf on HIV Pathogenesis and Treatment - 4th, 2007, Abstract WEPEA093.

15. Progenics Pharmaceuticals - Progenics Reports Positive Results From Phase I Clinical Trial of PRO 140, a Novel Monoclonal Antibody That Blocks HIV Entry [Press Release], September 9, 2005. Available at: http://www.progenics.com/releases.cfm. Accessed 10/16/07.

16. Conf Retroviruses Opportunistic Infect - 13th, 2006. Abstract 515.

17. Natap.org - Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. Available at: http://www.natap.org/2007/ICAAC/ICAAC_21.htm. Accessed 10/16/07.

18. Conf Retroviruses Opportunistic Infect - 13th, 2006. Abstract 515.

19. Natap.org - Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. Available at: http://www.natap.org/2007/ICAAC/ICAAC_21.htm. Accessed 10/16/07.

20. Conf Retroviruses Opportunistic Infect - 13th, 2006. Abstract 515.

21. IAS Conf on HIV Pathogenesis and Treatment - 3rd, 2005. Abstract TuOa0206.

22. Antimicrob Agents Chemother - 2006 Oct;50(10):3289-96

23. IAS Conf on HIV Pathogenesis and Treatment - 3rd, 2005. Abstract TuOa0206.

24. Antimicrob Agents Chemother - 2006 Oct;50(10):3289-96

25. Natap.org - Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. Available at: http://www.natap.org/2007/ICAAC/ICAAC_21.htm. Accessed 10/16/07.

26. IAS Conf on HIV Pathogenesis and Treatment - 3rd, 2005. Abstract WePe6.2C04.

27. Conf Retroviruses Opportunistic Infect - 13th, 2006. Abstract 515.

28. Natap.org - Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. Available at: http://www.natap.org/2007/ICAAC/ICAAC_21.htm. Accessed 10/16/07.

29. Natap.org - Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. Available at: http://www.natap.org/2007/ICAAC/ICAAC_21.htm. Accessed 10/16/07.

30. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 10/16/07.

31. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 10/16/07.

32. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 10/16/07.