Responses to Switching to Maraviroc-Based Antiretroviral Therapy in Treated Patients with Suppressed Plasma HIV-1-RNA Load

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Key Words

HIV-1 • Maraviroc • Genotypic tropism test • Drug tolerability • T cell activation

Abstract

Background: Maraviroc (MVC) has shown good efficacy and tolerability in treatment-naïve and treatment-experienced HIV-1-infected patients with CCR5-tropic virus. Data on patients switching to MVC while on suppressive antiretroviral therapy (ART) are limited. The aim of this study was to evaluate patients on suppressive ART switching to an MVC-containing regimen (MVC-CR), and test the hypothesis that the switch may have an impact on T cell activation. **Methods:** The study population comprised 20 treated adults who started MVC with a plasma HIV-1-RNA load (viral load, VL) of <50 copies/ml. Viral tropism was assessed by V3 loop sequencing using proviral DNA from peripheral blood mononuclear cells (PBMCs). Changes in clinical and laboratory parameters were evaluated at a median of 2 and 6 months of follow-up. T cell activation was determined by measuring soluble CD30 in plasma. **Results:** Reasons for switching to a MVC-CR were drug toxicity and tolerability, low CD4 cell count and ART simplification. Over median 7.5 months of follow-up, 3/20 patients discontinued MVC due to severe headache, fatigue

and VL rebound. A significant reduction in soluble CD30 levels in MVC-treated patients was observed during follow-up at both 2 ($p = 0.027$) and 6 months ($p = 0.001$). **Conclusions:** Switching suppressive ART to a MVC-CR based upon genotypic tropism prediction from proviral DNA improves tolerability. The observed impact on T cell activation warrants further investigation.

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Introduction

The commercialization of new classes of antiretroviral drugs in 2007 (CCR5 antagonists and integrase inhibitors) has increased therapeutic options, particularly in cases of multi-drug resistance and poor tolerability. Maraviroc (MVC) was the first CCR5 antagonist licensed for clinical use, in combination with other antiretrovirals, for both treatment-experienced and treatment-naïve patients with CCR5-tropic (R5) HIV-1 infection [1]. MVC does not display significant virological activity in patients harbouring chemokine receptor 4 (CXCR4)-using HIV variants as the dominant plasma species [2]. Therefore, prior determination of viral tropism is required, typically using plasma HIV-1 RNA.

The 48-week analysis of the MOTIVATE 1 and 2 studies demonstrated that patients receiving MVC with optimized background therapy achieved a significantly greater proportion of undetectable plasma HIV-1 RNA, with greater rises in CD4+ T cells, compared with those receiving optimized background therapy plus placebo. In addition, the adverse event profile of MVC was similar to that of placebo for all cause- and treatment-related adverse events, AIDS-defining events (CDC category C), non-AIDS-defining malignancies and grade 3 or 4 hepatic transaminase elevations [3, 4].

Data from the MERIT trial, in which MVC and efavirenz, each in combination with Combivir, were compared in treatment-naïve patients, showed that fewer patients discontinued MVC than efavirenz due to adverse events (4.2 vs. 13.6%, respectively); fewer lipid abnormalities were also observed [5]. More patients receiving MVC experienced virological failure in the primary analysis. However, a retrospective reanalysis, using an improved tropism test to exclude patients with CXCR4-using virus, demonstrated the non-inferiority of MVC versus efavirenz [5].

MVC was not associated with elevations in total cholesterol, LDL or triglycerides in this study, and showed beneficial effects on lipid profiles of dyslipidaemic patients [6]. More rapid decreases in CD38 expression on CD4+ T cells and in plasma D dimer concentrations compared to treatment with efavirenz suggest a potential anti-inflammatory activity of MVC [7]. CD30, a member of the tumour necrosis factor (TNF) receptor superfamily, appears to be preferentially expressed on CD4 and CD8 T cell clones capable of producing T helper (Th)2-type cytokines, which release soluble CD30 into the circulation [8]. In the absence of ART, HIV-infected patients show impaired secretion of Th1 cytokines and antiviral IFN- γ , with an increased production of Th2 cytokines, pro-inflammatory cytokines, and TNF- α . HIV-1-infected patients have elevated sCD30 compared to uninfected controls, and higher levels of sCD30 have been associated with more rapid disease progression, independent of baseline (BL) CD4 [9]. A decrease in sCD30 in treated patients is considered a marker of effective ART and CD4 Th1 cell recovery [10]. MVC thus offers the promise of good efficacy and tolerability and the potential for anti-inflammatory activity in patients. These include patients who may need to switch suppressive ART (e.g. due to poor tolerability) although controlled data are lacking [11].

