Vicriviroc maleate

Drug Class: **Entry and Fusion Inhibitors**

Drug Description

Vicriviroc, also known as SCH-D and vicriviroc maleate, is a piperazine-based CCR5 receptor antagonist designed to block the entry of HIV into CD4 cells. [1] [2]

HIV/AIDS-Related Uses

Vicriviroc is a piperazine-based CCR5 antagonist currently in Phase II/III trials.[3] [4] It is a novel, orally active entry and fusion inhibitor that holds promise for use in HIV infected patients who are resistant to enfuvirtide and other antiretrovirals.[5] Vicriviroc received fast-track approval status from the FDA in 2005.[6]

A Phase II trial in treatment-naive patients was discontinued in October 2005, because detectable viral levels returned in some patients taking vicriviroc and lamivudine/zidovudine compared with the patients in the control group who were taking efavirenz and lamivudine/zidovudine. No significant adverse events contributed to the discontinuation.[7]

A second Phase II trial testing vicriviroc in treatment-experienced patients without similar viral level concerns remains ongoing, and a set of Phase III trials in treatment-experienced patients was initiated in 2007.[8] [9]

Non-HIV/AIDS-Related Uses

Vicriviroc doses of 5, 10, and 15 mg once daily in addition to existing background regimens have been studied in one randomized, controlled trial of 40 patients who were coinfected with HIV and hepatitis C virus (HCV). In this setting, vicriviroc had no clinical impact on HCV viral load.[10]

Pharmacology

Chemokine receptors expressed on the surface of immune cells are known to play a critical role in HIV infection and transmission. Entry and fusion inhibitors act differently than other classes of anti-HIV drugs (e.g., protease inhibitors [PIs], nucleoside reverse transcriptase inhibitors) by preventing HIV from infecting and entering cells, rather than trying to eradicate HIV after the virus has infected a cell. The CCR5 receptor acts with the CD4 receptor on the surface of T cells to facilitate entry of HIV into cells. Because previous research has suggested that individuals who lack a functional CCR5 receptor are largely resistant to HIV infection, the CCR5 receptor has been a target of investigation in development of anti-HIV therapy.[11]

Vicriviroc is a small-molecule inhibitor that binds to the cell's CCR5 receptor. When the drug binds to the CCR5 receptor, the receptor's conformation changes. This prevents HIV's gp120 protein from binding to CCR5 and consequently prevents the virus from entering the cell.[12]

Vicriviroc has been safe and well tolerated in HIV infected, treatment-naive patients participating in vicriviroc Phase I trials receiving 10-, 25-, and 50-mg twice-daily dosages of the drug. At these doses, a nadir of HIV-1 viral load was observed after 10 to 14 days of dosing.[13] Phase I trial data in treatment-naive HIV patients suggest that vicriviroc's suppression of HIV viral load is dose dependent. Vicriviroc does not appear to induce cytochrome P450 (CYP) 3A4 and has an elimination half-life of approximately 24 hours.[14] Vicriviroc has excellent oral bioavailability, is rapidly absorbed, and has a large apparent volume of distribution. The rapid absorption and a half-life range of 28 to 33 hours both support once-daily dosing of vicriviroc.[15] [16] Minimum (trough) plasma concentrations, or trough concentrations (Cmin), of vicriviroc appear to predict virologic response, as evidenced in ACTG A5211, a Phase II study of vicriviroc 5, 10, or 15 mg given once daily in 86 HIV infected participants with CCR5-tropic virus. At 2 weeks, Cmins averaged 42.3 ng/ml with the 5-mg dose, 90.9 ng/ml with the 10-mg dose, and 121 ng/ml with the 15-mg dose. In participants with Cmins greater than or equal to 53.7 ng/ml, 70% had at least a 10-fold reduction in viral load levels compared with 44% of participants who had lower Cmins.[17]

In the Phase II ACTG A5211 trial, 118 treatment-experienced patients with CCR5-tropic

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Pharmacology (cont.)

