Antiretroviral-Experienced HIV-1-Infected Patients Treated with Maraviroc: Factors Associated with Virological Response

Cathia Soulie,¹⁻³ Gilles Peytavin,⁴⁻⁶ Charlotte Charpentier,⁵⁻⁷ Sidonie Lambert-Niclot,¹⁻³
Sophie Sayon,¹⁻³ Benoit Visseaux,⁵⁻⁷ Anne Simon,⁸ Christine Katlama,^{1,2,9} Yazdan Yazdanpanah,^{5,6,10}
Diane Descamps,⁵⁻⁷ Vincent Calvez,¹⁻³ and Anne-Geneviève Marcelin¹⁻³

Abstract

There are few data on the clinical and virological factors associated with the virological response (VR) of maraviroc (MVC) in clinical practice. This study aimed to identify factors associated with the VR to MVC-containing regimens in 104 treatment-experienced but CCR5 inhibitor-naïve HIV-1 patients. VR was defined at month 3 (M3) as HIV-1 RNA viral load (VL) < 50 copies/ml. The impact on VR of age, sex, baseline tropism, HIV subtype (B vs. non-B), nadir CD4 cell count and CD4 cell count, baseline VL, genotypic susceptibility score of treatment, once or twice daily treatment, presence of raltegravir in optimized background therapy, and MVC concentrations was investigated. Median baseline VL was 3.3 log₁₀ copies/ml (range 1.7–6.0 log₁₀ copies/ml) and CD4 cell count was 299 cells/mm³ (range 7–841 cells/mm³). At M3, 53.8% of patients were responders. In univariate analysis, a better efficacy of the MVC-containing regimen was associated with a high CD4 cell count ($p=0.0069$) and there was a trend for low baseline VL, high nadir CD4 cell count, and HIV subtype (B versus non-B). Only low baseline VL remained significantly associated with better VR in the multivariate analysis. This study demonstrated a VR of an optimized antiretroviral treatment including MVC in clinical practice similar to that observed in clinical trials. The factors associated with VR were higher baseline CD4 cell count in univariate analysis and lower baseline VL in multivariate analysis.

Introduction

AMONG THE NEW CLASSES of antiretrovirals (ARV), maraviroc (MVC) is the first and only CCR5 antagonist approved for treatment of HIV-1-infected patients with CCR5-tropic viruses. The MOTIVATE clinical trials demonstrated that MVC, when used with an optimized background therapy, can reduce plasma viral load (VL) in treatment-experienced patients infected with R5-tropic viruses.^{1,2} A retrospective analysis excluding patients with X4-tropic viruses in the MERIT study resulted in similar

response rates in both arms of the trial (MVC versus efavirenz in treatment-naïve patients both with zidovudine–lamivudine).³ In the MERIT study, lower response rates for MVC therapy among black patients and those infected with non-B subtype infections were observed.³ However, there are few data on the clinical and virological factors associated with MVC virological response (VR) in clinical practice.

The aim of this study was to identify the factors associated with VR to MVC-containing regimens in treatment-experienced patients in clinical practice.

¹Sorbonne Universités, UPMC Université Paris 06-UMR_S 1136 Pierre Louis Institute of Epidemiology and Public Health, Paris, France.

²INSERM-UMR_S 1136 Pierre Louis Institute of Epidemiology and Public Health, Paris, France.

³AP-HP, Laboratoire de Virologie, Groupe Hospitalier Pitié Salpêtrière, Paris, France.

⁴AP-HP, Service de Pharmacologie Clinique, Hôpital Bichat-Claude Bernard, Paris, France.

⁵IAME, UMR 1137-Université Paris Diderot, Sorbonne Paris Cité, Paris, France.

⁶INSERM UMR 1137, Paris, France.

⁷AP-HP, Laboratoire de Virologie, Hôpital Bichat, Paris, France.

⁸AP-HP, Service de Médecine Interne, Groupe Hospitalier Pitié Salpêtrière, Paris, France.

⁹AP-HP, Service de Maladies Infectieuses, Groupe Hospitalier Pitié Salpêtrière, Paris, France.

¹⁰AP-HP, Service des Maladies Infectieuses et Tropicales, Hôpital Bichat, Paris, France.