We report an observational study of 20 patients on suppressive ART switching to a MVC-containing regi-

men (MVC-CR) based upon a genotypic tropism test (GTT) performed on peripheral blood mononuclear cell (PBMC)-derived proviral DNA [12]. Immunological and virological response and tolerability after switching were evaluated. We hypothesized that MVC introduction would reduce sCD30 levels.

Materials and Methods

Study Population

The study population comprised 20 adults attending the Royal Free Hospital HIV Outpatients Clinic, who started MVC with a plasma HIV-1 RNA load (viral load, VL) of <50 copies/ml. Clinical and laboratory parameters after a median of 2 months [range 1–4; time point 1 (T1)] and 6 months (time point 2, T2) of follow-up were measured. Patients co-infected with HBV or HCV were excluded. We retrospectively evaluated trends of CD4+ cell count, VL, lipid profile (total cholesterol, HDL, LDL, triglycerides), estimated glomerular filtration rate, creatinine, alanine aminotransferase and aspartate aminotransferase at BL, T1 and T2 according to data collected in routine clinical practice.

The genotypic sensitivity scores of MVC-CRs were calculated according to the last genotypic resistance test available for each patient; a score of 1 was attributed to each active drug of the new regimen (MVC excluded), and a score of 0 was given to each inactive drug on the basis of the International AIDS Society-USA mutations panel from December 2010.

Genotypic Tropism Testing

HIV tropism was determined using proviral DNA extracted from PBMCs by sequencing the gp120 V3 region of the envelope gene using nested PCR as previously described [13]. Tests were conducted in triplicate. CCR5 tropism was predicted using the geno2pheno interpretation system, according to the clonal model with a false positive rate (FPR) set at 6–15% (FPR 15%) as previously described [12].

Soluble CD30

sCD30 was measured in plasma collected at BL, T1 and T2, and stored at -80° , using a plate ELISA (eBioscience, Hatfield, UK) according to the manufacturer's instructions.

Statistical Analysis

A Wilcoxon signed-rank test was used to assess statistical significance ($p < 0.05$).

Results

Study Population

The characteristics of the study population are shown in table 1. GTT was performed according to clonal and clinical models as shown in figure 1. ART combinations prior to regimen switch and their durations are described in table 2. MVC-CR comprised MVC + ritonavir-boosted

Table 1. Characteristics of the study population

Whole population, n	20
Median age (range), years	47.5 (37–65)
Gender: male, n (%)	15 (75)
Ethnicity, n (%)	
White	14 (70)
Black	5 (25)
Hispanic	1 (5)
Risk group, n (%)	
MSM	12 (60)
Heterosexual	6 (40)
Unknown	2 (10)
Median time (range) since starting ART, years	10.5 (3–23.5)
Median previous ARV regimens (range), n	7.5 (4–16)
Median nadir CD4+ count (range), cells/mm ³	169.5 (30–417)
AIDS diagnosis ^a , n	5
Median length VL <50 copies/ml pre-BL (range), years	4 (0.5–10)

ARV = Antiretroviral.

^a AIDS-defining illnesses recorded in the study: oesophageal candidiasis (1/20, 5%), cryptosporidiosis (1/20, 5%), cerebral toxoplasmosis (1/20, 5%), *Pneumocystis jiroveci* pneumonia (1/20, 5%), disseminated CMV infection (1/20, 5%), pulmonary tuberculosis (1/20, 5%), Kaposi's sarcoma (1/20, 5%).

Table 2. Antiretroviral combinations received immediately prior to switching to an MVC-containing regimen

HAART regimen before BL	Patients n (%)	Median ART regimen duration (range) months
2 NRTIs + LPV/r	5 (25)	39 (10–62)
2 NRTIs + ATV/r	4 (20)	20.5 (9–52)
DRV/r ^a	3 (15)	1 (1–8)
2 NRTI + DRV/r ^a	1 (5)	24
4 NRTIs + DRV/r ^a	1 (5)	6
2 NRTIs + T20 + DRV/r ^a	1 (5)	32
2 NRTIs + LPV/r + SQV	1 (5)	35
2 NRTIs + SQV/r	1 (5)	40
2 NRTIs + FPV/r	1 (5)	18
2 NRTIs + NVP	1 (5)	2
RAL + ATV	1 (5)	3

NRTIs comprised TDF, FTC (9/20, 45%); ABC, 3TC (1/20, 5%); ABC, 3TC, zidovudine, TDF (1/20, 5%); TDF either alone (1/20, 5%) or in combination with 3TC (2/20, 10%) or ABC (1/20, 5%); didanosine, 3TC (1/20, 5%).

