5-year Safety Evaluation of Maraviroc in HIV-1-Infected, Treatment-Experienced Patients

Running Head: 5-year Safety of Maraviroc

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ABSTRACT

Background: Maraviroc is unique among approved antiretroviral drugs in targeting the host-cell CCR5 receptor. With its novel mechanism of action, we sought to describe the 5-year safety profile of maraviroc.

Methods: Two large phase 3 studies of maraviroc enrolled HIV-infected, treatment-experienced patients and followed them for 5 or more years. Survival and selected clinical endpoints were identified and assessed.

Results: A total of 938 enrolled patients received maraviroc-containing regimens. Rates of death and selected clinical events (e.g., hepatic failure, malignancy, myocardial infarction) were low during follow-up.

Conclusions: Maraviroc was generally safe in treatment-experienced participants over more than 5 years.

Key words (3-10): maraviroc; CCR5 antagonist; HIV; antiretroviral therapy; safety; treatment-experienced patients
INTRODUCTION

Maraviroc is a first-in-class, selective chemokine co-receptor type-5 (CCR5) antagonist that demonstrated antiretroviral activity in early phase 2a studies of HIV-infected patients with CCR5-tropic (R5) virus [1]. Maraviroc has a unique mechanism of action among approved antiretrovirals in binding to a host protein, the CCR5 receptor, rather than a viral target. Maraviroc binds to the CCR5 receptor and prevents the interaction of the external membrane glycoprotein of R5 HIV-1, gp120, with the host-cell receptor. Given the unique mode of action and use of a host-cell target, initial concerns existed about the potential safety of CCR5 antagonists, including maraviroc [2]. Also, early development of other investigational CCR5 antagonists demonstrated potential class-specific effects: aplaviroc was associated with severe hepatotoxicity [3] and further clinical development was stopped; vicriviroc was initially associated with malignancies in a phase 2 study [4], although this was not confirmed in larger phase 3 studies [5].

In HIV-1 infected, treatment-experienced patients with R5 virus in the MOTIVATE 1 and MOTIVATE 2 phase 3 trials, maraviroc together with an optimized background antiretroviral regimen demonstrated superior 48-week virologic efficacy compared to placebo with no significant safety concerns [6]; these findings led to U.S. Food and Drug Administration approval of the drug. Follow-up results at 2 years demonstrated sustained antiretroviral activity and no new safety concerns [7]. Given the unique mechanism of action of CCR5 antagonists, and the potential for longer-term safety issues, the U.S. Food and Drug Administration requested extended, 5-year follow-up for all study subjects receiving these compounds. Here we report the pooled safety findings from the MOTIVATE 1 and MOTIVATE 2 phase 3 studies over more than 5 years, the longest term safety data available with a CCR5 antagonist.
METHODS

MOTIVATE 1 (NCT00098306) and MOTIVATE 2 (NCT00098722) were identically designed, parallel, randomized, double-blind, placebo-controlled, multicenter phase 3 studies. MOTIVATE 1 was conducted in Canada and the United States; MOTIVATE 2 was conducted in Australia, Europe and the United States. Eligible participants were treatment-experienced patients, aged at least 17 years old, who were infected with R5 HIV-1 (as documented by the original Trofile phenotypic co-receptor tropism assay), with screening plasma HIV-1 RNA levels more than 5000 copies/mL. Patients were randomized to receive the equivalent of maraviroc 300 mg once daily (QD), maraviroc 300 mg twice daily (BID), or placebo, depending on the planned use of concomitant antiretroviral drugs and other concomitant CYP3A4-active agents, together with an optimized background antiretroviral therapy (OBT) regimen. On the basis of prior drug-drug interaction data, patients who used a ritonavir (a CYP3A4 inhibitor)-boosted protease inhibitor (other than tipranavir) as part of their background regimen received a reduced dose of maraviroc 150 mg once or twice daily. Optimized background antiretroviral therapy was selected individually by the site investigators on the basis of the antiretroviral history of each study subject together with the results of genotypic and phenotypic drug-resistance testing.

The studies were designed with the primary endpoint of mean change of HIV-1 RNA ($\log_{10}$-transformed levels from baseline to 48 weeks) and study subjects were unblinded to treatment assignment after all subjects completed the week 48 visit (or discontinued the study early). Study subjects then were offered to change to open-label maraviroc 300 mg BID (or, as above, equivalent appropriate dose depending on concomitant medications) in an open-label phase of the study through 96 weeks, and then offered participation in a subsequent
observational phase extended through 5 years following each subject’s first dose of blinded study drug. Study subjects who previously discontinued the double-blind phase of the study early were offered participation in the open-label and observational phases. The study was approved by institutional review boards at each of the study sites and all study subjects provided written informed consent.