Materials and Methods

Patients

In total, 104 HIV-1 patients followed in two clinical centers (Pitié Salpêtrière and Bichat Hospital) signed individual consent forms. The study was approved by the Scientific Committee of AC11 ANRS. The 104 patients had received MVC (Celsentri, ViiV) as part of their current ARV treatment prescribed by their physician during routine medical care. They had a VL > 50 copies/ml at the beginning of this study. They had never previously been treated with CCR5 antagonists.

Virological testing

The VL (Cobas AmpliPrep/cobasTaqman HIV-1 test, Roche Diagnostics, Meylan, France) and CD4⁺ cell counts were measured after 3 months of treatment (M3). The co-receptor usage was determined from the V3 *env* region sequence by geno2pheno before the introduction of MVC (false-positive rate 10%).⁴ The reverse transcriptase, protease, and integrase resistance mutations were interpreted with the last ANRS genotypic algorithm (www.hivfrenchresistance.org). According to the ANRS algorithm, the genotypic susceptibility score of treatment (GSS) of the MVC cotreatment received by the patient was calculated as follows: 1 for a sensitive drug and 0 for a resistant or possibly resistant drug. The HIV-1 subtype was determined either by the Smartgene algorithm (Smartgene, Switzerland) or by phylogenetic analyses, by estimating the relationships among RT sequences and reference sequences of HIV-1 genetic subtypes and circulating recombinant forms (CRF) obtained from the Los Alamos Database (<http://hiv-web.lanl.gov>). Phylogenetic trees were inferred using the neighbor-joining method and two Kimura parameters with 1,000 bootstrap values. The GenBank (www.ncbi.nlm.nih.gov/GenBank) accession numbers for the RT are KP140846–KP140941.

Pharmacology methods

The MVC trough plasma concentrations, collected 12 h after the last drug intake, were determined using liquid chromatography coupled with tandem mass spectrometry (UPLC-TQD Acquity Waters) with some modification at M3.⁵

Statistical methods

The VR was defined at M3 as VL < 50 copies/ml. The impact of age, sex, baseline tropism, HIV subtype (B vs. non-B), nadir CD4 cell counts and CD4 cell counts, baseline VL, GSS, once or twice daily treatment, presence of raltegravir in optimized background therapy, and MVC concentrations at M3 was investigated. Comparisons between groups were then performed using the nonparametric Mann–Whitney and chi-squared tests. All variables providing a *p*-value < 0.20 in the univariate analysis were selected by the stepwise procedure to build the final multivariate model. Statview software v5.0 was used.

Results

The main characteristics of the study population are shown in Table 1. The HIV-1 was X4-tropic for 11/104 patients. The subtypes were distributed as follows: 76 B subtypes and 28

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION (*n* = 104)

Characteristic	% or median (range)
Male, % (frequency)	73 (76/104)
Age, median (range)	48 (22–69)
Subtype B, % (frequency)	73 (76/104)
Plasma HIV-1 RNA log ₁₀ copies/ml, median (range)	3.3 (1.7–6)
CD4 cell count/mm ³ , median (range)	299 (7–841)
Nadir CD4 cell count/mm ³ , median (range)	108 (1–812)
R5 tropism, % (frequency)	89 (92/103)
Genotypic susceptibility score, median (range)	2 (0–5)
Maraviroc twice daily, % (frequency)	95 (96/101)
Maraviroc doses, % (frequency)	
150 mg	42 (42/101)
300 mg	50 (51/101)
600 mg	8 (8/101)
Maraviroc cotreatment, % (frequency)	
NRTIs	72 (75/104)
NNRTIs	32 (33/104)
PIs	74 (77/104)
Raltegravir	45 (47/104)
Enfuvirtide	2 (2/104)

NRTIs, nucleos(t)ide reverse transcriptase inhibitors; NNRTIs, nonnucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.

non-B subtypes (one A subtype; 13 CRF02_AG; three CRF06_cpx; one CRF11_cpx; two CRF14; one D subtype; two F subtype; two G subtype; one J subtype; two undetermined subtype).

