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Tropism Switch in Patients Infected with HIV-1 and Its Clinical Implications for the Treatment with CCR5-receptor Inhibitors

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Abstract
CCR5 receptor inhibitors are currently being introduced into clinical practice. In some instances treatment failure is related to the selection of pre-existing CXCR4-tropic minority virus strains. Up to date it is unclear whether the outgrowth of a CXCR4 using reservoir is associated with accelerated HIV-disease.

In any case, treatment with CCR5 inhibitors should only be initiated in the absence of a relevant CXCR4-tropic minority. Otherwise treatment failure and the accumulation of mutations may ensue. Tropism tests, clinical data and other laboratory parameters help to determine the risk for an individual patient to harbour CXCR4 tropic virus strains, although the negative predictive value of each of these parameters and tests is quite low.

If treatment fails re-assessment of viral tropism can help to differentiate between failure due to the development of CCR5 inhibitor resistance or the selection of CXCR4-tropic virus strains.

This article presents and discusses available data on viral tropism and tropism testing in the context of CCR5 inhibitor treatment.

Introduction

HIV-infection of CD4+ T-lymphocytes typically begins when a virus particle attaches to the cell surface and fuses its envelope with the cell membrane. This step in the HIV life cycle is called entry. It involves the binding of the HIV glycoprotein gp120 to the cellular CD4-receptor. The resulting conformational changes in the gp120 protein uncover additional binding sites that interact with distinct cellular membrane proteins known as chemokine receptors [1-3]. The clinical importance of these co-receptors was recognized almost 10 years ago when several groups described cohorts of long term non-progressors and exposed but uninfected individuals who lacked the CCR5 chemokine receptor [4-6]. Surprisingly the genetic variant called delta32 was not associated with any obvious clinical disease.

Two chemokine receptors designated CCR5 and CXCR4 have been identified as the major co-receptors for viral entry [1-3, 6]. CCR5 is used by the so called macrophage-tropic HIV-1 strains, which predominate during the asymptomatic phase of HIV-disease while CXCR4 is used by the so called T-cell tropic strains, which are sometime isolated in patients with clinical AIDS [7-9]. As opposed to macrophage tropic strains, whose ability to fuse with the cell membrane heavily depends on the presence of CCR5, T-cell tropic virus strains are almost always dual- or "multi-tropic", which means that they can use various chemokine receptors with CXCR4 being the most important one [10].

Formerly, viral isolates were classified according to their ability to induce syncytia in cultured PBMC or MT-2 cells. CCR5-tropic strains generally do not induce syncytia while CCR4-tropic strains do [11], which illustrates the enhanced fusogenicity of the latter. The degree of fusogenicity, however, has been recognized as a major determinant for the rate of HIV replication and T-cell destruction [12], thereby directly linking co-receptor usage to the speed of disease progression.

Only 10 years after the recognition of the chemokine receptors as co-receptors for HIV-entry CCR5-inhibitors are in various stages of clinical development and the FDA and EMEA have approved the first CCR5 receptor inhibitor. The drug has proven its high antiviral potency in clinical trials in both treatment-naive and treatment-experienced patients. 1 and 2 studies). However, throughout the entire development process of CCR5 receptor inhibitors concerns about the inhibition of CCR5 receptor mediated entry, its implications on viral tropism and its possible clinical consequences have been mounting up. HIV has been feared to escape from CCR5 receptor inhibition by starting the use of CXCR4 and other co-receptors. It was unclear whether mutations in the envelope gene could induce a tropism switch transforming a (previously multiresistant) CCR5 tropic virus into a dual- or even multi-tropic virus with enhanced fosogenicity.

In this scenario CXCR4 or dual tropic virus populations, once selected would continue to expand even after the stop of CCR5 receptor antagonists, leaving the patients with a super bug that relentlessly drives them into immunodeficiency at high speed.