Adverse events were identified and assessed real-time by the site investigators. Protocol-specified clinical events included: AIDS-defining events, deaths, hepatic failure, infections reported as serious adverse events (SAEs), malignancies, myocardial infarctions and cardiac ischemia events, and rhabdomyolysis. Protocol-specified survival and clinical events were retrospectively identified from the double-blind and open-label active phases of the study by mapping the investigator-identified adverse events to the clinical events of interest. Protocol-specified survival and clinical events were prospectively identified by the site investigators during the observational phase of the study. The incidence and both the raw event rate (based on total number of events and total exposure) and the incidence rate (using a conventional time-to-first event approach) were calculated for each event. Study subjects who terminated the study drug early and entered the observational phase “on study, off study drug” were not included in the analyses.

RESULTS

Of a total of 3244 patients screened for the study, 1075 study subjects were randomized originally to the two phase 3 MOTIVATE studies, although 26 of them never received study treatment. Of the 1049 who received double-blinded study treatment, 426 received maraviroc 300 mg (or equivalent) twice-daily, 414 received maraviroc 300 mg (or equivalent) once-daily, and 209 received a matching placebo. Patient disposition is shown in the figure. Ultimately, a
total of 938 study subjects (including 98 study subjects originally randomized to placebo) received maraviroc and contributed to a total maraviroc exposure of 2639 patient-years with a median exposure of 908 days (range 1, 2220 days). Demographic and baseline characteristics for the 938 maraviroc-exposed study subjects were balanced among the 3 study treatment groups, with the study population comprising over 85% men, with over 80% white, a mean age of 46 years, a mean pre-study baseline HIV RNA level of 4.8 log_{10} (geometric mean, 63,100) copies/ml and a pre-study median CD4 count of 169 cells/μL.

Incidences and rates of survival and selected clinical events occurring over 5 years of the study are reported in the table. In total, 46 deaths were reported in the study, 8 occurring more than 28 days after discontinuation of maraviroc, and 1 occurring at an indeterminate time. The causes of death were varied, with malignancies (28% of deaths; n=13 study subjects, including 4 with lymphoma, 2 with lung cancer, 1 with leukemia, 1 with anal cancer, and 5 with various other cancers), infectious diseases (17%; n=8 study subjects, including 5 with pneumonia due to various causes), and cardiac/respiratory arrest (11%; n=5 study subjects) being the most common causes. Of the observed selected clinical endpoints, the most common were infections judged by the investigators to be a serious adverse event (12%; n=114 study subjects; incidence rate 4.7/100 patient-years), followed by AIDS events (8%; n=78 study subjects; 3.1/100 patient-years), malignancies (6%; n=61 study subjects; 2.4/100 patient-years), and cardiac events (3%; n=26 study subjects; 1.0/100 patient-years). Hepatic failure and rhabdomyolysis were uncommon (0.5%; n=5 study subjects each; 0.2/100 patient-years).

DISCUSSION
Maraviroc was approved by the U.S. Food and Drug Administration in 2007 as part of combination antiretroviral therapy for adults infected with CCR-tropic (R5) HIV-1 on the basis of 48-week results from the two phase 3 MOTIVATE studies [6]. Two-year follow-up, including a year of open-label maraviroc, revealed durable virologic suppression and no new safety issues [7]. With extended follow-up over more than 5 years, we found the incidence of death and selected clinical endpoints was low in this HIV-infected, treatment-experienced patient population exposed to maraviroc. As HIV-infected patients take antiretroviral drugs for prolonged periods and are living longer, it is critical to continue to assess the long-term safety and tolerability of antiretroviral regimens. Few phase 3 antiretroviral clinical trials have formally assessed longer-term safety in study participants, with a few exceptions such as the STARTMRK studies of raltegravir with 5 years of reported data [8].

Although the labeling information for maraviroc contains a boxed warning for hepatotoxicity, a prior analysis of the maraviroc clinical development program revealed no increased hepatotoxicity compared to comparator regimens with follow-up of up to 96 weeks [9]. Our extended analysis of the phase 3 maraviroc studies found hepatic failure events were uncommon (n=5, 0.5%).