Among the 104 patients included in the present analysis, 53.8% (56/104) were responders at M3. The durability of the VR was checked after 6 months (M6): 67% (48/71) of patients had a VL < 50 copies/ml. Among all of the studied factors, only CD4 T cell counts at baseline were associated with VR in univariate analysis (234 cells/mm³ in median for the patients with VL > 50 copies/ml and 353 cells/mm³ in median for patients with VL < 50 copies/ml, respectively; *p* = 0.069). It is of interest that nadir CD4 cell count, baseline VL, and HIV subtypes (B or non-B subtypes) tend to be associated with the VR (Table 2). These factors were then analyzed in a multivariate statistical analysis and only the baseline VL was associated with the VR (3.8 log₁₀ copies/ml in median for the patients with VL > 50 copies/ml and 3.3 log₁₀ copies/ml in median for patients with VL < 50 copies/ml, respectively; Table 2). Furthermore, there was a trend toward an association of HIV subtypes with the VR. The patients with subtype B viruses had a lower VL than patients with non-B viruses at M3 (1.6 log₁₀ copies/ml and 1.9 log₁₀ copies/ml for the B and non-B subtype-infected patients, respectively), although the patients with subtype B viruses had a higher VL at baseline (3.5 log₁₀ copies/ml and 3.1 log₁₀ copies/ml for the B and non-B subtype-infected patients, respectively). There was also a difference in CD4 cell count between subtypes B and non-B (323 versus 214 cells/mm³, respectively; *p* = 0.0122). As the non-B subtype group could not be homogeneous, multivariate analysis was also performed removing the B vs. non-B analysis. Only the baseline VL was associated with the VR as previously demonstrated (*p* = 0.0553).

TABLE 2. FACTORS STATICALLY ASSOCIATED WITH THE VIROLOGICAL RESPONSE TO A TREATMENT INCLUDING MARAVIROC AT M3 IN UNIVARIATE AND MULTIVARIATE ANALYSIS

	Univariate analysis	Multivariate analysis
HIV subtype (B versus non-B)	$p=0.1127$	$p=0.0854$
Nadir CD4 cell count	$p=0.0719$	$p=0.6432$
Baseline CD4 cell count	$p=0.0069$	$p=0.4321$
Baseline viral load	$p=0.0604$	$p=0.0418$
Age	$p=0.3008$	na
Sex	$p=0.2531$	na
Baseline tropism	$p=0.7511$	na
Genotypic susceptibility score	$p=0.3391$	na
Once or twice daily treatment	$p>0.9999$	na
Raltegravir	$p=0.7496$	na
Maraviroc concentrations at M3	$p=0.6833$	na

na, nonapplicable.

The VR was studied according to the baseline tropism. For the 48 patients with a VL > 50 copies/ml at M3, 6 and 42 of the patients had X4- and R5-tropic viruses at baseline, respectively. The HIV-1 tropism was not associated with the VR ($p=0.7867$). For the 42 patients with R5-tropic viruses at baseline, the tropism was available for 22 nonresponder patients at M3 (16 patients remained with R5-tropic viruses and six patients had a change of tropism). No statistical differences were observed for these 22 nonresponder patients for VL, CD4 cell count, nadir CD4 cell count, and subtypes according to the tropism at failure (Table 3).

Discussion

In this study, 53.8% of patients were responders at M3 to an ARV treatment including MVC, and better VR was associated with a high baseline CD4 cell count in univariate analysis and there was a trend for low baseline VL, high nadir CD4 cell count, and HIV subtype. Only low baseline VL remained significantly associated with VR in the multivariate analysis.

In the present study, we observed a VR in clinical practice similar to what was previously described in clinical trials, even if the background treatment was nonstandardized. Indeed, suppression of viral replication at week 48 was achieved in 42% (once daily) and 47% (twice daily) in

MOTIVATE 1, 45% in MOTIVATE 2 (ARV-experienced patients), and 65.3% in MERIT (ARV-naïve patients).^{1,3}

A high baseline VL was independently associated with a worse VR as was previously demonstrated in the ANRS Genotropism study.⁴ We also showed in the present study that a low baseline CD4 cell count was associated with worse VR. In the MODERN trial, the proportion of subjects with HIV-1 RNA viral load < 50 copies/ml was always lower for the maraviroc-darunavir/ritonavir arm compared to the darunavir/ritonavir plus emtricitabine/tenofovir arm according to CD4 strata.⁶ As it was previously shown that the presence of R5X4/X4-tropic viruses was linked to a low CD4 cell count, X4-tropic viruses could have been present but not detected by bulk sequencing.⁷ It would be interesting to evaluate the determination of HIV-1 tropism by ultra-deep sequencing and the impact on VR in clinical practice.

