Racivir

Drug Class: **Nucleoside Reverse Transcriptase Inhibitors**

Drug Description

Racivir, also known as RCV, is an oxothiolane nucleoside reverse transcriptase inhibitor similar to emtricitabine and lamivudine. [1] Racivir is a 50:50 mixture of emtricitabine and its positive enantiomer. [2]

HIV/AIDS-Related Uses

Racivir is an investigational drug that displays potent and selective activity against both HIV-1 and hepatitis B virus (HBV) in cell culture and in animal models.[3] [4] Racivir has been compared to lamivudine, an approved cytosine analog, in clinical trials as part of a triple-agent regimen with stavudine and efavirenz. Racivir is now being studied in phase II/III clinical trials as part of combination therapy for the treatment of HIV-1 infection.[5] [6]

Non-HIV/AIDS-Related Uses

Racivir is active in vitro against HBV.[7]

Pharmacology

Racivir, a 50:50 racemic mixture of the (-)- and (+)-beta-enantiomers of emtricitabine, is being developed for the treatment of HIV infection. The (+)-enantiomer of emtricitabine is approximately 10- to 20-fold less potent than (-)-emtricitabine, but it selects for a different HIV mutation in human lymphocytes.[8]

In a Phase I/II dosing study, racivir was administered to HIV infected, treatment-naive, male volunteers in combination with stavudine and efavirenz for 14 days. Racivir was administered once daily at doses of 200, 400, or 600 mg. The combination regimens resulted in a rapid initial drop in viral load, with mean 10-fold reductions by Day 4. Mean HIV RNA levels continued to drop, though more slowly, through the end of treatment on Day 14, resulting in a greater than 20-fold reduction in viral load. Upon cessation of therapy, HIV RNA levels remained suppressed from all doses for more than 2 weeks. Viral load remained steady through Day 28. By Day 35, HIV RNA levels began to increase but still remained at least 10-fold less than baseline levels.[9] [10]

Racivir displays excellent oral bioavailability in human preclinical studies.[11] In a Phase I/II study of racivir in treatment-naive men, pharmacokinetic parameters were dose proportional across 200, 400, and 600 mg dose levels.[12]

A Phase II, randomized, double-blind, placebo-controlled study was conducted to assess the safety, tolerability, and antiviral effect of a racivir 600 mg dose compared with lamivudine in HIV infected, treatment-experienced participants with the M184V mutation who have been on lamivudine as part of a combination regimen. One group of 16 participants continued on existing therapy with lamivudine, and the second group of 26 participants received racivir in place of lamivudine in existing regimens. Participants received 28 days of blinded therapy followed by 20 weeks of open-label treatment. After 28 days of blinded treatment, the mean viral load rose by 34.9% in the lamivudine group and dropped by 60.2% in the racivir group ($p=0.02$). A subset analysis of 14 participants in the racivir-treated group revealed that the change in viral load was largely due to a positive antiviral response in participants who had an HIV mutation pattern that included M184V and less than three thymidine analog mutations with or without non-nucleoside reverse transcriptase inhibitor or protease inhibitor mutations. Replacing lamivudine with racivir in their existing therapies caused a mean drop in viral load of 80% ($p=0.004$) in the second week of treatment.[13] [14]

Racivir has demonstrated antiviral activity in patients harboring HIV with the lamivudine-associated M184V mutation and with less than three thymidine-associated mutations. Because such mutations are consistent with first-line therapy failure, racivir may be useful as part of a combination second-line treatment regimen.[15]

Adverse Events/Toxicity

Single and multiple doses of racivir appear well

Racivir

Adverse Events/Toxicity (cont.)

tolerated in early studies, with mild headache and fatigue occurring no more frequently than with placebo.[16] In a 14-day, Phase I/II study conducted in HIV infected men, racivir 200, 400 and 600 mg doses were well tolerated in combination with stavudine and efavirenz.[17]

In an ongoing Phase II trial of 42 HIV infected patients comparing racivir to lamivudine as part of a combination regimen, no severe adverse effects attributed to therapy were noted over the 28 days. As open-label dosing of racivir continues in this trial, safety data will be presented.[18]

Drug and Food Interactions

In previous clinical trials, racivir was administered with stavudine and efavirenz. There was no evidence that coadministration of stavudine and efavirenz had an adverse effect on the pharmacokinetics of racivir.[19]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral.[20]

Dosage Form: Tablets containing racivir 50 mg and 200 mg. Racivir is dosed once daily as part of a combination regimen.[21] [22] Clinical trials have evaluated racivir dosages of 200, 400, and 600 mg once daily for up to 14 days.[23]

Chemistry

CAS Name:
2',3'-Dideoxy-5-fluoro-3'-thiacytidine[24]

CAS Number: 143491-54-7[25]

Molecular formula: C8-H10-F-N3-O3-S[26]

C39.0%, H4.1%, F7.3%, N17.1%, O19.5%, S13.0%[27]

Molecular weight: 247.25[28]

Other Names

RCV[29]

(+)/(-)FTC[30]

Further Reading

Herzmann C, Arasteh K, Murphy RL, Schulbin H, Kreckel P, Drauz D, Schinazi RF, Beard A, Cartee L, Otto MJ. Safety, pharmacokinetics, and efficacy of (+/-)-beta-2',3'-dideoxy-5-fluoro-3'-thiacytidine with efavirenz and stavudine in antiretroviral-naive human immunodeficiency virus-infected patients. Antimicrob Agents Chemother. 2005 Jul;49(7):2828-33.

