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DRUG DISCOVERY

Maraviroc CCR5 antagonosit for HIV

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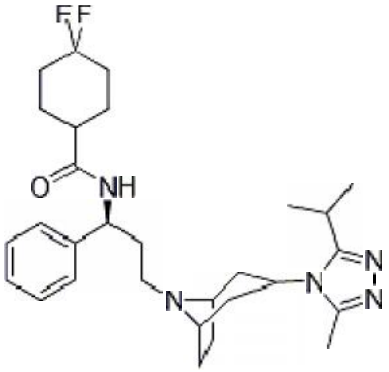
ABSTRACT

Maraviroc (UK-427,857) is a selective CCR5 antagonist with potent anti-human immunodeficiency virus type 1 (HIV-1) activity and favorable pharmacological properties. Maraviroc is the product of a medicinal chemistry effort initiated following identification of an imidazopyridine CCR5 ligand from a high-throughput screen of the Pfizer compound file. Maraviroc demonstrated potent antiviral activity against all CCR5-tropic HIV-1 viruses tested, including 43 primary isolates from various clades and diverse geographic origin (geometric mean 90% inhibitory concentration of 2.0 nM). Maraviroc was active against 200 clinically derived HIV-1 envelope-recombinant pseudoviruses, 100 of which were derived from viruses resistant to existing drug classes. There was little difference in the sensitivity of the 200 viruses to maraviroc, as illustrated by the biological cutoff in this assay (= geometric mean plus two standard deviations [SD] of 1.7-fold). The mechanism of action of maraviroc was established using cell-based assays, where it blocked binding of viral envelope, gp120, to CCR5 to prevent the membrane fusion events necessary for viral entry. Maraviroc did not affect CCR5 cell surface levels or associated intracellular signaling, confirming it as a functional antagonist of CCR5. Maraviroc has no detectable in vitro cytotoxicity and is highly selective for CCR5, as confirmed against a wide range of receptors and enzymes, including the hERG ion channel (50% inhibitory concentration, >10 μM), indicating potential for an excellent clinical safety profile. Studies in preclinical in vitro and in vivo models predicted maraviroc to have human pharmacokinetics consistent with once- or twice-daily dosing following oral administration. Clinical trials are ongoing to further investigate the potential of using maraviroc for the treatment of HIV-1 infection and AIDS.

1. INTRODUCTION



Maraviroc is the first CCR5 co receptor antagonist to receive marketing approval from the Food and Drug Administration (FDA) for the treatment of CCR5-tropic human immunodeficiency virus (HIV) infection as part of an optimized antiretroviral regimen in treatment-experienced patients. As 50% or more of treatment-experienced patients may be infected with CXCR4-tropic virus, a tropism assay should be performed before initiating maraviroc therapy. The majority of evidence supporting maraviroc's use comes from two studies of HIV-infected, treatment-experienced patients. Pooled analysis from these two studies revealed that twice-daily maraviroc decreased HIV-1 RNA by 1.84 log copies/mL, compared with 0.78 log copy/mL with placebo. Forty-six percent of subjects attained an HIV-1 RNA concentration of <50 copies/mL, compared with only 17% with placebo. In a trial of treatment-naive HIV-infected individuals, maraviroc failed to show noninferiority to efavirenz. Maraviroc is metabolized by cytochrome P-450 isoenzyme 3A4 and is subject to interactions with inhibitors and inducers of that isoenzyme, such as the protease inhibitors (except tipranavir), efavirenz, and rifampin. Resistance has been reported with maraviroc, but specific mechanisms are still poorly understood. The most common adverse effects reported with maraviroc were diarrhea, nausea, fatigue, and headache (Gulick et al. 2008).

Highly active antiretroviral therapy (HAART) has revolutionized the treatment of human immunodeficiency virus (HIV) infection over the past 10 years. Patients and clinicians have more choices in antiretroviral agents now than in the early 1990s or even at the beginning of this decade. New agents for previously identified drug targets, such as reverse transcriptase and protease, have been approved for marketing, along with a new fusion inhibitor and integrase inhibitor. Despite these advances in the treatment of HIV, the complete eradication of infection with the virus is still not possible. Increasing resistance, nonadherence to medications, and toxicity have fueled virological failure and the need for additional agents active against HIV. The concept of HIV-entry inhibition was introduced into practice in 2003 with the approval of enfuvirtide, the first HIV fusion inhibitor. Coreceptor CCR5 antagonists, which provide a novel mechanism of action, are a recent addition to the armamentarium of antiretroviral agents.