Resistance Conferred by Selection of Dual-, Mixed-, or CXCR4-tropic Minorities

Ever since the development of CCR5 receptor inhibitors began, many have worried that preventing HIV from entering its target cells via CCR5 would force it to use other co-receptors such as CXCR4. In-

deed, the CCR5-inhibitor trials conducted so far have unanimously shown that some individuals do experience a tropism switch under CCR5 inhibitor treatment. In the Motivate trials (which included treatment experienced patients who received maraviroc together with an optimised background regimen) a large proportion of patients on maraviroc showed the emergence of CXCR4-tropic virus at failure. However, a closer look reveals the true nature of this phenomenon. During ten days of maraviroc monotherapy CXCR4 receptor using virus strains appeared in a small proportion of patients [13]. The phylogenetic analysis of envelope clones from pre- and posttreatment time points indicated that in these patients the CXCR4-tropic strains emerged by outgrowth of a pretreatment CXCR4-using reservoir, rather than via mutation of a CCR5-tropic strain [14]. The results from the Motivate trials corroborate these data: All patients whose circulating virus turned CXCR4-tropic during treatment either had mixed tropic or minority CXCR4-tropic strains at baseline which were only detected by clonal analyses of the baseline bulk virus population.

The tropism question is not only complicated by limitations of current assays to detect minority virus populations but also by naturally occurring changes in the predominant virus population. A post hoc analysis of trial A4001029 (whose objective was to study maraviroc for the treatment of patients with non-CCR5-tropic virus) demonstrated that the TrofileTM assay used in this trial detected different patterns of tropism at screening and baseline in 11% of patients. Individual patients on placebo also experienced tropism switches from dual/mixed tropic virus to CCR5 or CXCR4 receptor using virus populations. Similar results were reported from the Motivate trials, which found that 8% of individuals screened as having only CCR5-tropic virus, experienced the emergence of CXCR4-tropic virus by the time treatment was started some weeks later. These findings highlight the importance of a critical appraisal of tropism test results and the possibility of spontaneous tropism switches even in the absence of selective pressure from CCR5 inhibitors.

Development of Resistance to CCR5-receptor Inhibitors under Selection Pressure

The main steps involved in the fusion of HIV with a target cell are i) attachment of the viral glycoprotein gp120 to the CD4 antigen of a target cell, ii) binding of the gp120 to a co-receptor and iii) fusion of the viral and cellular membranes. The interaction of the gp120 with the CD4 receptor triggers a conformational change in the gp120, which exposes sites that interact with chemokine receptors [15, 16]. Besides the major co-receptors CCR5 and CXCR4, HIV can use a number of other chemokine receptors, but their role *in vivo* has not yet been established. Gp120 binds to any of these co-receptors through the V3 loop and a number of other regions but viral tropism appears to be determined by the amino acid sequence of the V3 loop [17-20].

Small molecule co-receptor inhibitors mimic the natural ligands and inhibit the gp120-chemokine-receptor interaction after binding to the particular co-receptor.

Several *in vitro* experiments were conducted to investigate the mechanism of resistance to chemokine-receptor inhibitors. Virus isolates were passaged in CD4 positive U87 cells, which either carried CCR5 or CXCR4. In the presence of increasing concentrations of the CCR5 inhibitor TAK-652 the escape variants evolving from CCR5-tropic virus did not show any increased ability to infect CXCR4 positive cells. These escape variants were resistant to TAK-652 and partially cross-resistant to the related TAK-779. In contrast the structurally different CCR5 inhibitor TAK-220 retained its activity [21]. Amino acid changes in the V3 loop of the exterior glycoprotein gp120 play a key role in the emergence of resistance to CCR5 inhibitors [22], but substitutions in the other variable regions V1, V2, V4 and V5, as well as in the conserved regions C1-C4 also seem to contribute [23]. Mutations in these areas seem to be specific for each of the different drugs in development as viral isolates that emerged during maraviroc treatment of infected cell cultures have demonstrated that maraviroc resistant strains continue susceptible to other CCR5 inhibitors [24]. Phenotypic susceptibility assays suggest that maraviroc resistant virus is characterised by its ability to utilise maraviroc-bound CCR5 for entry [25]. A tropism switch, however, induced by mutations in the envelope gene has rarely been observed *in vitro* [23, 26] and remains to be demonstrated *in vivo*. Why does HIV retain its original tropism under selective pressure? The reason may be the complex sequence of amino acid changes in the V3 loop paralleled or even preceded by changes in other regions necessary for changing co-receptor tropism [27-29].