ABC = Abacavir; ATV/r = atazanavir/ritonavir; FPV/r = fosamprenavir/ritonavir; HAART = highly active antiretroviral therapy; NRTIs = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; RAL = raltegravir; SQV/r = saquinavir/ritonavir; 3TC = lamivudine; T20 = enfuvirtide.

^a 800 mg DRV and 1000 mg ritonavir were administered once daily in 5 out of 5 patients on DRV treatment.

Fig. 1. Clonal and clinical FPR values of patients at BL. Data were available in 19 patients. In 11 patients, GTT were performed and tropism predicted using clonal and clinical FPR cutoffs of 6 and 15%, respectively. In 8 patients, GTT were performed and tropism predicted using a clonal FPR of 15% alone, due to the absence of clinical data including nadir CD4 counts and percentages.

darunavir (DRV/r) in 10/20 (50%) patients, including 7/20 (35%) patients who received dual therapy with MVC + DRV/r alone. Nine out of 20 patients were not on a boosted protease inhibitor (PI) regimen (table 3).

The determining factors to decide to switch to MVC-CR included problems of drug toxicity and tolerability, low CD4 cell counts and ART simplification (table 4).

The genotypic sensitivity score of the MVC-CRs (MVC excluded) was 1.75 (range: 1–3).

Changes in median (range) laboratory values at T1 and T2 are summarized in table 5. Compared to BL, no statistically significant changes in the laboratory values were seen at T1. Findings were confirmed at T2, with a slight reduction of –0.2 mmol/l (range –3.5, +0.7, $p = 0.12$) in tryglyceride levels from BL to a median level of 1.3 mmol/l at T2.

At T2, all 20 patients enrolled in the study had a VL <50 copies/ml. One patient who received MVC with darunavir 800 mg and ritonavir 100 mg once daily experienced a transient VL rebound to 549 copies/ml during 6 months of follow-up when he spontaneously discontinued therapy, but regained viral suppression after restarting the same regimen.

Gastrointestinal disorders were reported by 6 patients prior to BL, 4 of them on a previous regimen containing lopinavir/ritonavir (LPV/r); all these restrictions were resolved at T2.

Fig. 2. Levels of soluble CD30 in plasma measured longitudinally at 3 time points in treated patients with suppressed VL before and after switching to MVC-based therapy.

MVC was discontinued in 3/20 (15%) patients due to severe headache, chronic fatigue and VL rebound at 3, 6 and 4 months after switching, respectively. The patient who experienced VL rebound showed a VL of 154 copies/ml 4 months after switching to a MVC, DRV and ritonavir-containing regimen; a genotypic resistance test was unable to amplify the target sequence. The patient switched to efavirenz, DRV and ritonavir treatment, and achieved VL suppression within 1 month. The other 2 patients maintained a suppressed VL on DRV/r monotherapy and tenofovir (TDF), emtricitabine (FTC), DRV/r and enfuvirtide, respectively.

Soluble CD30

Changes in plasma sCD30 levels between BL, T1 and T2 in patients with a suppressed VL at BL following the commencement of MVC are shown in figure 2.

Plasma sCD30 measurement was performed on 15 points with stored plasma samples. A median decrease in sCD30 at time point T1 of 8.22 ng/ml (interquartile range: 0.84–48.77) compared to BL ($p = 0.027$) was observed (fig. 2). This response was sustained at T2, where a median decrease in plasma sCD30 of 12.80 ng/ml (interquartile range: 3.85–53.13) compared to BL ($p = 0.001$) was seen. A reduction in sCD30 at both T1 and T2 appeared to be maximal in those patients with very high levels of T cell activation prior to MVC therapy, namely the sub-cohort of patients with BL sCD30 levels above the 25th percentile.