Maraviroc (Selzentry, Pfizer Inc., New York, NY) was approved for marketing by the Food and Drug Administration (FDA) on August 6, 2007, for use in combination with other antiretroviral agents in the treatment of HAART-experienced adult patients whose HIV infection is resistant to multiple classes of anti-retroviral drugs. In addition, maraviroc is labeled for use only in patients infected with CCR5-tropic HIV-1, who have evidence of ongoing viral replication, and who are resistant to multiple antiretroviral agents. Maraviroc is the first approved CCR5 antagonist and has a novel mechanism of action. Maraviroc is a prescription medicine approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV infection in adults. Maraviroc is always used in combination with other anti-HIV medicines (Lalezari et al. 2007).

Maraviroc is a type of anti-HIV medicine called a CCR5 receptor antagonist (a type of entry inhibitor). A CCR5 receptor is a protein located on the surface of certain immune cells. In some people, HIV binds to the CCR5 receptor to enter cells. Maraviroc works by blocking the CCR5 receptors on healthy immune cells. This prevents HIV from entering and infecting the cells. When used with other anti-HIV medicines, maraviroc may lower the amount

of HIV in the blood. Maraviroc should be used only in people whose strain of HIV uses the CCR5 receptor. Maraviroc is not recommended for people whose HIV uses another receptor called CXCR4 or whose HIV uses both the CCR5 and CXCR4 receptors. Maraviroc does not cure HIV/AIDS. It is not known if maraviroc reduces the risk of passing HIV to other people.

2. CCR5/ G PROTEIN COMPLEX

Maraviroc inhibits MIP-1β-stimulated γ-S-GTP binding to HEK-293 cell membranes, indicating its ability to inhibit chemokine-dependent stimulation of GDP-GTP exchange at the CCR5/G protein complex. Maraviroc also inhibits the downstream event of chemokine-induced intracellular calcium redistribution, with IC50s ranging from 7 to 30 nM obtained against MIP-1β, MIP-1α and RANTES. In the same experiments, Maraviroc does not trigger release of intracellular calcium at concentrations up to 10 μM, indicating that it is devoid of CCR5 agonist activity. Consistent with this, Maraviroc fails to induce CCR5 internalization. Maraviroc is active at low nanomolar concentrations against HIV-1 Ba-L. Maraviroc inhibits all 200 pseudotyped viruses with a geometric mean IC90 of 13.7 nM.

3. PRECLINICAL STUDY DETAILS

The half-life values of Maraviroc are 0.9 hour in the rat and 2.3 hours in the dog. Following oral administration (2 mg/kg) to the dog, the Cmax (256 ng/ml) occurred 1.5 hours post-dose, and the bioavailability is 40%. For the rat, approximately 30% of the administered dose is absorbed from the intestinal tract. Female RAG-hu mice are challenged vaginally with HIV-1 an hour after intravaginal application of the Maraviroc gel. Maraviroc gel treated mice are fully protected against vaginal HIV-1 challenge in contrast to placebo gel treated mice which all became infected. Vaginal administration of Maraviroc fully protects mice against HIV-1 vaginal challenge. While there is a clear pattern of CD4 T cell decline in placebo-gel treated and viral challenged mice, their levels are stable in mice receiving Maraviroc gel.

For initial treatment of HIV infection, adult and adolescent guidelines of the U.S. Department of Health and Human Services designate the combination of maraviroc + zidovudine/lamivudine as "acceptable" and maraviroc + 2 other nucleoside pairs as "may be acceptable but more definitive data are needed." Maraviroc is effective only in persons with exclusively CCR5-tropic HIV. Tropism testing should be performed before initiating treatment with maraviroc, to verify that no CXCR4-tropic virus is present.