The analysis of virus from maraviroc-treated individuals from the Motivate and Merit trials further confirms these findings: All maraviroc-resistant virus isolates from patients who entered the study with purely CCR5-tropic virus showed unchanged CCR5-tropism [30, 31]. Most individuals whose virus turned to dual- or CXCR4-receptor usage had harboured CXCR4-tropic viral minorities at baseline, which was demonstrated retrospectively by sub species analyses of the baseline bulk virus populations.

Despite the growing evidence that tropism switch via mutation of CCR5-tropic strains is not a major pathway of resistance the consequences of long-term treatment with CCR5 inhibitors remain to be established in clinical practice and monitoring of patients receiving CCR5-inhibitors should be very close.

Clinical Implications of the Tropism Issue

CCR5-tropic virus is the predominant virus during the early stages of HIV infection. In a number of cohorts and trial populations studied in regions with clade B subtypes, the vast majority (>80%) of treatment naïve patients carry CCR5-receptor-using virus strains.

The patients most likely to have CXCR4-tropic virus strains are those individuals with advanced HIV-disease [32]. This includes patients with a history of

opportunistic infections whose CD4 cell counts have recovered following successful antiretroviral treatment [33]. Although virus strains capable of using CXCR4 are found more often in treatment experienced patients, most of these strains are dual or mixed tropic and even in the most advanced patients pure CXCR4 tropism is rather an exception [32, 34, 35]. During the natural course of HIV infection a switch from a CCR5 co-receptor using virus population to a CXCR4 co-receptor using virus population coincides with an acceleration of CD4 T-cell depletion and progression of HIV-disease [8, 36]. However, the switch from CCR5- to CXCR4- or dual-tropic virus does not seem to be a prerequisite for the development of severe immunodeficiency or clinical disease as CCR5-tropic virus predominates in as many as 50% of patients with severe immunodeficiency including those with opportunistic infections [37]. Interestingly, a tropism switch from CCR5 to CXCR4 also seems to occur in cellular reservoirs in patients with fully suppressive antiretroviral therapy even in the absence of CCR5-inhibitors [33]. Pooled data from CCR5 inhibitor trials show that in some patients virologic failure was associated with the selection of CXCR4 tropic virus populations. In most of these cases minority CXCR4-tropic strains could be detected by clonal analysis of the baseline bulk virus population. Once the CCR5 receptor was stopped the CXCR4 tropic virus strains were rapidly outperformed and replaced by CCR5-tropic virus populations. The selection of the CXCR4-tropic strains did not lead to an unusually dramatic acceleration of disease as demonstrated by the patterns of virus load rebound and CD4 cell decline which were comparable to those seen with the failure of other drugs like nucleoside and non-nucleoside reverse transcriptase inhibitors or protease inhibitors. No unexpected clinical events or opportunistic diseases were reported (lit).

Considering these findings it is still unclear whether the emergence of dual or CXCR4-tropic strains is a marker for disease progression or its cause.

Although it has been demonstrated that a shift towards CXCR4 tropism usually does not occur via mutation in the envelope gene and the overgrowth of a CCR5 tropic strain under selective pressure is not associated with an exceptionally rapid progression of disease it is a general belief that a tropism shift during CCR5 inhibitor treatment should prompt the discontinuation of the CCR5 inhibitor and its replacement by an other active drug. It is also clear that the presence of CXCR4-tropic minorities must be ruled out before the start of CCR5 inhibitor containing regimens. Although the selection of pre-existing CXCR4 minority populations per se may not lead to an acceleration of disease, treatment options may be lost as resistance to other components of the treatment regimen may develop. Unfortunately, the currently available phenotypic assays are too insensitive to detect CXCR4-tropic minorities as long as they don't account for more than five percent of the total virus population. Consequently a considerable proportion of patients tested to have pure CCR5-tropic virus will receive partly inactive treatment, which puts them at risk of treatment failure and evolution of resistance. Great efforts are being made to establish genotypic tropism assays but like their phenotypic counterparts these tests will face similar difficulties in detecting co-existing minority populations.