Although in this study only 28 patients were infected with the non-B subtype, which could represent a limitation in addressing the impact of HIV-1 subtype on MVC activity, we noticed a trend in the impact of subtype on VR that had previously been approached in the MERIT and MOTIVATE studies.¹⁻³ It is still unclear if there are any variations in intrinsic MVC activity against the B vs. non-B subtype or lack of sensitivity or specificity in the determination of tropism.⁸⁻¹¹ However, the HIV-1 tropism determination method does not seem to have an impact as the MVC effect on the non-B subtype was similar whatever method was used: phenotypes in MERIT and MOTIVATE or genotypes in our study.

This study demonstrated in clinical practice that MVC remained a valuable therapeutic option in an optimized background regimen for HIV-1-experienced patients, similar to that observed in clinical trials. In addition, our results showed that VR to MVC is better for patients with a high CD4 cell count and low VL, providing information for clinical practice.

Acknowledgments

We thank G. Le Mallier and P. Grange for their technical assistance. This study was supported by the ANRS (National French Agency for AIDS Research). The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013), under the project "Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN)"—grant agreement no. 223131 and ARVD (Association de Recherche en Virologie et en Dermatologie).

Author Disclosure Statement

No competing financial interests exist.

References

1. Gulick RM, Lalezari J, Goodrich J, *et al.*: Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med* 2008;359:1429–1441.
2. Fatkenheuer G, Nelson M, Lazzarin A, *et al.*: Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. *N Engl J Med* 2008;359:1442–1455.
3. Cooper DA, Heera J, Goodrich J, *et al.*: Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naïve subjects with CCR5-tropic HIV-1 infection. *J Infect Dis* 2010;201:803–813.

TABLE 3. CHARACTERISTICS OF 22 PATIENTS WITH AVAILABLE TROPISM AT M3

	M3 R5-tropic viruses (n = 16)	M3 X4-tropic viruses (n = 6)	Statistical test
Baseline viral load, median, log ₁₀ copies/ml	3.9	3.8	>0.9999
Baseline CD4 cell count cells/mm ³	272	186	0.6058
Nadir CD4 cell count cells/mm ³	105	6	0.1844
Subtype B (%)	62.5	100	0.2663

4. Recordon-Pinson P, Soulie C, Flandre P, *et al.*: Evaluation of the genotypic prediction of HIV-1 coreceptor use versus a phenotypic assay and correlation with the virological response to maraviroc: The ANRS GenoTropism study. *Antimicrob Agents Chemother* 2010;54:3335–3340.
5. Jung BH, Rezk NL, Bridges AS, *et al.*: Simultaneous determination of 17 antiretroviral drugs in human plasma for quantitative analysis with liquid chromatography-tandem mass spectrometry. *Biomed Chromatogr* 2007;21:1095–1104.
6. Stellbrink H-J, Szlavik J, Murphy D, *et al.*: Maraviroc (MVC) dosed once daily with darunavir/ritonavir (DRV/r) in a 2 drug-regimen compared to emtricitabine/tenofovir (TDF/FTC) with DRV/r; 48-week results from MODERN (Study A4001095). 20th International AIDS Conference. Melbourne, Australia, 2014.
7. Soulie C, Fourati S, Lambert-Niclot S, *et al.*: Factors associated with proviral DNA HIV-1 tropism in antiretroviral therapy-treated patients with fully suppressed plasma HIV viral load: Implications for the clinical use of CCR5 antagonists. *J Antimicrob Chemother* 2010;65:749–751.
8. Dina J, Raymond S, Maillard A, *et al.*: Algorithm-based prediction of HIV-1 subtype D coreceptor use. *J Clin Microbiol* 2013;51:3087–3089.
9. Raymond S, Delobel P, Rogez S, *et al.*: Genotypic prediction of HIV-1 CRF01-AE tropism. *J Clin Microbiol* 2013;51:564–570.
10. Raymond S, Delobel P, Chaix ML, *et al.*: Genotypic prediction of HIV-1 subtype D tropism. *Retrovirology* 2011;8:56.
11. Raymond S, Delobel P, Mavigner M, *et al.*: Genotypic prediction of human immunodeficiency virus type 1 CRF02-AG tropism. *J Clin Microbiol* 2009;47:2292–2294.

Address correspondence to:

Cathia Soulié
Laboratoire de Virologie-CERVI
Groupe Hôpital Pitié Salpêtrière
45-83 Bd de l'hôpital
75013 Paris
France

E-mail: cathia.soulie@psl.aphp.fr