HIV were randomized to receive vicriviroc 5, 10, or 15 mg once daily or placebo in addition to ritonavir-boosted, PI-containing regimens. Vicriviroc demonstrated potent and sustained viral suppression through 48 weeks of therapy. At Day 14 and at Week 24, the median viral load reductions from baseline were statistically greater in the 5-, 10- and 15-mg vicriviroc groups (approximately 85% and 97%, 90% and 99%, and 85% and 98%, respectively) than in the placebo group (slight increase and 50% reduction, respectively). At Week 48, patients in the 10- and 15-mg treatment groups achieved a median decrease in viral load of 99% and 96%, respectively, and a median CD4 count increase from baseline of 130 and 96 cells/mm3, respectively. More patients in the vicriviroc groups had undetectable virus at 48 weeks (HIV-1 viral load less than 50 copies/ml) compared with those in the placebo group (57/37% and 43/27% vs. 14/11%, respectively), and fewer patients in the vicriviroc groups experienced virologic failure compared to those in the placebo group (27 and 33% vs. 86%, respectively).[18] Among participants in the 10- and 15-mg treatment groups who had viral load levels less than 50 copies at Week 24, 70% retained that level through Week 48. Although all participants had CCR5-tropic virus at baseline screening, 12 participants (10%) had dual/mixed virus when the study regimen began. The time to virologic failure tended to be faster in people with dual/mixed virus when the study began than in those with R5-only virus. In addition, tropism switches from CCR5-tropic to CXCR4- or dual/mixed-tropic virus occurred in 7 (12%) of 60 participants taking vicriviroc 10 or 15 mg and in 8 participants taking vicriviroc 5 mg. Among 26 vicriviroc-treated people who had a virologic failure, 9 (35%) saw their virus change coreceptor preference from CCR5 to CXCR4 or dual/mixed tropism. After dual/mixed or X4-using virus emerged in people taking vicriviroc, viral loads and CD4 counts remained relatively stable through Week 48.[19] [20]

After completion of the expanded, 48-week ACTG A5211 trial, 39 HIV infected participants voluntarily continued taking vicriviroc 15 mg in combination with optimized background therapy (OBT). Two-year results of the open-label study showed long-lasting viral load reductions of more than 99% from prestudy levels. Sixty percent of participants maintained viral load levels less than 50 copies. In addition, CD4 levels after 2 years of vicriviroc treatment were approximately 84 cells/mm3 greater than prestudy levels. Two patients experienced viral load rebound, and 6 patients experienced a tropism switch from CCR5-tropic virus to either CXCR4- or dual/mixed-tropic virus.[21] [22] This study found that patients with dual/mixed-tropic virus had significantly lower CD4 counts than patients with CCR5-tropic virus only. This finding emphasizes the importance of evaluating coreceptor use in the clinical development of CCR5 and CXCR4 inhibitors.[23]

Another Phase II trial, VICTOR-E1, is ongoing to compare vicriviroc 20 and 30 mg with placebo in combination with a ritonavir-boosted, PI-containing antiretroviral regimen.[24] [25] VICTOR-E1 is a randomized, double-blind, placebo-controlled, dose-finding study in 116 antiretroviral-experienced participants with CCR5-tropic HIV-1. At Week 12, during a safety evaluation, CD4 levels were generally sustained or increased. Tropism changes from CCR5-tropic to dual/mixed-tropic virus were noted in six participants after screening but before drug administration began. Further, treatment-emergent tropism shifts generally did not result in reduced CD4 counts and were not associated with immune decline.[26] This trial also examined coreceptor usage and tropism-associated variables. Approximately 35% of screened participants had dual or mixed-tropic virus, 4% had CXCR4-tropic virus, and 45% had CCR5-tropic virus; the assay failed in the remaining 15%. Dual/mixed- or CXCR4-tropic virus at screening was associated with lower mean CD4 counts than CCR5-tropic virus; participants with CCR5-tropic virus experienced significantly greater CD4 counts compared with those with non-CCR5-tropic virus. In contrast, age, resistance mutations, gender, and baseline viral load levels had no correlation with coreceptor usage.[27] Efficacy of both vicriviroc 20 and 30 mg was examined at a Week 24 analysis, and viral load was reduced significantly in both groups compared with placebo. HIV RNA was reduced by -2.04 log in both treatment arms.

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Pharmacology (cont.)

However, undetectable HIV RNA levels (less than 50 copies/ml) were achieved in 64% of patients on vicriviroc 30 mg but in 58% of patients on vicriviroc 20 mg.[28] At a Week 48 analysis, vicriviroc 20 and 30 mg continued to display efficacy in reducing HIV RNA. Viral load was reduced to less than 50 copies/ml in 56% of patients on vicriviroc 30 mg and in 52% of patients on vicriviroc 20 mg. On the basis of the Week 24 and Week 48 efficacy at achieving undetectable virus, the manufacturer continued further study in Phase III trials with the 30-mg dose as the more efficacious option.[29]

