Off-label use of maraviroc in HIV-1-infected paediatric patients in clinical practice

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Maraviroc (MVC) is not approved for HIV-1-infected paediatric patients. This is the first assessment of the use of MVC-based salvage therapy in vertically HIV-1-infected paediatric patients in clinical settings. The results suggest that MVC-based salvage therapy is useful in children and adolescents with extensive resistance profile leading to maintained virological suppression in up to 88% of the patients with CCR5-tropic virus. The likelihood of treatment success might increase when MVC is combined with other active drugs.

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Introduction

Long-term survivors of vertically acquired HIV-1 infection have to deal with a range of issues associated with the transition to adolescence that may hinder compliance to antiretrovirals [1,2]. In addition, overcoming extensive drug resistance might limit future treatment options in these patients. Maraviroc (MVC)

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(Celsentri/Selzentry: ViiV Healthcare, Brentford, UK) is currently the only C-C chemokine receptor type five (CCR5) antagonist [3] approved for clinical use in HIV-1-infected adults carrying the CCR5-tropic virus [4–7]. In addition, new therapeutic strategies such as highly active antiretroviral therapy (HAART) intensification based on MVC were recently evaluated for HIV-1-infected individuals with suboptimal $CD4^+$ T-cell recovery [8,9]. MVC-based HAART intensification may also reduce the latent HIV-1 reservoir in memory T cells in chronically HIV-1-infected patients [10,11]. Finally, promising research indicates MVC as a suitable option for HIV-1-infected individuals with severe comorbidities [12,13]. MVC is not approved for paediatric patients and is currently under evaluation in CCR5-tropic HIV-1-infected treatment-experienced children aged 2–17 years [14–16]. To our knowledge, this is the first study designed to evaluate the use of MVC-based salvage HAART in treatment-experienced paediatric patients with previous virological failure.

This is a multicenter retrospective study of vertically HIV-1-infected patients included in the Cohort of the Spanish Paediatric HIV Network (CoRISpe) who were treatment-experienced and started MVC-based HAART (combination of three or more drugs) under the Spanish compassionate use programme [17]. Individuals were monitored from baseline (i.e. the date of MVC initiation) until the administrative censoring date (31 May 2014) or MVC discontinuation, if occurred. Testing for viral tropism was performed by phenotypic assays (Trocai [18] and Trofile [19]; Monogram Biosciences, San Francisco, California, USA) or the genotypic test Geno2pheno (Max Planck Institute, Saarbrücken, Germany) [20], based on population sequencing of the V3 region, according to the Spanish guideline of tropism testing [21]. MVC was administered in tablet formulation and doses ranged from 100 to 300 mg twice daily for children (2–12 years old) and 150–600 mg twice daily for adolescents (13–19 years old), according to body weight and co-medications. Optimized background therapy was based on published guidelines [17,22,23]. Plasma viral load (HIV-1 RNA) was measured by Amplicor Monitor assay (Roche Diagnostic Systems Inc., Branchburg, New Jersey, USA) and real-time NASBA (Easy Mag y Nuclisens Easy Q; BioMerieux, Marcy l'Etoile, France) with a detection limit of 50 copies/ml (undetectable viral load, uVL). Virological failure was defined as the inability to achieve or maintain suppression of viral replication to a viral load less than 50 copies/ml. Resistance genotyping was obtained with the Trugene HIV Genotyping Kit (Siemens Healthcare Diagnostics Inc., Tarrytown, New York, USA) assay and the analysis of drug resistance was based on the Stanford University HIV Drug Resistance Database. Major mutations from the IAS-USA mutation list 2014 were used to define resistance [24]. Ethical approval for the survey was obtained from the Ethical Committees of all hospitals and informed consent was obtained from parents or guardians.