Otto MJ. New nucleoside reverse transcriptase inhibitors for the treatment of HIV infections. Curr Opin Pharmacol. 2004 Oct;4(5):431-6.

Study Comparing Racivir and Lamivudine in Treatment-Experienced HIV Subjects. Available at:

Racivir

Further Reading (cont.)

Manufacturer Information

Racivir
Pharmasset, Inc.
US Research Operations
1860 Montreal Road
Tucker, GA 30084
(678) 395-0035

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• 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. Urol Nurs - 2005;25(3):225-31

2. Antimicrob Agents Chemother - 2005;49(7):2828-33

3. Pharmasset, Inc - Product Pipeline: Racivir. Available at: http://www.pharmasset.com. Accessed 05/18/07.

4. Pharmasset, Inc - Investor Center: Press Releases: Pharmasset's Reverset and Racivir Advance Toward Phase 2 [press release], March 26, 2003. Available at: http://investor.pharmasset.com/releasedetail.cfm?ReleaseID=233723. Accessed 05/18/07.

5. Urol Nurs - 2005;25(3):225-31

6. HIV and Hepatitis.com - Conference Coverage: Racivir Demonstrates Good Safety and Efficacy in Patients with NRTI-resistant HIV. Available at: http://www.hivandhepatitis.com/2007icr/croi/docs/040307_b.html. Accessed 05/18/07.

7. Conf Retroviruses Opportunistic Infect - 10th, February 2003. Abstract P552.

8. Antimicrob Agents Chemother - 2005;49(7):2828-33

9. Antimicrob Agents Chemother - 2005;49(7):2828-33

10. Conf Retroviruses Opportunistic Infect - 10th, February 2003. Abstract P552.

11. Pharmasset, Inc - Investor Center: Press Releases: Pharmasset Study Shows Sustained Anti-HIV Effect of Racivir Combined with Zerit and Sustiva [press release], February 12, 2003. Available at: http://investor.pharmasset.com/releasedetail.cfm?ReleaseID=233724. Accessed 05/18/07.

12. Antimicrob Agents Chemother - 2005;49(7):2828-33

13. Pharmasset, Inc - Product Pipeline: Racivir. Available at: http://www.pharmasset.com. Accessed 05/18/07.

14. Conf Retroviruses Opportunistic Infect - 14th, 2007. Abstract 488.

15. Conf Retroviruses Opportunistic Infect - 14th, 2007. Abstract 488.

16. Pharmasset, Inc - Investor Center: Press Releases: Single and Multiple Dose Pharmacokinetic and Safety Data on Racivir from an HIV Clinical Study [press release], December 18, 2002. Available at: http://investor.pharmasset.com/releasedetail.cfm?ReleaseID=233727. Accessed 05/18/07.

17. Antimicrob Agents Chemother - 2005;49(7):2828-33

18. Conf Retroviruses Opportunistic Infect - 14th, 2007. Abstract 488.

19. Pharmasset, Inc - Investor Center: Press Releases: Single and Multiple Dose Pharmacokinetic and Safety Data on Racivir from an HIV Clinical Study [press release], December 18, 2002. Available at: http://investor.pharmasset.com/releasedetail.cfm?ReleaseID=233727. Accessed 05/18/07.

20. Pharmasset, Inc - Product Pipeline: Racivir. Available at: http://www.pharmasset.com. Accessed 05/18/07.

21. Pharmasset, Inc - Investor Center: Press Releases: Single and Multiple Dose Pharmacokinetic and Safety Data on Racivir from an HIV Clinical Study [press release], December 18, 2002. Available at: http://investor.pharmasset.com/releasedetail.cfm?ReleaseID=233727. Accessed 05/18/07.

22. Pharmasset, Inc - Product Pipeline: Racivir. Available at: http://www.pharmasset.com. Accessed 05/18/07.

23. Antimicrob Agents Chemother - 2005;49(7):2828-33

24. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 05/18/07.

25. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 05/18/07.

26. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 05/18/07.

27. Calculation. -

28. Calculation. -

29. Conf Retroviruses Opportunistic Infect - 10th, February 2003. Abstract P552.

30. J Clin Invest - 2001 Feb;107(4):449-455