Once daily maraviroc 300 mg or 150 mg in combination with ritonavir-boosted darunavir 800/100 mg

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Objective: To describe the pharmacokinetics of maraviroc when dosed at 150 or 300 mg once daily with 800/100 mg of darunavir/ritonavir.

Methods: A retrospective case-note review of HIV-infected adults taking maraviroc was conducted. Patients on a maraviroc-based regimen for a minimum of 5 weeks were grouped as receiving: (i) 300 mg of maraviroc twice daily with 245 mg of tenofovir/200 mg of emtricitabine; (ii) 300 mg of maraviroc once daily with 800/100 mg of darunavir/ritonavir once daily; and (iii) 150 mg of maraviroc once daily with 800/100 mg of darunavir/ritonavir once daily. Ctrough and Cpeak data were collected at 2, 12 or 24 h post-dose.

Results: Sixty-six patients were included, providing 115 samples. The median (IQR) Cpeak was 378 (350–640) ng/mL for 300 mg of maraviroc twice daily with 245 mg of tenofovir/200 mg of emtricitabine (n=9), 728 (378–935) ng/mL for 300 mg of maraviroc once daily with darunavir/ritonavir (n=29) and 364 (104–624) ng/mL for 150 mg of maraviroc once daily with darunavir/ritonavir once daily; Ctrough, and Cpeak data were collected at 2, 12 or 24 h post-dose.

Conclusions: Once daily coadministration of 300 mg of maraviroc with 800/100 mg of darunavir/ritonavir was well tolerated and had favourable pharmacokinetics when compared with 300 mg of maraviroc twice daily with 245 mg of tenofovir/200 mg of emtricitabine. A 24% higher Ctrough and 107% higher Cpeak was seen in black patients compared with white patients.

Keywords: pharmacokinetics, HIV antiviral pharmacology, drug interactions

Introduction

Maraviroc was the first licensed CCR5 receptor antagonist used in combination with other antiretrovirals (ARVs) for the treatment of R5-tropic HIV-1. Maraviroc is metabolized primarily by CYP3A4 and is also a substrate of the ABC1B1 (P-glycoprotein) efflux transporter.1–3 Coadministration with compounds that inhibit CYP3A4 and/or ABC1B1 can lead to an increased half-life, as drug clearance is reduced.2 Consequently, when administered with potent CYP3A4 inhibitors or inducers the recommended maraviroc twice-daily dose differs. Interaction studies with maraviroc and ritonavir-boosted protease inhibitors (bPIS) have resulted in a reduction in the licensed dose from 300 mg twice daily to 150 mg twice daily when coadministered.1 However, as an aid to adherence, there is increasing interest in dosing ARV therapy, including maraviroc, as part of a once-daily regimen. Maraviroc has a half-life of ~16 h when administered without interacting drugs.5 This is increased further in the presence of bPIS, making the option of using the drug once daily a theoretical possibility. Furthermore, in the MOTIVATE study, when maraviroc was dosed either once daily or twice daily in combination with bPIS, both arms had favourable virological outcomes.4
Ritonavir and bPIs such as darunavir/ritonavir are known to increase maraviroc plasma concentrations, and recent pilot studies have suggested that maraviroc, when dosed at 150 mg once daily with 300/100 mg of atazanavir/ritonavir, achieves concentrations that are comparable to a 300 mg twice-daily regimen without bPIs. The mounting evidence has led to the increased use of bPIs and once-daily maraviroc in clinical practice. An average maraviroc plasma concentration ($C_{\text{ave}}; \frac{C_{\text{AUC}}}{t}$) of 75 ng/mL has been associated with maximum virological efficacy. However, measuring the $C_{\text{ave}}$ is not practical in the clinical setting. The minimum effective concentration of maraviroc has not yet been defined, but trough concentrations $>25$ ng/mL were associated with a good virological response in the MERIT study. In addition, plasma concentrations $>1000$ ng/mL have been associated with maraviroc-related toxicity, namely postural hypotension. The aim of this investigation was to describe the pharmacokinetics (PK) of maraviroc when dosed at 150 or 300 mg once daily with 800/100 mg of darunavir/ritonavir for a UK-based patient cohort with varied population demographics using $C_{\text{peak}}$ and $C_{\text{trough}}$, and to compare these values to the PK of maraviroc when dosed at the standard licensed dose of 300 mg twice daily with 200 mg of emtricitabine and 245 mg of tenofovir.