3.1. Maraviroc, a CCR5 coreceptor antagonist that blocks entry of human immunodeficiency virus type 1

Inhibition of the human immunodeficiency virus type 1 (HIV-1) coreceptor is an encouraging new approach to pharmacotherapy against HIV. The HIV-1 strain makes use of either the CCR5 or the CXCR4 coreceptor to gain access into host CD4+ cells. Maraviroc, the first HIV-1 CCR5 coreceptor antagonist, blocks entry of HIV-1. This recently approved drug has demonstrated clinically significant decreases in plasma concentrations of HIV-1 RNA and increases in CD4+ cell counts; however, it is indicated only for use as salvage therapy. Drug resistance is a concern, as is selective pressure on viral coreceptor use, because viral coreceptor targets may switch as disease progresses. In addition, before maraviroc therapy can be started, costly assays are required to determine the host's viral coreceptor tropism (Nelson et al. 2007). Emerging therapies targeting CXCR4, the other HIV coreceptor, have shown promise in decreasing plasma concentrations of HIV-1 RNA. Long-term studies with both targets are required to explore the critical issues of efficacy and immunologic safety, as the function of these coreceptors is linked to host chemokine pathways.

4. CLINICAL STUDY DETAILS

In previously untreated patients, a randomized controlled study compared maraviroc with efavirenz, each drug being given in combination with zidovudine + lamivudine. All patients had only CCR5-tropic HIV according to the tropism assay available at the time of study entry. At 48 weeks, by intention-to-treat analysis, the maraviroc group had lower rates of virologic suppression to <50 copies/mL than the efavirenz group (65% vs 69%); this result did not meet the study's criteria for noninferiority of maraviroc. However, researchers later reanalyzed the baseline tropism status of the study subjects using a more sensitive tropism assay and found that 15% were erroneously identified as CCR5 tropic; when these patients were excluded from the analysis, the rates of virologic suppression to <50 copies/mL at 48 weeks were essentially the same in the two groups, 68.5% in maraviroc recipients and 68.3% in efavirenz recipients; there also was no significant difference between the treatment groups in patients whose baseline HIV RNA was >100,000 copies/mL. The mean increase in CD4 count was greater in the maraviroc group (174 cells/μL vs 144 cells/μL for the efavirenz group).

In patients with advanced HIV disease, prior exposure or documented resistance to at least 3 classes of antiretroviral medications, and ongoing viral replication, 2 randomized controlled Phase 2b/3 studies (described above in "Approval") compared maraviroc with placebo, each given in combination with a background regimen. All study patients had exclusive CCR5-tropic virus at screening, according to tropism assay. In pooled analysis, the groups that received maraviroc (dosed either twice daily or once daily) had superior virologic outcomes at 24 and 48 weeks. At 48 weeks, the group that received maraviroc twice daily had greater mean decreases in HIV RNA (1.84 $\log_{10}$ copies/mL vs 0.79 $\log_{10}$ copies/mL) and higher rates of viral suppression to <400 copies/mL (56% vs 22%) and to <50 copies/mL (45% vs 23%) than the group that received placebo. These differences were statistically significant ($p < .001$). The efficacy of maraviroc-containing regimens correlated with the number of other active antiretroviral agents used concomitantly, indicating the importance of including at least 2 agents with potent activity in the antiretroviral regimen. The mean increase in CD4 count was greater in the maraviroc groups (at 48 weeks, 124 cells/μL for the twice-daily dosing group) than in the placebo group (61 cells/μL), ($p < .001$). It is not known whether the superior virologic and CD4 cell count responses seen with the maraviroc recipients in these studies will result in improved clinical outcomes. In a small group of treatment-experienced patients with virus that used both CCR5 and CXCR4 coreceptors at baseline (dual- and mixed-tropic HIV), treatment with maraviroc (either once or twice daily) plus an optimized antiretroviral background did not result in greater decreases in HIV RNA in comparison with placebo plus an optimized regimen at 24 weeks.

5. CONCLUSION

Available data support the use of maraviroc, the first CCR5 antagonist to receive FDA marketing approval, as part of an optimized antiretroviral regimen in treatment-experienced patients infected with CCR5-tropic HIV.

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