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HIV-1 Entry Inhbitors: An Overview

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Abstract

Purpose of review—This review provides an overview of HIV-1 entry inhibitors, with a focus on chemokine receptor antagonists.

Recent findings—Entry of HIV-1 into target cells is an ordered multi-step process involving attachment, co-receptor binding and fusion. Inhibitors of each step have been identified and shown to have antiviral activity in clinical trials. Phase 1-2 trials of monoclonal antibodies and small-molecule attachment inhibitors have demonstrated activity in HIV-1-infected subjects, but none has progressed to later phase clinical trials. The post-attachment inhibitor ibalizumab has shown activity in phase 1 and 2 trials; further studies are anticipated. The CCR5 antagonists maraviroc (now been approved for clinical use) and vicriviroc (in phase 3 trials) have shown significant benefit in controlled trials in treatment-experienced subjects; additional CCR5 antagonists are in various stages of clinical development. Targeting CXCR4 has proven to be more challenging. Although proof of concept has been demonstrated in phase 1-2 trials of two compounds, neither proved suitable for chronic administration. Little progress has been reported in developing longer acting or orally bioavailable fusion inhibitors.

Summary—ACCR5 antagonist and a fusion inhibitor are approved for use as HIV-1 entry inhibitors. Development of drugs targeting other steps in HIV-1 entry is ongoing.

Keywords

attachment; chemokine receptor antagonist; fusion inhibitor; HIV-1 envelope

Introduction

The entry of HIV-1 into susceptible target cells is an ordered, multi-step process that leads ultimately to the fusion of viral and cell membranes. Each step in the entry process affords a unique opportunity for the development of antiretroviral drugs. This review summarizes progress in the development of HIV-1 entry inhibitors with an emphasis on the chemokine receptor antagonists.

HIV-1 entry

The first step in virus entry is binding of the viral envelope to its primary receptor, CD4, on the surface of macrophages or T-helper lymphocytes. Binding to CD4 is mediated by gp120, the surface subunit of the envelope. In its native form, the envelope glycoprotein is a

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heterotrimer of three gp120 molecules and three molecules of gp41, the transmembrane subunit, which remain attached through non-covalent interactions [1,2]. Conformational changes in gp120 triggered by CD4 binding expose structural elements that engage one of two chemokine receptors, either CCR5 or CXCR4. Co-receptor binding allows the hydrophobic N-terminus, or fusion peptide, of the gp41 ectodomain to insert into the target cell membrane. The anti-parallel association of two helically coiled heptad repeats (HR-1 and HR-2) in the gp41 ectodomain to form a six-helix bundle leads to the close approximation of the cell and virus membranes, resulting in fusion [3].

Attachment inhibitors

Early attempts to develop specific inhibitors of HIV-1 entry centered on the design and testing of recombinant soluble CD4 (rsCD4) molecules. Such molecules lack the transmembrane and cytoplasmic domains of CD4, but retain the ability to bind gp120, thereby functioning as molecular decoys. Although these molecules showed good in vitro activity against tissue culture-adapted strains of HIV-1, activity in early phase clinical trials was disappointing. Laboratory studies showed that low-passage HIV-1 isolates are substantially less sensitive to neutralization by rsCD4 than laboratory-adapted isolates [4-6]. Conjugation of rsCD4 to *Pseudomonas aerugniosa* exotoxin PE40 to create an immunotoxin (sCD4-PE40) led to similarly disappointing results [7]. More promising data were generated in preliminary studies of PRO 542, a tetravalent CD4-immunoglobulin fusion protein that contains the D1 and D2 domains of human CD4 fused to the heavy and light chain constant regions of human IgG2,κ [8,9]. Modest reductions in plasma HIV-1 RNA levels were observed in a phase 1-2 trial of PRO 542 in patients with advanced HIV disease. No additional studies of PRO 542 are ongoing at this time (www.clinicaltrials.gov).

Small molecule inhibitors that block the gp120-CD4 interaction show greater promise [10, 11]. The prototype molecule, BMS-378806, has potent activity in vitro against HIV-1 subtype B, but is less active against other subtypes and inactive against HIV-2 [11]. The compound binds to a specific region within the CD4 binding pocket of gp120 [10]. Evidence of antiviral activity in vivo is provided by a proof-of-concept study with the related compound, BMS-488043, which resulted in 1-$\log_{10}$ reductions in plasma HIV-1 RNA in treatment-naive subjects [12]. However, relatively high doses were required (1800 mg), and this compound is not being developed further.

