Maraviroc for Treatment-Naive Patients with HIV-1 Infection: Is the Glass Half Empty or Half Full?

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In 2007, the US Food and Drug Administration (FDA) approved maraviroc for the treatment of human immunodeficiency virus type 1 (HIV-1) infection, making it the first (and to date only) CCR5 antagonist available for clinical use. Approval stipulated that maraviroc be used only in treatment-experienced patients who have viremia with a virus using the CCR5 receptor (R5 virus)—the latter being a critical limitation because maraviroc has no antiviral activity against non-CCR5-using viruses. Because a substantial proportion of treatment-experienced patients harbor these strains—roughly 50% in surveys using the original tropism assay [1]—maraviroc use thus far has been necessarily limited.

Unlike in treatment-experienced patients, R5 viruses are the dominant type in transmission and predominate early during HIV disease, with an estimated 80% of untreated patients having R5 strains [2]. It is therefore plausible that maraviroc would have its greatest role earlier during HIV disease, especially among those who have never received therapy. In this issue of the Journal, investigators report results of the MERIT (Maraviroc versus Efavirenz in Treatment-Naive Patients) study, a large, double-blind, prospective randomized trial comparing maraviroc to efavirenz as part of initial treatment [3]. More than 1700 subjects were recruited from study sites from 5 continents and were eligible if they had never received treatment and were found to have R5 virus at screening.

Ultimately, 721 patients entered the study for the comparison of interest here, with 360 receiving twice-daily maraviroc and 361 receiving once-daily efavirenz, along with matching placebos for maraviroc and efavirenz and coformulated zidovudine-lamivudine. In the primary 48-week analyses, maraviroc was noninferior to efavirenz at the <400 copies/mL threshold (70.6% response rate for maraviroc vs 73.1% for efavirenz) but not at the <50 copies/mL threshold (65.3% for maraviroc vs 69.3% for efavirenz). Importantly, the study used a relatively strict 10% threshold for noninferiority; nonetheless, virologic failure was 3 times more common with maraviroc than with efavirenz (11.9% vs 4.2%), with a substantial proportion of maraviroc failures occurring in study subjects who harbored non–CCR5-using virus at baseline that, in hindsight, was not detected on screening. Regardless of the explanation, the primary results favored efavirenz, which remarkably has still not been bettered with respect to virologic response in a clinical trial despite its FDA approval more than a decade ago.

In addition to these results, several other concerns—some from this study, some about the CCR5 antagonist class of drugs in general—are important if a clinician were to consider using maraviroc as part of a first-line antiretroviral regimen. Before starting maraviroc-based therapy, patients must undergo viral tropism testing; only 1 tropism test, the original Trofile assay (Monogram Biosciences), has been prospectively validated in clinical trials to correlate with antiviral response to a CCR5 antagonist. Such testing excludes a significant minority of even treatment-naive patients: in the MERIT study, 26% of 1730 patients screened did not have an evaluable tropism result, and 17% had X4 virus. Furthermore, the Trofile assay is relatively expensive compared with other baseline tests in patients with HIV infection—the price is ∼4–5 times higher than that for resistance genotype testing—and as a modification of resistance phenotype testing typically requires 3 weeks or longer for results to return to the clinician. While this delay is rarely of clinical significance, people with HIV infection who are ready to begin treatment are understandably eager to do so as soon as possible. Fortunately, more rapid and less expensive viral tropism tests are under
Maraviroc must be given twice daily—a once-daily dosing strategy in MERIT was stopped prematurely because insufficient virologic response—whereas most of the other first-line treatments in wide use are given once a day. In addition, the nucleoside reverse-transcriptase inhibitors (NRTIs) chosen for the study were zidovudine plus lamivudine, a combination no longer considered to be a preferred NRTI pair for initial therapy because of inferior tolerability and safety compared with abacavir-lamivudine or tenofovir-emtricitabine [4, 5]. Although there is no specific reason to believe that maraviroc with these newer NRTIs would be ineffective, study data on these combinations in treatment-naive patients are not available.

An additional concern about the use of maraviroc for initial therapy relates to the mechanism of action of CCR5 antagonists. When virologic failure occurs, CCR5 antagonist use can result in the predominant circulating viruses being X4 strains, which likely arise from low levels of variants not detected before therapy. Both detection of X4 viruses in untreated patients and the switch from R5 to X4 have been associated with more rapid HIV disease progression [2, 6, 7]. Fortunately, studies of patients treated with CCR5 antagonists do not show that emergence of X4 viruses leads to more rapid CD4 cell depletion [8], but the long-term effects of the selection of a predominant X4 strain will bear ongoing monitoring.