Table 3. MVC-containing regimens at BL

Regimen	Patients, n
DRV 800 mg + RTV	7
TDF + FTC	4
ABC + 3TC	2
3TC + DRV 800 mg + RTV	1
TDF + FTC + DRV 800 mg + RTV	1
DRV 600 mg b.i.d. + RTV	1
TDF + DRV 800 mg + RTV	1
3TC + ATV	1
TDF + 3TC + NVP	1
TDF + 3TC	1

In 6 of these patients the dosage of DRV/RTV was 800/100 mg once daily and 1 patient was given 600/100mg b.i.d. MVC dosage was 150 mg b.i.d. in 4 patients, 150 mg once daily in 2 patients and 300 mg once daily in 1 patient, respectively.

Of 8 patients on treatment with MVC + 2 NRTIs, the NRTIs used comprised TDF + FTC (5/20, 25%), TDF + 3TC (1/20, 5%) and ABC + 3TC (2/20, 10%), respectively. In 7/8 patients on 2 NRTIs, MVC was administered at the standard dose of 300 mg b.i.d. However, in the patient on TDF + 3TC, MVC was administered at a dosage of 600 mg once daily.

One patient (1/20; 5%) was on an ATV-containing treatment and one was on an NVP-based regimen. In these patients, MVC dosage was 150 mg and 300 mg b.i.d., respectively, as licensed.

During follow-up, 2 patients changed their backbone treatment from ABC to DRV/RTV and from ATV to fosamprenavir because of an onset of unspecified multiple lesions in the CNS and renal stone formation, respectively.

ABC = Abacavir; ATV = atazanavir; NRTIs = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; RTV = ritonavir; 3TC = lamivudine.

Table 4. Factors determining the switch to a MVC-containing regimen

Reason for switching	Patients	
	n	%
Dyslipidaemia	4	20
Gastrointestinal disorders	4	20
Renal dysfunction	2	10
ART simplification	2	10
Low CD4 count	1	5
Diarrhoea and fatigue	1	5
Diabetes and dyslipidaemia	1	5
Cutaneous rash	1	5
Dyslipidaemia, diarrhoea and renal dysfunction	1	5
Headache and dysthymia	1	5
Diabetes, dyslipidaemia, chronic renal impairment, ischaemic heart disease and hypertension	1	5
Ischaemic heart disease, dyslipidaemia and hypertension	1	5

Table 5. Laboratory values (range) at BL, T1 and T2

Laboratory marker	Median value at BL	Median value at T1	Median change from BL to T1	p value	Median value at T2	Median change from BL to T2	p value
Total cholesterol, mmol/l	5.2 (3.2–11.4)	5.2 (3.1–7.0)	–0.10 (–5.5, +1.4)	0.61	5.2 (3.2–7.1)	+0.1 (–4.30, +1.2)	0.59
HDL, mmol/l	1.3 (0.7–2.5)	1.3 (0.8–2.7)	0.0 (–0.9, +1.4)	0.97	1.4 (0.8–2.1)	0.0 (–0.8, +0.5)	0.93
LDL, mmol/l	3.2 (1.6–9.2)	3.1 (1.4–4.8)	–0.2 (–5.0, +0.6)	0.19	3.2 (1.6–5.1)	+0.05 (–4.1, +1.0)	0.85
Triglycerides, mmol/l	1.55 (0.6–5.7)	1.3 (0.7–6.0)	–0.1 (–4.7, +3.0)	0.11	1.3 (0.8–4.6)	–0.2 (–3.5, +0.7)	0.12
Creatinine, mmol/l	89 (61–909)	92 (59–175)	–2 (–735, +26)	0.49	90 (58–152)	–1 (–757, +16)	0.48
eGFR, ml/min	74 (47–87)	74 (23–90)	0 (–24, +6)	0.90	73 (33–88)	–1.5 (–14, +13)	0.54
ALT, IU/l	37 (16–77)	26 (10–128)	–4 (–55, +93)	0.90	30 (11–113)	+2 (–62, +73)	0.73
AST, IU/l	28 (13–58)	30 (14–79)	–1 (–28, +39)	0.77	27 (15–67)	0 (–31, +32)	0.97
Glucose, mmol/l	5 (3.7–16.9)	4.9 (4.2–15.5)	0.0 (–1.4, +1.9)	0.72	4.8 (3.6–8.2)	0 (–8.7, +3.0)	0.77
CD4, cells/mm ³	557 (287–1,446)	556 (263–1,314)	–7 (–690, +499)	0.63	595 (363–960)	39 (–698, +290)	0.96
CD4, %	28 (16–50)	26.5 (19–39)	0 (–24, +6)	0.41	28 (16–43)	0 (–11, +7)	0.81

eGFR = Estimated glomerular filtration rate.