Post-attachment inhibitors (ibalizumab)

The monoclonal antibody (mAb) ibalizumab (formerly TNX-355 and Hu5A8) is a humanized IgG4 mAb that binds to the second (C2) domain of CD4 [13]. In contrast to attachment inhibitors, ibalizumab does not prevent gp120 binding to CD4, but is thought to decrease the flexibility of CD4, thereby hindering access of CD4-bound gp120 to CCR5 and CXCR4. The mAb is a potent inhibitor of HIV-1 in vitro, and shows synergy when combined with gp120 antibodies or the fusion inhibitor enfuvirtide [14,15]. Ibalizumab does not appear to interfere with immunological functions that involve antigen presentation [16,17].

Phase 1 studies of ibalizumab showed promising activity, with up to a 1.5-$\log_{10}$ reduction in plasma HIV-1 RNA levels 14-21 days after a single dose [18], but resistance emerged after administration for 9 weeks [19]. A phase 2 study of ibalizumab showed that this mAb plus an optimized background regimen (not including enfuvirtide) resulted in significantly greater reductions in plasma HIV-1 RNA compared to the background regimen alone [20]. Additional dose-finding studies are planned, but have not been initiated as of this writing.

Chemokine receptors and HIV-1 tropism

Early after infection with HIV-1, most patients harbor virus that uses CCR5 exclusively as co-receptor (termed R4 viruses). Later in infection, CXCR4-using (X4) variants can be found in many patients [21,22]. Viruses with dual tropism (i.e., able to use both CCR5 and CXCR4, termed R5/X4 viruses), as well as mixtures of R5 and X4 viruses can also be found. Because commonly used tropism assays cannot distinguish between dual-tropic virus and a mixture of R5 and X4 viruses, such samples are referred to as having "dual-mixed (D/M)" tropism.

Whether chemokine receptor usage plays a role in determining the rate of HIV disease progression remains controversial. The prevalence of X4 variants increases with decreasing CD4+ cell count, and several studies show a significantly increased risk of disease progression among patients with D/M or X4 (SI) virus [21,23,24**]. That emergence of X4 variants is a consequence, rather than a cause, of advancing immunodeficiency nevertheless remains a plausible alternative explanation for the apparent association of X4 virus with disease progression. The possibility that treatment with CCR5 antagonists would promote emergence of X4 viruses, thereby accelerating disease progression, was a significant concern during early clinical trials with these agents. As discussed below, these fears have not been borne out in studies conducted to date.

CCR5 antagonists

Different approaches have yielded a range of molecules that block the interaction between HIV-1 and CCR5, including small molecule antagonists, mAbs, and covalently modified natural CCR5 ligands (e.g., AOP-RANTES). Because the RANTES analogues and CCR5 mAbs are covered by other reviews in this issue, they will be omitted here.

The small molecule CCR5 antagonists have been given generic names with the suffix "-viroc", an abbreviation for viral receptor occupancy. Four of these compounds—aplaviroc, maraviroc, vicriviroc and INCB009471—have progressed to at least phase 2 clinical trials. They exhibit potent inhibition of HIV-1 replication in vitro against laboratory-adapted and primary isolates across all clades of group M HIV-1. These agents have no agonist properties and do not affect surface expression of CCR5.

Aplaviroc

Aplaviroc (formerly GSK 873140) is a CCR5 antagonist that demonstrated antiviral activity during short-term monotherapy studies with minimal toxicities. Although aplaviroc blocks MIP-1α at nanomolar concentrations, RANTES-mediated signaling is less susceptible to aplaviroc inhibition [25]. Administration of aplaviroc at various dosages produced up to a 1.6-$\log_{10}$ reduction in plasma HIV-1 RNA levels during 10 days of treatment [26]. Unfortunately, drug-induced hepatitis occurred in 5 subjects in phase 2b and 3 trials [27**]. No deaths were noted and the hepatitis resolved with aplaviroc discontinuation, but clinical development of the drug was terminated.

INCB009471

The CCR5 antagonist INCB009471 has nanomolar activity against HIV-1 in vitro, and a plasma half-life of 60 hr, making once daily dosing feasible. Subjects who received the 200-mg daily dose in a 14-day phase 2a study experienced mean peak reductions in plasma HIV-1 RNA of 1.8 $\log_{10}$ copies/mL [28]. No clinically significant chemistry, hematology or ECG changes were observed. At this time, however, no further studies are planned (http://www.incyte.com/drugs_product_pipeline.html; accessed October 13, 2008).