### Patients and methods

A retrospective case-note review of HIV-infected adults taking maraviroc was conducted in two large UK treatment centres (North Middlesex University Hospital and Birmingham Heartlands Hospital). Standardized clinical protocols were followed for non-licensed dosing regimens.

### Results

Sixty-six patients were included in the analysis and provided a total of 115 samples. The median (IQR) $C_{\text{peak}}$ was 378 (350–640) ng/mL for 300 mg of maraviroc twice daily with 245 mg of tenofovir.

### Table 1. Patient demographic, physical and pharmacological characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MVC 300 mg once daily + DRV/r (n = 35)</th>
<th>MVC 150 mg once daily + DRV/r (n = 17)</th>
<th>MVC 300 mg twice daily + TDF/EMC (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg), median (range)</td>
<td>76 (53–143)</td>
<td>77 (53–143)</td>
<td>68 (50–83)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (range)</td>
<td>26 (17–42)</td>
<td>27 (20–42)</td>
<td>22.7 (18–28)</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>46 (32–58)</td>
<td>44 (40–64)</td>
<td>44 (26–61)</td>
</tr>
<tr>
<td>Female, % (n)</td>
<td>34 (12)</td>
<td>47 (8)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Ethnicity, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>46 (16)</td>
<td>24 (4)</td>
<td>64 (9)</td>
</tr>
<tr>
<td>black</td>
<td>49 (17)</td>
<td>76 (13)</td>
<td>29 (4)</td>
</tr>
<tr>
<td>other</td>
<td>6 (2)</td>
<td>0 (0)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Hepatitis B/C coinfection, % (n)</td>
<td>3 (1)</td>
<td>6 (1)</td>
<td>21 (3)</td>
</tr>
<tr>
<td>eGFR &lt;80 mg/mL, % (n)</td>
<td>40 (14)</td>
<td>35 (6)</td>
<td>21 (3)</td>
</tr>
<tr>
<td>Time on MVC (weeks), median (range)</td>
<td>22 (7–116)</td>
<td>19 (9–63)</td>
<td>47 (15–88)</td>
</tr>
<tr>
<td>CD4 (cells/mm³), median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before MVC switch</td>
<td>446 (44–1330)</td>
<td>440 (168–1040)</td>
<td>490 (262–1052)</td>
</tr>
<tr>
<td>after MVC switch</td>
<td>528 (53–1520)</td>
<td>430 (154–920)</td>
<td>560 (312–1060)</td>
</tr>
<tr>
<td>Viral load (copies/mL), median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before MVC switch</td>
<td>222 (39–69782)</td>
<td>81 (39–211505)</td>
<td>39 (39–42984)</td>
</tr>
</tbody>
</table>

MVC, maraviroc; DRV/r, darunavir/ritonavir; TDF, tenofovir; EMC, emtricitabine; eGFR, estimated glomerular filtration rate; BMI, body mass index.
200 ng/mL for 300 mg of maraviroc once daily with darunavir/ritonavir (n = 29) and 364 (104–624) ng/mL for 150 mg of maraviroc once daily with darunavir/ritonavir (n = 2; P = 0.24). The median (IQR) C\text{trough} was 46 (33–61) ng/mL for 300 mg of maraviroc twice daily with 245 mg of tenofovir/200 mg of emtricitabine (n = 12), 70 (49–97) ng/mL for 300 mg of maraviroc once daily with darunavir/ritonavir (n = 34) and 43 (35–55) ng/mL for 150 mg of maraviroc once daily with darunavir/ritonavir (n = 17; P = 0.001) (Figure 1).

Maraviroc C\text{trough} and C\text{peak} plasma concentrations were not correlated with demographic factors, such as weight, gender, age or renal function. Maraviroc C\text{trough} concentrations in patients treated with 300 mg once daily were expectedly higher in patients treated with 150 mg once daily (P = 0.002) but also higher with 300 mg twice daily with 245 mg of tenofovir/200 mg of emtricitabine (P = 0.004). No statistically significant differences were observed for the corresponding C\text{peak}.