Consistent with a previous report of pooled maraviroc phase 2b/3 studies with a median of 82 weeks of follow-up [10], we found no excess occurrence of malignancies in maraviroc-treated patients after more than 5 years. The malignancy rate of 2.4 events per 100 patient-years in the current two treatment-experienced studies of maraviroc was comparable to the malignancy rate reported in a pooled analysis of the BENCHMRK 1 and 2 studies of raltegravir that enrolled a similar study population of treatment-experienced patients with advanced HIV disease failing their antiretroviral regimen who randomized to raltegravir (3.0 events per 100 patient-years) or
matching placebo (2.6 events per 100 patient-years), in addition to optimized background antiretroviral therapy [11]. Although in a prior phase 2 study of another investigational CCR5 antagonist, vicriviroc, 12 (11%) of 113 of subjects who received vicriviroc developed malignancies [4], ultimately two larger phase 3 studies of vicriviroc reported malignancies occurred rarely and without differences between the vicriviroc and placebo arms [5] and therefore did not confirm an association.

In the current studies of treatment-experienced patients with virologic failure on their pre-study antiretroviral regimen, the myocardial infarction/cardiac ischemia rate was 1.1 events per 100 patient-years. This was consistent with a previous analysis of ischemic cardiovascular events from this study with shorter follow-up [12]. Other cohorts have reported lower rates of cardiac events, for example, in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, the rate of myocardial infarctions was 0.32 events per 100 patient-years [13] and in a Kaiser Permanente cohort, the rate of coronary heart disease events (including myocardial infarction) was 0.35 events per 100 patient-years [14]. Two important differences between our study and these cohort studies are important to recognize: (1) our study used a broader definition of cardiac events that included cardiac ischemia and (2) our study population was treatment-experienced and had advanced HIV disease (median pre-study CD4 count <200 cells/µL) in contrast to the patient populations in the D:A:D and Kaiser cohorts who were treatment-naïve patients at all stages of HIV infection.

The expanded access program for maraviroc enrolled and assessed 1032 participating patients who had a median maraviroc exposure of 174 days and found the safety and occurrence of adverse events were generally similar to the current MOTIVATE studies [15]. An additional study, the Prospective Observational Epidemiologic Study of Maraviroc’s Safety (POEM; Study
A4001067), currently is in progress and will continue to compare safety data for five years in 1500 patients on maraviroc with 1500 patients not taking a CCR5 antagonist.

In summary, in a population of HIV-infected, treatment-experienced patients with over five years of exposure to maraviroc, the incidence of death and other selected clinical events, including hepatic failure, malignancies, and myocardial infarctions, was low and no new safety signals were reported. Maraviroc appears generally safe and well-tolerated over at least 5 years in treatment-experienced patients.

ACKNOWLEDGMENTS

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REFERENCES


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Table: Incidence of 5-year death and selected clinical events in 938 subjects receiving maraviroc (total exposure 2639 patient-years)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Number (% of study subjects)</th>
<th>Number of events</th>
<th>Raw event rate (events per 100 patient-years)*</th>
<th>Incidence rate (events per 100 patient-years)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>death</td>
<td>46 (5%)</td>
<td>46</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>AIDS event</td>
<td>78 (8%)</td>
<td>98</td>
<td>3.7</td>
<td>3.1</td>
</tr>
<tr>
<td>hepatic failure</td>
<td>5 (0.5%)</td>
<td>5</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>infection judged to be a serious adverse event</td>
<td>114 (12%)</td>
<td>163</td>
<td>6.2</td>
<td>4.7</td>
</tr>
<tr>
<td>malignancy</td>
<td>61 (6%)</td>
<td>79</td>
<td>3.0</td>
<td>2.4</td>
</tr>
<tr>
<td>myocardial infarction or cardiac ischemia</td>
<td>26 (3%)</td>
<td>30</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>rhabdomyolysis</td>
<td>5 (0.5%)</td>
<td>5</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

* (total number of events per total patient-years of exposure) X 100

** based on time-to-first event
45 study subjects completed the double-blind phase but did not enter the open-label phase.

140 study subjects did not complete the double-blind phase, but entered the open-label phase, including 29 from the maraviroc bid group, 29 from the maraviroc qd group, and 82 from the placebo group.

146 study subjects who terminated study treatment prematurely and entered the observational phase as “in study, off study drug” are not included above.

Abbreviations: bid, twice daily; OBT, optimized background therapy; qd, once daily