Maraviroc

Maraviroc (formerly UK 427,857) is a spirodiketopiperazine CCR5 antagonist with potent in vitro and in vivo anti-HIV-1 activity. The molecule is a pure CCR5 antagonist that blocks MIP-1- α and RANTES-mediated signaling at nanomolar concentrations [29]. In a 10-day monotherapy trial conducted in HIV-1-infected subjects with R5 virus, administration of maraviroc at doses up to 600 mg daily resulted in $\geq$1.6 $\log_{10}$ reductions of plasma HIV-1 [30].

The efficacy of maraviroc was confirmed in a pair of phase 3 randomized, placebo-controlled trials (MOTIVATE 1 and 2) [31**,32**]. Eligible subjects had evidence of resistance to drugs from three antiretroviral classes or were triple-class experienced, had plasma HIV-1 RNA levels >5,000 copies/mL, and had exclusively R5 virus at screening by the Trofile assay (Monogram Biosciences, South San Francisco, CA). Subjects were randomized to receive one of two dosages of maraviroc (300 mg given once or twice daily) or placebo; all subjects also received an optimized background regimen based on drug resistance testing and treatment history. In both studies, subjects in the maraviroc arms experienced plasma HIV-1 RNA reductions that were more than twice as great as those in the control arms (-1.7 to -1.9 log10 copies/mL versus 0.8 log10 copies/mL, respectively) [31**,32**]. Similarly, more than twice as many maraviroc recipients achieved a plasma HIV-1 RNA level below 50 copies/mL compared to placebo recipients (42-47% versus 16%, respectively). Increases in CD4 cell counts ranged from 110-130 cells/mm^3 in the maraviroc arms as compared to 50-70 cells/mm^3 in the placebo arms. The frequency of adverse events was similar in all groups.

Virologic failure was associated with emergence of CXCR4-using virus in 57% of subjects in whom a repeat tropism test was obtained at the failure timepoint [32**]. Although CD4 count increases were smaller in this subgroup than among those with R5 virus at failure, a greater increase in CD4 counts was nevertheless observed among maraviroc recipients with D/M or X4 virus at failure when compared to the placebo group overall. Although all subjects had R5 virus at screening, 8% were found to have dual/mixed virus at baseline (day 0) [32**]. Subjects with D/M virus at baseline who received maraviroc had a lower rate of virologic response, shorter time to virologic failure, and smaller CD4 increases as compared to those with R5 virus .

Subjects found to be ineligible for the MOTIVATE trials due to presence of D/M, X4 or non-typable virus at screening were offered entry into a parallel phase 2 study that tested the effect of maraviroc (300 mg once or twice daily) versus placebo in subjects with CXCR4-using virus. Overall, this study found no significant virologic or immunologic benefit of maraviroc as compared to placebo, although CD4 counts increased from baseline to weeks 24 and 48 in all treatment groups [33]. Taken together, these results and those of the MOTIVATE trials suggest that although presence or emergence of CXCR4-using virus blunted the virologic and immunologic response to maraviroc, it was not associated with rapid CD4 decline or disease progression over the 48-week course of the study.

Another phase 3 study compared maraviroc (300 mg once or twice daily) to efavirenz in treatment-naïve patients; both drugs were given together with zidouvdine plus lamivudine [34]. The once-daily maraviroc arm was closed due to inferior efficacy that became apparent at an interim analysis. Final study results showed that the twice-daily maraviroc arm failed to demonstrate non-inferiority to the efavirenz-based regimen. The extent to which minority CXCR4-using variants present but undetected at screening contributed to this result is the subject of ongoing analyses .

Vicriviroc

Vicriviroc, (formerly SCH417690 or SCH-D), is an orally bioavailable small molecule CCR5 antagonist that is an order of magnitude more potent than the first generation compound (Schering C [SCH-C]) [35]. Like MVC, this molecule blocks signaling by the C-C chemokines at nanomolar concentrations [35]. Pre-clinical studies produced seizures in animals at high doses, but no CNS side effects of vicriviroc have been observed in human clinical trials to date. Data from a 14-day monotherapy trial demonstrated a reduction of plasma HIV-1 RNA by approximately 1.0-1.5 $\log_{10}$ copies/mL [36*]. A phase 2b trial of vicriviroc in treatment-naïve HIV-1-infected subjects was discontinued due to increased rates of virologic failure in the vicriviroc arms compared to the control efavirenz arm (all subjects also received zidovudinvine plus lamivudine as a fixed-dose combination [ZDV/3TC]) [37*].

