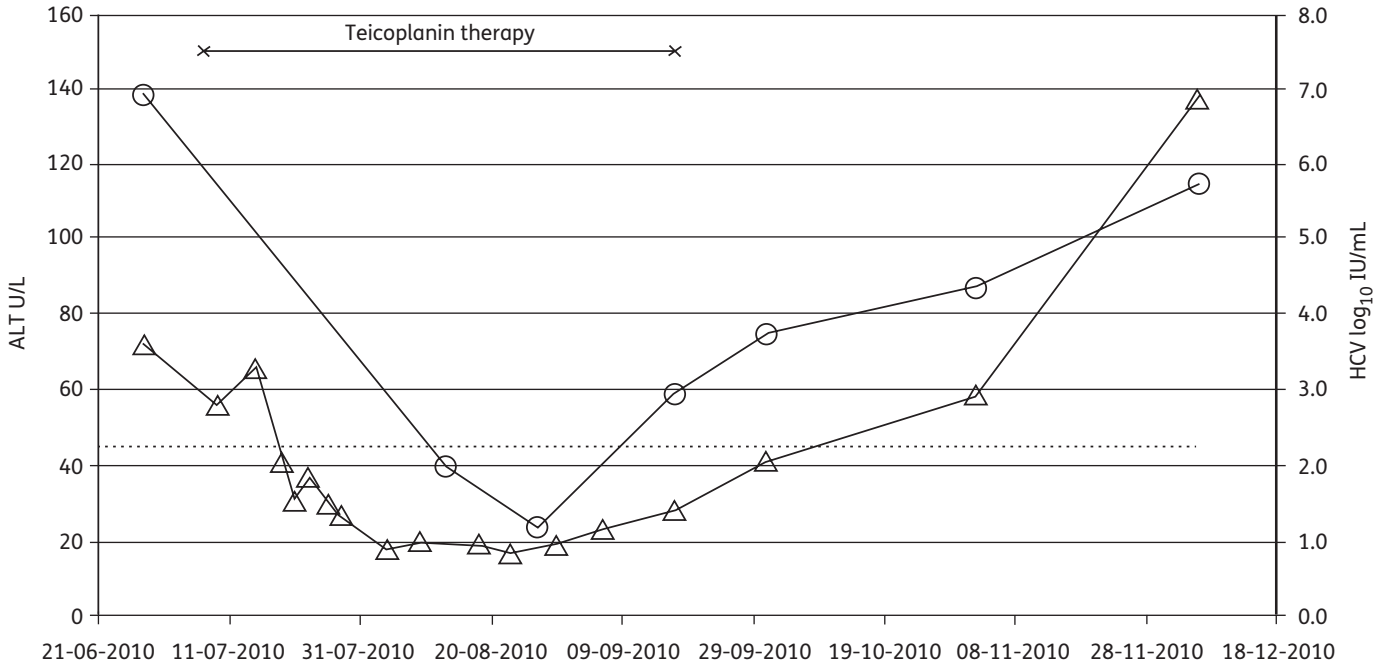

Figure 1. Hepatitis C virus (HCV) load and alanine aminotransferase (ALT) levels during and after teicoplanin therapy. Open circles, HCV load. Open triangles, ALT levels (the horizontal broken line corresponds to the upper level of the normal range).

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

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J Antimicrob Chemother 2012
doi:10.1093/jac/dks240
Advance Access publication 22 June 2012

Long-term maraviroc use as salvage therapy in HIV-2 infection

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Keywords: CCR5 antagonists, HIV-2 CCR5 tropism, therapeutic drug monitoring, second-line HIV-2 therapy, persistent low CD4 cell count

Sir,

Maraviroc is a chemokine CCR5 coreceptor antagonist that is currently used in treatment-experienced R5-tropic HIV-1-infected patients. Despite the fact that very few data are available on this new antiretroviral drug in HIV-2 infection, *in vitro* maraviroc activity against R5 HIV-2 has very recently been shown.[1,2] However, the clinical usefulness of maraviroc in HIV-2 infection

is a generally unaddressed issue.[3,4] Indeed, as Peterson and Rowland-Jones[5] have recently highlighted, long-term data on maraviroc HIV-2 treatment are required. In order to provide insight into this new topic, we report on the long-term successful control of viral replication, using maraviroc-based salvage combined antiretroviral therapy (cART), in an HIV-2-infected patient.