Two large, Phase III trials of vicriviroc 30 mg once daily in combination with a ritonavir-boosted, PI-containing OBT have also been initiated in 2007 in treatment-experienced participants with multidrug-resistant HIV and with CCR5-tropic virus at baseline screening. VICTOR-E3 and -E4 will evaluate the efficacy of the addition of vicriviroc to OBT compared with OBT alone. They will also evaluate the safety and tolerability of vicriviroc compared with placebo. The primary efficacy endpoint of both studies will be the proportion of patients with viral load levels less than 50 copies/ml at Week 48.[30] [31] [32]

Mutation in V3 loop sites of HIV's env gene have occurred in some participants who experienced treatment failure in Phase II studies. None of these mutations developed in participants who received vicriviroc 15 mg. The V3 mutations arose at different loop sites in each case and did not correlate directly with reduced viral susceptibility to vicriviroc; thus, it is unlikely that these mutations explain these instances of virologic failure. Although all participants with virologic failure initially had CCR5-tropic virus, repeat testing after failure identified CXCR4-tropic virus; this may explain the treatment failure, although that link is also unclear.[33] [34]

Further study of the effect of mutations on viral resistance to vicriviroc has found that mutations in the V3 loop stem introduce resistance to vicriviroc and cross resistance to TAK779, another investigational CCR5 antagonist agent. Increased susceptibility to HGS004, a third investigational CCR5 antagonist agent, likely was caused by decreased binding of vicriviroc to the CCR5 receptor.[35]

Adverse Events/Toxicity

No drug-specific toxicity was identified in a small Phase I study in HIV infected, treatment-naive patients; vicriviroc was safe, well tolerated, and active at all dose levels tested in the study.[36] [37] In a Phase II study of vicriviroc that was conducted in 118 treatment-experienced patients, 4 cases of lymphoma and 1 case of stomach cancer occurred in the vicriviroc-treated group. A causal association between vicriviroc and the lymphoma cases could not be established at the time, and all those who developed cancers had very advanced HIV disease.[38]

In another Phase II, dose-escalating study of vicriviroc, there were no significant differences in Grade 3 or 4 adverse events across the vicriviroc and placebo groups, but eight patients randomly assigned to receive vicriviroc 5 mg and two patients randomly assigned to receive placebo developed malignancies. The relationship of malignancy development to vicriviroc is uncertain. The study consequently was unblinded in March 2006, and the 5-mg dose group was discontinued.[39] [40] [41]

A safety evaluation of 116 participants enrolled on the Phase II VICTOR-E1 trial showed no safety concerns after a mean duration of 14 weeks (range of 12 to 28 weeks) of treatment with vicriviroc 20 or 30 mg compared with placebo. Specifically, no hepatotoxicity, malignancies, or drug-related seizures were noted. At Week 48, vicriviroc was well tolerated in both treatment arms, and Grade 3/4 adverse events occurred in approximately 20% of these and the placebo arms. Vicriviroc 20 mg and 30 mg administered once daily in combination with a ritonavir-boosted, PI-containing ART regimen appear well tolerated in this treatment-experienced population.[42] [43]

Safety data at Week 24 of an ongoing Phase III trial showed no evidence of safety concerns regarding cardiac toxicity, hepatotoxicity, drug related seizures, infections or malignancy; most adverse events were mild to moderate and were similar to

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Adverse Events/Toxicity (cont.)

placebo. The most common adverse events included nausea, headache, and fatigue.[44] [45] Other common adverse events noted in 2-year follow-up of Phase II studies included pharyngitis, abdominal pain, and fatigue. Fatigue was the only Grade 3 adverse event reported in more than 1% of the participants.[46]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral.[47]

Dosage Form: Clinical studies of vicriviroc have evaluated 5-, 10-, 15-, 25-, 30-, and 50-mg tablets.[48] [49] [50]

The 5-mg dose was discontinued early in trials conducted in treatment-experienced patients. This dose was associated with poor efficacy, and eight patients receiving vicriviroc developed malignancies.[51] [52]

The manufacturer is continuing study of vicriviroc 30 mg once daily in multiple phase III trials.[53]

Chemistry

CAS Name: 1-((4,6-dimethyl-5-pyrimidinyl) carbonyl)-4-(4-(2-methoxy-4-(trifluoromethyl) phenyl) ethyl-3-methyl-1-piperazinyl)-4-methylpiperidine (vicriviroc)[54]

CAS Number: 599179-03-0 (vicriviroc maleate)[55]

Molecular formula: C28-H38-F3-N5-O2 x C4H4O4 (vicriviroc maleate)[56]

Molecular weight: 649.7 (vicriviroc maleate)[57]

Other Names

SCH 417690[58]

Vicriviroc[59]

VCV[60]

SCH-D[61]

Further Reading

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Manufacturer Information

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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

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