Discussion

An R5 virus tropism test is recommended prior to the introduction of MVC therapy by British and American HIV treatment guidelines. The use of MVC was initially limited in part by the need to perform a phenotypic test available exclusively in the USA (Trofile), and required a VL >1,000 copies/ml. In recent years, several studies have demonstrated reliable prediction of HIV-1 tropism from envelope V3 loop sequence analysis [11, 14, 15]. GTT is now endorsed by European guidelines, as it offers greater accessibility, lower cost, performance at lower copy number and faster turnaround time than centralized phenotypic testing [16].

Despite the good efficacy and tolerability profile of MVC, and the potential for a favourable impact on CD4 cell count and inflammatory markers [4], the requirement for tropism testing initially hampered the usage of MVC in patients with suppressed viral replication. Two strategies have been suggested to circumvent this problem: the analysis of stored plasma HIV-1 RNA collected prior to suppression, or the use of proviral DNA obtained from PBMCs [11, 16]. While data indicate that viral tropism seldom changes during suppressive ART, stored plasma is not always readily available. Thus, the option of testing proviral DNA in patients with suppressed viraemia would facilitate the use of CCR5 inhibitors as part of switching, simplification or treatment intensification strategies [17]. Recent studies demonstrated a good correlation between tropism predictions from proviral DNA

and results derived from viral RNA, although data from large cohorts and the overall clinical utility of this assay are still to be determined [12].

Our study population, although small, demonstrated a good virological response following a switch of suppressive ART to a MVC-CR. Overall 18/20 patients maintained virological suppression: in one case a transient rebound was observed when the patient spontaneously discontinued therapy, followed by resuppression on the same regimen. The second patient showed a rebound 4 months after switching from TDF, LPV/r and saquinavir to dual MVC-DRV/r therapy; the patient subsequently switched treatment to a DRV and etravirine-based regimen, and regained viral suppression. The observation that 90% of the study population maintained a VL below 50 copies/ml after switching to a MVC-CR, with a median genotypic sensitivity score of the accompanying therapy of 2 and in the absence of a ritonavir-boosted PI in 9/20 patients, provides initial support for using proviral DNA to assess viral tropism. Further controlled studies are warranted.

We observed good tolerability of MVC with an improvement of gastrointestinal disorders following a switch from a ritonavir-boosted PI. Headache and fatigue which led to MVC discontinuation in 2 of our patients are described as possible side effects of MVC intake; after discontinuation, the patients reported complete resolution.

Based upon the hypothesized immunomodulatory properties of MVC in terms of its potential capability of

assisting CD4+ count recovery [5], several studies have investigated ART intensification strategies using MVC [18, 19]. Results have been variable. A study conducted by Rusconi et al. [19] showed reduction of T cell CD4+ and CD8+ activation and proliferation. In contrast, a recent study by Hunt et al. [20] showed an increase in CD4 and CD8 T cell activation in the gut and peripheral blood of patients on a MVC intensification regimen.

In our cohort, we observed a statistically significant decrease in plasma levels of sCD30, a marker of T cell activation, when comparing BL values with those at months 2 and 6 after commencing MVC. BL values have been evaluated in patients on triple antiretroviral treatment with no MVC experience; therefore, we can consider them as control data for a comparison with CD30 values collected 2 and 6 months after introducing MVC. As all the patients had suppressed VL at BL, it may be proposed that the observed decline was specific to the introduction of MVC in therapy rather than being reflective of the suppression of viral replication. This is consistent with a possible role for MVC in modulating immune function and cellular activation independently of its antiviral effect. Of

particular note, those patients who showed the largest decreases in plasma sCD30 had BL sCD30 levels within the upper 25th percentile. Although our patient cohort was relatively small, the data presented here suggest that suppression of T cell activation may be an important aspect of the activity of MVC; this warrants investigation in a controlled study.

This data set was not large enough to correlate the degree of decline in sCD30 with changes in CD4 cell count, which could potentially indicate a role for sCD30 measurement in those patients with low CD4+ cell counts despite successful viral suppression.

Dual therapy MVC and DRV/r was the most frequent regimen prescribed by physicians in London at the Royal Free Hospital in 2010 for treatment-experienced patients with severe side effects: new-generation drug combinations are preferred due to their demonstrated good tolerability. Further investigations and a longer time of follow-up will help to clarify the efficacy of this combination.

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