What's New in HIV/AIDS

Serious Doubts on Safety and Efficacy of CCR5 Antagonists

CCR5 Antagonists Teeter on a Knife-Edge

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Development of a New Drug Class

Entry inhibitors constitute a new drug class for treatment of HIV-1 infection. They are divided into subclasses, each aiming at a crucial step during the complex event of HIV entry into the target cell. Attachment inhibitors are designed to prevent the HIV envelope glycoprotein gp120 attachment to CD4 receptors, co-receptor antagonists to inhibit, e.g., CCR5 co-receptor binding after conformational changes within gp120 and fusion inhibitors to hamper fusion of viral and cellular membranes, the latter subgroup disposing of the only approved substance, enfuvirtide. Thus, entry inhibitors protect target cells from viral intrusion while other antiretroviral agents inhibit HIV replication post entry. Of the assortment of small-molecule CCR5 antagonists in the developmental pipeline, three substances have entered clinical trials: GlaxoSmithKline's aplaviroc (formerly GSK-873140), Pfizer's maraviroc (UK-427857) and Schering–Plough's vicriviroc (SCH-417690 or SCH-D), these outriders being followed by various other CCR5 antagonizing substances including small molecules, chemokines and their derivatives, and monoclonal antibodies.

Unfavorable Evolution of CCR5 Antagonists in Clinical Trials

In healthy volunteers, aplaviroc, maraviroc and vicriviroc were safe and almost as well-tolerated as placebo. They exhibited an efficacy similar to that of potent protease inhibitors or efavirenz when given as short-term monotherapy to HIV-positive individuals with CCR5-tropic strains [1–3]. The development of this seemingly ideal drug was eagerly awaited as it was expected to powerfully prevent the propagation of virus strains with all kinds of mutations, and probably even prove useful in prophylactic application areas. In September 2005, though, GlaxoSmithKline (GSK) surprisingly announced the termination of all clinical trials involving aplaviroc in HIV patients. Out of 336 HIV-positive mainly therapy-naïve patients with CCR5-tropic virus strains enrolled in two phase IIb studies a good dozen of patients evolved liver toxicity that was attributed to the test substance in four cases. After a mean of 13 weeks under medication with AZT/3TC and either efavirenz or aplaviroc or lopinavir/ritonavir plus either AZT/3TC or aplaviroc the four patients, two of whom were hepatitis B or C co-infected, developed severe liver enzyme elevation. Three of four patients had concomitant hyperbilirubinemia, a potentially deadly combination in drug-induced hepatitis. Vicriviroc reportedly had not caused liver problems in comparable study settings, which suggests an aplaviroc-specific toxic effect rather than a drug-class problem. Considering, however, that there had been no liver problems during the 10-day monotherapy with aplaviroc, the substance might be toxic after a certain cumulative dose, in certain drug combinations or under certain individual conditions only. Nevertheless, neither a restart of clinical trials with aplaviroc nor further development of the substance is currently being scheduled. Pfizer had been testing ma...
raviroc in a phase 2b/3 placebo-controlled trial in over 1,000 HIV-positive therapy-naive and experienced patients with CCR5-tropic virus strains since April 2005. In November 2005, an obviously toxic drug cocktail including maraviroc, AZT, 3TC, INH, paracetamol and TMP/SMX led to liver transplantation in one patient after four maraviroc doses, but the event could not reliably be attributed to the test substance. Concomitant INH medication became an exclusion criterion for Pfizer’s maraviroc trial which is now in week 28 without any further liver problems or virologic failure. A couple of weeks after notification of the bad news from GSK and Pfizer, though, Schering–Plough stopped their vicriviroc phase II clinical trial. 92 HIV-positive therapy-naive patients with CCR5-tropic virus strains had been administered AZT/3TC with efavirenz or vicriviroc. Vicriviroc did poorly to an extent that an independent expert committee eneacted the termination of the study after 24 weeks. In the vicriviroc group, HIV serum load had started to rise after approximately 16 weeks, a time span coinciding with that described for in vitro appearance of resistance [4].

Resistance to CCR5 Antagonists Is Not Due to Switch in Co-receptor Use

Naturally, this second setback arouses serious doubts about the long-term efficacy of small-molecule CCR5 antagonists in general. GSK’s aplaviroc had worked well for the 13-week duration, but we know that evolution of resistance to CCR5 antagonists might take longer under in vitro conditions [4]. The time span of clinical testing for aplaviroc might simply not have been long enough to observe a virologic failure similar to that with vicriviroc. So how does resistance to CCR5 antagonists evolve? HIV-1 strains can be categorized by co-receptor tropism – their ability to utilize CCR5 (CCR5-tropic), CXCR4 (CXCR4-tropic) or both (dual-tropic) as a co-receptor for entry into susceptible cells. CCR5 seemed a promising target for co-receptor antagonists, as a natural deletion in the CCR5 encoding region enables individuals to resist HIV infection or delay HIV disease progression. The most frequently sexually transmitted strains are CCR5-tropic but in advancing HIV disease, HIV-positive individuals might switch to a CXCR4-tropic virus population which is associated with a less favorable disease course. Selection of CXCR4-tropic virus strains which would likely cause resistance to all CCR5 antagonists was a particular concern during the development of CCR5 antagonists. Several authors have shown, though, that a newly gained ability to enter cells via CXCR4 or any alternative co-receptor is not the dominant in vitro escape pathway for small molecule CCR5 entry inhibitors. Instead, HIV-1 obviously acquires the faculty to use CCR5 in the presence of the inhibitor [5, 6]. We do not know why HIV-1 does not follow what seems the line of least resistance but instead, adopted an apparently more complex escape route. Encouragingly, this instance provides a chance that resistance to a single CCR5 antagonist will not lead to drug-class resistance.

Resistance to CCR5 Antagonists Seems More Complex than in Other Antiretroviral Drugs

Maroszán et al. [7] found an increased affinity for CCR5 that enabled an HIV escape mutant to outcompete the inhibitor. This mechanism occurred to some degree during the early stages of escape process from AD101 (SCH-350581), a vicriviroc-related substance, but seemed unlikely to cause the subsequent > 20,000-fold resistance. The ability of HIV escape mutants to use a CCR5 configuration that has been changed by CCR5 antagonists within the gp120 binding region thus remains a more plausible explanation for resistance. Single amino acid changes which might relate to a capacity of this kind would likely be found within the gp120 gene. Gp120 attachment to the CD4 receptor induces conformational changes within gp120 uncovering a formerly hidden gp120 region, the viral V3 loop, which attaches to the co-receptor. Indeed, resistance to AD101 was induced in vitro by four critical amino acid changes within the V3 region of gp120 [7], a change which induced resistance to SCH-C, a precursor substance to vicriviroc, as well. A different R5 primary isolate had escaped from SCH-C via V3 sequence changes, too [4]. HIV-1 resistant to TAK-779, one of the developmental small-molecule CCR5 antagonists of Takeda exhibited five amino acid changes in the V3 loop without any other gp120 mutations [8]. Maraviroc evoked a triple deletion in the V3 loop of a HIV subtype G virus that differed from those evoked by SCH-C [9]. Surprisingly though, two distinct clones fully resistant to vicriviroc had V3 sequences identical with those of the corresponding, wild-type input HIV isolates. The authors assume that resistance to vicriviroc maps to other gp120 regions, C3 and V2. Resistance might be due to genetic changes anywhere else in the envelope gene even without V3 changes [7]. Gp120 sequence data from patients with therapy failure under vicriviroc