CCR5 antagonists exert their antiviral effect through binding to a transmembrane CCR5 coreceptor pocket; they are therefore unique among available antiretroviral agents in having a cellular rather than a viral target. Congenital absence of the CCR5 receptor with Δ32 homozygosity appears to have a generally benign clinical course, but it is not known whether pharmacologic blockade of this receptor will have different long-term effects. Indeed, the reporting of more severe West Nile and tickborne encephalitis virus infections among individuals with the Δ32 mutation [9, 10] raises the possibility that CCR5 antagonists will have potential immunomodulatory effects, some of which may be deleterious. For now, safety concerns related to this class of drugs (and maraviroc in particular) have been mostly reassuring, but in one study of the investigational CCR5-antagonist vicriviroc more cancers were reported in those receiving the drug than in the comparator arm [11]; importantly, the relationship between this treatment and the specific cancers diagnosed remains unknown.

With these concerns, might there still be a place for maraviroc (and potentially other CCR5 antagonists) as part of initial therapy? Aside from the narrow miss on the protocol’s 10% noninferiority threshold for virologic failure, additional data from the MERIT study are quite supportive, and the distinctive mechanism of action of the drug class may incur benefits outside of antiviral activity alone. Of critical importance to predicting the virologic efficacy of the drug was the subsequent development of an improved Trofile assay that is 10–100-fold more sensitive in detecting minor X4 populations [12]. Indeed, when this enhanced sensitivity tropism assay was retrospectively applied to the original 721 treated patients in MERIT, 107 were excluded as a result of having detectable X4 virus; the virologic response for the remaining 614 treated study subjects yielded a noninferior result for the maraviroc arm. Although the current Trofile assay will exclude a greater proportion of patients from receiving the drug—perhaps even some with such low levels of X4 virus that they could respond to maraviroc—clinicians can now prescribe maraviroc with much greater confidence that it will be a virologically active agent. In light of these retrospective data, in 2009 the FDA granted approval of maraviroc for first-line treatment of HIV-1 infection.

A major advantage of maraviroc seen in the MERIT study was a lower rate of adverse effects compared with efavirenz, including those adverse events severe enough to lead to drug discontinuation—in fact, this occurred at a rate >3-fold higher in the efavirenz arm than in the maraviroc arm (14% vs 4%; \( P < .001 \)). In addition, maraviroc-treated subjects had fewer malignancies and AIDS-defining events; although the differences were not statistically significant, they are somewhat reassuring given that maraviroc did not lead to unanticipated immunosuppression. Data not included here but presented elsewhere in abstract form showed that lipid changes with maraviroc were generally more favorable than those seen with efavirenz [13]. Overall, these data add to a body of evidence from studies conducted in treatment-experienced patients indicating that maraviroc is both safe and well tolerated.

The above-mentioned cellular target of maraviroc may well have salutary immunologic effects. A consistent finding of this and other comparative studies of maraviroc is that CD4 cell count increases are greater than those in maraviroc comparator arms, with the effect being of greater magnitude than would be anticipated on the basis of a reduction in HIV RNA level alone. In MERIT, 48-week CD4 cell count increases were 170 cells/μL for maraviroc and 144 cells/μL for efavirenz (\( P = .008 \)). Although the mechanism of this effect is not known, proposed explanations include the blocking of gp120-driven apoptosis or a reduction in systemic inflammation and immune activation [14, 15]. Studies are under way to evaluate whether maraviroc will increase CD4 cell counts among those who already have virologic suppression and inadequate CD4 cell responses, although pilot studies of this strategy have to date been negative [16, 17].

CCR5 antagonists may one day have a particularly effective role in the prevention of HIV infection, both because they prevent entry of HIV-1 and, as noted above, because R5-tropic viruses are the predominant type involved in HIV transmission. The pharmacokinetic properties of mar-
aviroc in particular seem ideal: in one study conducted in HIV-negative women, concentrations of the drug in cervicovaginal fluid exceeded those found in plasma [18]. Although ex vivo tests of maraviroc as a topical microbicide showed less activity than expected [19], a case report of successful control of HIV through a bone marrow transplant from a donor homozygous for the Δ32 mutation provides hope that potent blockage of CCR5 may ultimately play a broader role in HIV prevention [20].

How then should maraviroc be considered among first-line choices for initial antiretroviral therapy—is the glass half empty or half full? If only because of the extraordinary antiviral potency and tolerability of the existing preferred choices, for now maraviroc-based regimens must be considered an alternative choice, something to be used only when existing non-nucleoside reverse-transcriptase inhibitor–based, boosted protease inhibitor–based, and integrase inhibitor–based regimens cannot be used. However, if cheaper and more rapid tropism testing becomes available and if additional studies demonstrate distinctive strengths of the drug related to immune response, metabolic changes, and prevention, one could envision a greater first-line role for maraviroc—or other CCR5 antagonists—in the future.

References