In the face of limitations of current assays to detect minority virus populations other parameters must also be considered when screening patients for CCR5 inhibitor treatment.

There are a number of factors associated with the absence of CXCR4-tropic virus populations. i) Early stage of HIV infection, ii) high CD4 cell count (>300 μl) iii) low viral load (< 5000c/ml) [35, 38]. Furthermore a recent study found a significant association of higher numbers of natural killer cells (NK) and CCR5-receptor usage [34]. These parameters should be used to establish the pre-test probability for the existance of a CXCR4-tropic minority in each patient. Pre-test probability and tropism test taken together should help minimise the number of patients treated with an inactive drug. Repetition of the tropism assay on the day treatment is initiated probably identifies another 10% of patients with CXCR4 tropic minorities at baseline. Even though the results of the second test will only be available some time after the start of treatment, patients with XCXR4-tropic virus detected by the second test might benefit from the rapid replacement of the CCR5 receptor inhibitor.

For practical reasons, the monitoring of patients that have initiated treatment with CCR5 receptor inhibitors should follow, with some modifications, the recommendations that apply for the treatment with any other drug combination: During the initial treatment phase viral load and CD4 cell count should be determined monthly to rapidly detect early treatment failure. In treatment experienced patients with multiresistant HIV virologic failure caused by the outgrowth of a pre-existing CXCR4-tropic minority will probably take less time than in treatment naive patients whose background regimen is still fully active but data to guide the clinician as when to assume the patient to be virologically stable are lacking.

Unfortunatley, tests to positively prove and analyse the resistance to CCR5 inhibitors are currently unavailable. Therefore, re-asessment of viral tropism will help to determine whether virologic failure is the result of the development of resistance or the selection of a previously undetectable CXCR4-tropic minority. In the absence of a CXCR4 tropic virus and mutations conferring resistance to the other components of the treatment regimen resistance to the CCR5 inhibitor must be assumed and the drug should be stopped. In the future when further CCR5 inhibitors become available maraviroc may be replaced by another compound. If virologic failure results from the selection of a CXCR4-tropic virus the CCR5 inhibitor should be stopped and the patient should never receive any other drug from this class as there is no evidence for residual activity or immunological benefit when the drug is maintained.

DISCUSSION

The safety and efficacy of maraviroc has been investigated in both treatment experienced and naïve patients with CCR5-tropic HIV 1. In patients with dual or

mixed tropic viruses maraviroc is virologically inactive. Treatment failure of maraviroc and other CCR5 inhibitors is associated with the emergence of CXCR4-tropic virus. However neither *in vitro* nor *in vivo* data suggest that CCR5 receptor inhibition induces a tropism switch from CCR5 to CXCR4 by mutations in the envelope gene. The emergence of the CXCR4-tropic virus rather results from the outgrowth of pre-existing reservoirs. Therefore the detection of pre-existing dual-, mixed- or CXCR4-tropic minorities is crucial. The identification of patients with dual-, mixed- or CXCR4-tropic minorities is hampered by the lack of sensitivity of current test systems to detect viral reservoirs. Clinical parameters and additional laboratory tests can help to increase the likelihood of spotting these patients. Repeating the test on the day treatment is started probably identifies another 10% of patients with CXCR4-tropic HIV. A more sensitive assay, preferably a genotypic one is urgently needed.

If virologic failure occurs, resistance due to the selection of CXCR4-tropic virus must be discriminated from resistance due to decreased activity of maraviroc against virus that continues CCR5-tropic. Currently, there are no tools to screen for the latter situation, therefore the detection of CCR5-tropic virus in the absence of genotypic resistance against the other components of the regimen suggest that HIV has acquired the ability to enter its target cells via inhibitor-bound CCR5.

The pace of clinical deterioration during maraviroc failure with CXCR4-tropic virus and failure with other antiretroviral regimens seems to be comparable. As evidence for residual activity is lacking and to avoid a possible acceleration of the HIV disease, the authors recommend stopping the CCR5 inhibitor in the setting of CXCR4-tropic virus outgrowth.

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