Six children and 14 adolescents born between 1991 and 2001 were enrolled [median age: 15.1 (12.9–16.3)]. Patients mainly harboured HIV-1 subtype B strains (85%). Sixteen (80%) had confirmed CCR5 tropism by Trofile (11/16), Trofile and Trocai (1/16), and Geno2pheno (4/16); one had dual/mixed-tropic variant by Trofile and three had not reportable tropism data by Trofile. At baseline, patients had been exposed to HAART for a median of 10.5 (interquartile range, IQR: 9.4–12.8) years. Fifteen (15%) had also received monotherapy and/or dual therapy for 2.0 (1.2–3.0) years. Baseline resistance profiles were available for 19 patients and revealed a median of three major protease inhibitor (PI) mutations, two nonnucleoside reverse-transcriptase inhibitors mutations, and five nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) mutations (see supplementary file SDC1, http://links.lww.com/QAD/A777). Ten (53%) patients showed high-level resistance to at least five NRTIs and 10 (53%) had high-level triple-class antiretroviral resistance. At least one fully active drug was prescribed to 18 (95%) patients as backbone, of whom 17 (94%) received MVC with one or more new drugs. HAART included raltegravir in six (30%) patients, and boosted darunavir with raltegravir or etravirine in four (20%) individuals. A total of 11 participants received MVC with a potent CYP3A4 cytochrome inhibitor (PI-based regimens). At baseline, median viral load and $CD4^+$ cell count were 9925 (1565–68 620) copies/ml and 382 (191–662) cells/μl (22.0%), respectively. Five patients presented severe immunosuppression and half of the study population had a clinical stage C.

The median follow-up with MVC-based treatment was 115.6 weeks (25.1–198.2). Fourteen (70%) patients were exposed for at least 54 weeks. Sixteen (80%) patients reached uVL [(median at 12.6 weeks, (5.2–35.5)] with a median viral load decrease of 1.7 $\log_{10}$ (see supplementary file SDC1, http://links.lww.com/QAD/A777). Twelve out of 16 maintained uVL for a median of 105 weeks (IQR: 44–208) of which nine of 12 (75%) patients maintained uVL until the end of the follow-up for a median of 131.6 weeks (50.4–230.1). Among the 16 patients who achieved uVL, two experienced virological failure during the follow-up. Among patients with confirmed R5 tropism, 14/16 (88%) reached uVL [(median at 18.1 weeks, (IQR: 5.5–38.5)] with a median viral load decrease of 1.7 log; 11/16 (69%) maintained uVL for 120.1 weeks (IQR: 49.4–227.6).

Regarding the response to MVC in the patients who did not have tropism data before initiate MVC, a child reached uVL at 2 weeks of follow-up, experiencing a decrease in HIV-1 RNA from baseline of 1.7 log and immunological improvement with an increase of $CD4^+$ cell count of 1000 cells/μl. The antiretroviral regimen

Table 1. Outcome of the use of maraviroc in the study population.

Measurement	Values
Weeks of MVC regimen; median (IQR)	115.6 (25.1–198.2)
Responders (HIV-1 RNA <50 copies/ml)	16 (80%)
Maintained	14 (70.0)
Not maintained	2 (10.0)
HIV-1 RNA copies/ml; median (IQR)	50 (37–7468)
$CD4^+$ cell count, cells/μl; median (IQR) ($N=19$)	558 (429–880)
$CD4^+$ percentage, cells/μl; median (IQR) ($N=18$)	27.3 (23.2–32.1)
$CD8^+$ cell count, cells/μl; median (IQR) ($N=17$)	848 (560–1057)
$CD8^+$ percentage, cells/μl; median (IQR) ($N=17$)	42.6 (36.4–53.6)
Adherence; *n* (%)	
Complete	4 (20.0)
Good	9 (45.0)
Moderate	2 (10.0)
Poor	5 (25.0)
Laboratory data	
Hypercholesterolemia (>170 mg/dl)	9 (45.0)
Hypertriglyceridemia (>150 mg/dl)	12 (60.0)
HDL reduction ($N=12$) (<45 mg/dl)	1 (8.3)
ALT increase ($N=19$)*	4 (21.1)
AST increase ($N=17$)*	–
Comorbidities	
Iron deficiency anaemia	1 (5.0)
Acute bronchitis	1 (5.0)
Urinary tract infection	1 (5.0)
Cause of MVC interruption	
Death	2 (10.0)
Simplification	3 (15.0)
Virological failure	1 (5.0)
X4 or D/M variants emergence	3 (15.0)
Poor adherence	1 (5.0)
Underlying cause of death ($N=2$)	
Hypertensive cerebral haemorrhage	1 (50.0)
Wasting syndrome	1 (50.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; D/M, dual/mixed-tropic variants; HDL, high-density lipoprotein; MVC, maraviroc; X4, CXCR4-tropic variants.
*ALT and AST increases were classified according to the following references: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l40_c_met_aspartate_aminotransferase.pdf and http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/biopro_d_met_alt.pdf.