Despite these early challenges, a placebo-controlled phase 2b study conducted in antiretroviral-experienced demonstrated potent suppression of HIV-1 by vicrivoric (given at 5, 10 or 15 mg daily) in combination with an optimized background regimen that included a ritonavir-boosted protease inhibitor (PI) [38*]. Mean changes in plasma HIV-1 RNA levels at 24 weeks ranged from 1.5 to 1.9 $\log_{10}$ copies/mL in the vicriviroc arms as compared to 0.29 $\log_{10}$ copies/mL in the placebo arm. Follow-up data at 48 weeks showed similar results [39]. Interim data raised concern about a possible association between vicriviroc and the occurrence of malignancies, but this association has not been borne out in other trials [38*]. A follow-on study that explored higher doses of vicriviroc showed that 56% of treatment-experienced subjects receiving vicriviroc (30 mg daily) plus an optimized background regimen containing a ritonavir-boosted PI as compared to 14% of placebo recipients [40]. Phase 3 trials using the 30-mg dose of vicriviroc are underway.

CXCR4 antagonists

The development of CXCR4 inhibitors has proceeded more slowly than that of the CCR5 antagonists. In contrast to CCR5, there are no known naturally occurring mutations that lead to absence of CXCR4, but short-term animal toxicology studies with two small molecule inhibitors (AMD3100 and AMD11070) suggested that it was safe to proceed with human studies.

One problem unique to CXCR4 inhibitors is that whereas R5 viruses are found on their own in 50% or more of patients, X4 viruses usually are present as mixtures together with R5 viruses [22,41*]. Inhibition of just the X4 component of the virus population may not lead to measurable declines in overall plasma viremia, thereby complicating assessment of drug activity. Co-administration of CCR5 and CXCR4 antagonists might be uniquely effective, if the safety of such combinations can be established.

Preliminary studies with AMD3100 showed inhibition of the X4 component of the virus population, but development of this parenterally administered drug as an antiretroviral agent was discontinued due to QTc prolongation [42]. One side effect noted in those early studies was a substantial leukocytosis. Further investigation revealed that CXCR4 blockade releases myeloid cells from the bone marrow into the blood. Also released are plurioptent (CD34+) stem cells [43]. This observation led to the subsequent development of AMD3100 (now called plerixafor) as an adjunct to G-CSF stimulation of the bone marrow, resulting in substantially increased stem cell yields. A proof of concept study with a back-up compound, AMD-11070, showed reductions in the CXCR4-using component of the HIV-1 population in subjects infected with D/M virus [44]. Further clinical development of this drug has been put on hold, however, due to the finding of abnormal liver histology in animals during long-term dosing studies. Whether the toxicities of these two compounds are related to CXCR4 blockade is unknown, as is the long-term safety of targeting CXCR4.

Fusion inhibitors

Enfuvirtide (T-20) is a 36-mer synthetic oligopeptide whose sequence corresponds to that of the HR-2 region of the HIV-1 envelope gp41 subunit. Binding of enfuvirtide to the trimeric HR-1 complex prevents the association of HR-1 with HR-2, thereby inhibiting fusion and blocking virus entry [45]. Enfuvirtide became the first entry inhibitor approved for clinical use as a result of phase 3 clinical trials that demonstrated efficacy of the drug when combined with an optimized background regimen [46,47]. Because the drug is an oligopeptide, it must be administered by subcutaneous injection. The drug has minimal systemic toxicity, but the frequent occurrence of painful injection site reactions has limited long-term use. Co-administration of enfuvirtide significantly improved response rates to newer agents such as tirapanavir, darunavir and maraviroc in clinical trials conducted in highly treatment-experienced patients [32**,48*,49]. When given as part of a regimen that does not succeed at fully suppressing HIV-1 replication, resistance to enfuvirtide emerges rapidly. Enfuvirtide is covered in greater detail in the review by Reynes in this volume.

Conclusion

A variety of inhibitors that target different steps in HIV-1 entry are in various stages of clinical development. Maraviroc, a small-molecule CCR5 antagonist, and enfuvirtide, an oligopeptide fusion inhibitor, are approved for clinical use. Results to date with CCR5 antagonists have shown these drugs to be safe, even when administered to patients with CXCR4-using virus, but continued monitoring is needed to assess longer term safety. Although proof-of-concept has been established with candidate CXCR4 antagonists, safety concerns have prevented these drugs from moving forward in clinical development.

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