Black patients had statistically significantly higher C\text{trough} and C\text{peak} than white patients (24% and 107%, respectively). The C\text{trough} in black patients (n = 34) was 61 (45–110) ng/mL and in white patients (n = 29) it was 49 (42–70) ng/mL (P = 0.04). The C\text{peak} in black patients (n = 20) was 800 (397–1060) ng/mL versus 387 (336–723) ng/mL in white patients (n = 20; P = 0.02). In multivariate analysis, dose (P = 3.4 × 10^-5) and ethnicity (P = 0.01) were independently associated with the C\text{trough}. In patients for which C\text{trough} and C\text{peak} data were available (n = 39), a correlation between the maraviroc C\text{trough} and darunavir/ritonavir C\text{trough} was observed (p = 0.39; P = 0.02). All regimens were well tolerated, with no cases of symptomatic postural hypotension identified.

Discussion

These are the first data available for the use of once-daily maraviroc in combination with ritonavir-boosted darunavir in the clinical setting. Our preliminary data suggest that maraviroc dosed at either 150 mg once daily or 300 mg once daily both produce maraviroc trough concentrations above the target of 25 ng/mL. Further, the 300 mg once-daily dose produced trough maraviroc concentrations approximately double those achieved with the 150 mg once-daily dose. Whether this increased trough concentration will translate into virological and clinical benefit remains to be seen.

Mills et al.\(^5\) (study A4001078) conducted a 24 week analysis of 121 patients and showed that patients randomized to 300/100 mg of atazanavir/ritonavir with 245 mg of tenofovir/200 mg of emtricitabine or to 300/100 mg of atazanavir/ritonavir with 150 mg of maraviroc once daily showed viral load <50 copies/mL responses of 89% and 80%, respectively. Interim PK analysis in 15 patients showed all patients achieved the proposed C\text{trough} target of 75 ng/mL, but not all had achieved the C\text{trough} target of 25 ng/mL. Although these are encouraging data, it cannot be assumed that the interaction between maraviroc and different bPIs will be the same, as the interaction is not solely based on the effects of ritonavir.\(^1,8\) Therefore, care should be taken when extrapolating between different bPIs.

In our analysis, only 9% (6/66) of patients had had a measured C\text{peak} >1000 ng/mL. Our analysis is limited in that we measured C\text{peak} at 2 h post-drug ingestion and, thus, we may have missed the true T\text{max} which may have occurred outside that time period. Nevertheless, no patients had symptomatic postural hypotension as predefined by standard methods. The maraviroc C\text{peak} observed in the 300 mg once-daily arm with bPI was higher than that seen in the unboosted 300 mg twice-daily arm; however, this was not shown to be statistically significant and there was a fair degree of overlap with the concentration ranges.

The observed 24% higher C\text{trough} and 107% higher C\text{peak} seen in black patients compared with white patients was statistically significant. Furthermore, in the multivariate analysis black ethnicity was independently associated with a higher maraviroc C\text{trough} when other demographic factors, including weight and renal function, were controlled for. Differences in maraviroc concentrations between black and white populations have previously been described, but not of this magnitude.\(^2\)

This may, in part, be due to novel metabolic pathways that are still being identified for maraviroc, which may explain its varied PK profile across different cohorts of patients and with the bPIs. Maraviroc was recently shown to be an OATP1B1 substrate and polymorphisms in the SLCO1B1 gene may be useful predictors of maraviroc concentrations.\(^1\)

In summary, 300 mg of maraviroc once daily when coadministered with 800/100 mg of darunavir/ritonavir was well tolerated and had favourable PK when compared with 300 mg of maraviroc twice daily with 245 mg of tenofovir/200 mg of emtricitabine. The debate on the optimum dose to achieve long-term efficacy in maraviroc-based ARV therapy regimens lies between potential virological failure if drug doses are too low versus drug toxicity if they are too high.\(^3\) In general, the lower C\text{trough} that is obtained with once-daily dosing when compared with twice-daily dosing may increase the risk of virological failure, so caution needs to be taken with unlicensed regimens, especially when lower doses are used. However, genetic variability may prove a factor in the dosing regimen and one dose may not be suitable for all patients.
The significantly higher maraviroc $C_{\text{peak}}$ observed in black subjects when compared with white subjects warrants further investigation.

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References