was modified in this patient for simplification. The second child with good HAART compliance experienced an increase of 0.5 $\log_{10}$ in HIV-1 RNA. This patient had a long-term exposure to bitherapy before MVC initiation and did not receive any fully active drug in combination with MVC (stavudine, abacavir). He experienced immunological benefit ($CD4^+$ cell count: Δ314 cells/μl; Δ4.4 CD4%) over a follow-up of 3 weeks, when MVC was discontinued because of poor response to treatment. The third patient was coinfected with hepatitis B virus. She reached uVL at 11 weeks of follow-up but experienced viral failure thereafter mainly caused by a lack of treatment compliance.

Immunological improvement was experienced by 11/16 (69%) responders who achieved uVL, with a median increase of $CD4^+$ cell count of Δ223 cells/μl (130–455). Of those, three had a recovery above 500 cells/μl, three maintained $CD4^+$ cell count more than 500 cells/μl, whereas only one had $CD4^+$ cell count less than 200 cells/μl at the end of follow-up. On the contrary, 5/16 (31%) responders experienced a median decrease of Δ124 cells/μl (72–207), with all but one maintaining $CD4^+$ cell count more than 400 cells/μl at the end of follow-up. Among no responders, three patients experienced immunological benefit with increase of 200–300 cells/μl at 1 month of follow-up, whereas one experienced immunological failure with a decrease of Δ208 cells/μl. The evolution of coreceptor tropism was observed in three patients with virological failure, two of them were no responders (did not achieve uVL) and the third achieved uVL at week 29 but did not maintain low HIV-1 RNA levels over time. The first no responder had a tropism switch from R5 to D/M-tropic variants and the second had a switch from R5 to X4; the patient with virological failure had a switch from R5 to X4 variants. They were all tested using the Trofile assay. Mild laboratory abnormalities were reported (Table 1), whereas two adolescents died during follow-up. Underlying causes of dead, HAART adherence and cause of MVC discontinuation are summarized in Table 1.

Together, our data indicate that MVC has a favourable safety profile and is useful as salvage therapy in paediatric patients with confirmed R5 tropism and extensive resistance profile. The virological response achieved on average at the third month of follow-up was durable and, allowing for the limitations of cross-study comparisons, is in agreement with the response rates observed in the interim data of the ongoing MVC A4001031 trial [15–16]. The likelihood of the treatment's success might increase when MVC is combined with other active drugs. However, the high presence of CXCR4-tropic variants observed previously in HIV-1-infected paediatric patients [25] compared with adults may limit the use of CCR5 antagonist family in those patients. Moreover, despite our study did not allow to assess the possible impact of the type of tropism assay on the response to MVC, being the majority of the patients tested by Trofile, it is important to stress the possible association of virological failure of MVC with outgrowth of D/M or X4 virus from preexisting minority population present at levels below the limit of assay detection. Overall, these findings contribute to furthering scientific knowledge on treatment options for children and adolescents.

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Conflicts of interest

The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. The authors have no commercial or other association that might pose a conflict of interest.

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