Herein we report the clinical case of a patient diagnosed HIV-2 positive in April 2005. At that time, a viral load test was not available for HIV-2 RNA and the CD4 cell count was 41 cells/mm^3 (6%). The patient received a protease inhibitor-based cART including lopinavir/ritonavir plus abacavir and lamivudine. Also, co-trimoxazole for *Pneumocystis jiroveci* pneumonia prophylaxis and valganciclovir for herpes simplex virus prophylaxis were prescribed. However, due to intolerance and consequent poor adherence to lopinavir/ritonavir, this was replaced by atazanavir/ritonavir. Six months later, and despite the persisting poor immunological status [CD4+ cell count of 118 cells/mm^3 (17%)], the HIV-2 RNA was <200 copies/mL. Nevertheless, a few months later, the patient experienced treatment failure [CD4 count of 94 cells/mm^3 (15%) and HIV-2 RNA of 87 348 copies/mL]. According to the existing knowledge at the time, the subsequent cART was protease inhibitor double-boosting with atazanavir and saquinavir. In September 2007, a genotypic resistance test became available and viral susceptibility was found to zidovudine, stavudine and tenofovir. Also, resistance mutations for saquinavir and nelfinavir were found. The selected treatment regimen was zidovudine/lamivudine, tenofovir and indinavir. Eight months later, raltegravir (400 mg twice daily) plus ritonavir-boosted darunavir (600/100 mg twice daily) replaced indinavir and, once renal function started declining, tenofovir was also suspended. According to genotyping analysis, zidovudine/lamivudine was continued. Further, 1 year later, the viral load was undetectable in spite of low CD4 count maintenance. In May 2009, the patient reported non-specific worsening of her general condition and poor adherence to the drug regimen. The HIV-2 viral load was 4275 copies/mL and the CD4+ count was 111 cells/mm^3 (13%). A genotyping test revealed high-level resistance codons to nucleoside reverse transcriptase inhibitors (Q151M and M184V) and to protease inhibitors (I54M, I64V, L90M, L99F). Even though it was not tested, it was considered possible that resistance to raltegravir was also present, given the even lower HIV-2 genetic barrier for this integrase inhibitor. In October 2010, an investigational tropism test was performed,[1] and a combination of tenofovir (325 mg once daily), boosted darunavir (600/100 mg twice daily) and maraviroc (150 mg twice daily) was selected. Presently, the patient is virologically suppressed (HIV-2 RNA <40 copies/mL) with a low but stable CD4 count [CD4=162 cells/mm^3 (15.8%)].

While clinical trials to establish optimal maraviroc doses in HIV-2 infection are urgently needed, it should be emphasized that subtherapeutic dosages might promote the selection of X4 variants, which in HIV-2 infection has been associated with CD4 depletion, disease progression[6] and resistance to neutralization.[7]

An understanding of the pharmacokinetic/efficacy relation for maraviroc in the clinical setting, even in the context of HIV-1 infection, is limited as this drug has only recently become available. Moreover, maraviroc is a CYP3A4 substrate with high interpatient variation in its exposure and high potential for drug–drug interactions; therefore, therapeutic drug monitoring of this CCR5 antagonist has been advised. Maraviroc antagonist potency is higher in HIV-1 than in HIV-2, as well as in asymptomatic patients as opposed to those with advanced disease.[1] Furthermore, CD4 depletion in HIV-2 infection is associated with a higher frequency of memory CD4 T cells expressing CCR5.[8] This increased resistance in advanced disease might imply different dosage requirements depending on the disease stage or dose escalation on a CD4 cell count basis. This argues for tropism tests along with phenotypic resistance tests and therapeutic drug monitoring in order to ensure a fully active maraviroc-based cART. Also, we highlight the need for randomized clinical trial data, to properly guide therapy in HIV-2 infection.

Ethics

All patient-related information contained herein has the informed consent of the patient.

Acknowledgements

We are thankful to Mr Michael Bright for reviewing the English.

Funding

No specific funding has been received for this study. Data have been generated as part of the routine work of Centro Hospitalar de Lisboa Central (CHLC) and Centro de Estudos de Doenças Crónicas (CEDOC).

Transparency declarations

None to declare.

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