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GAVIN PUBLISHERS

Annals of Case Reports

Weimer LE, et al. Ann Case Reports 10: 215.

Case Report

DOI: 10.29011/2574-7754/100215

No Progression of Recurrent Coinfection and Cardiovascular Disease in a HIV-1 Patient with Long-Term Experience of Maraviroc. Limited Side Effects

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Citation: Weimer LE, Brescini L, Cirioni O, Morroni G, Giacometti A (2019) No Progression of Recurrent Coinfection and Cardiovascular Disease in A HIV-1 Patient with Long-Term Experience of Maraviroc. Limited Side Effects. Ann Case Reports 10: 215. DOI: 10.29011/2574-7754/100215

Received Date: 01 April, 2019; **Accepted Date:** 29 April, 2019; **Published Date:** 08 May, 2019

Background

Since the registration of Maraviroc (a small molecule and the first oral CCR5 receptor antagonist class) as antiretroviral agent in 2007, only studies with a follow-up time shorter than five years were published. Therefore, little is known about its long-term safety and efficiency in clinical practice. In this Case Report study, data on long-term follow-up of MVC-treatment in routine practice was analysed. Maraviroc, used in the treatment of HIV infection and it has proven potent efficacy in treatment-experienced patients with multiple drug failure. This drug classed as an entry inhibitor, was developed by the drug company Pfizer in its UK labs located in Sandwich.

On April 24, 2007 the U.S. Food and Drug Administration advisory panel reviewing Maraviroc's New Drug Application unanimously recommended approval for the new drug [1], and the drug received full FDA approval on August 6, 2007 for use in treatment experienced patients. Maraviroc is extensively metabolized by CYP3A4, with renal clearance accounting for approximately 23% of total clearance and has been shown to achieve an undetectable HIV-1 RNA level in clinically advanced, class three antiretroviral treatment-experienced adults with evidence of CCR5-tropic HIV-1 replication despite ongoing antiretroviral therapy. It is well tolerated and its development is responding to a desperate need for new classes of antiretroviral agents that can target novel steps of the HIV lifecycle and do not share cross resistance with currently available therapy [2]. This CCR5 receptor antagonist reviews clinically relevant pharmacological, long term therapeutic efficacy.

Our case report aims to explain the impact of Maraviroc co-administered with agents from all classes of antiretroviral therapy in a HIV-1 experienced patient along seven years of antiretroviral experience with recurrent coinfection and cardiovascular disease.

Keywords: HIV-1 infection; HCV coinfection; Limited side effects; Long-term Maraviroc observation

Case Description

Our patient, female, heterosexual 54-years-old, Italian, with HIV-1 infection diagnosed in September 1995, coinfected HCV genotype 4a (in Mars 1991 for screening), presenting in the Hospital of Ancona (October 2011) with CD4 count of 110 cells/µl, HIV-RNA 2604 cp/ml (detection limit 50 copies/ml) and multidrug resistance, hepatitis C diagnosis and cardiovascular disease -examinations for body mass index, diastolic blood pressure and blood testing (C-reactive protein, fibrinogen, triglycerides, total cholesterol, high-density and low-density lipoprotein cholesterol, fasting glucose), abnormal ECG, clinical symptoms.

Our patient has a long antiretroviral therapy experience with severe side effects (in 1995 zidovudine (AZT) + didanosine (ddI), in 1997stavudine d4T+ lamivudine 3TC + saquinavir-suspended per cutaneous rash-in 1999 stavudine d4T + lamivudine 3TC + nelfinavir – suspended for a sustained increase of viral load, in 2000 zidovudine (retrovir) + didanosine (videx 250 mg) + INN-saquinavir (fortovase 500 mg) + ritonavir (norvir) – suspended for gastrointestinal disease; in 2003 trizivir (zidovudine 300 mg + abacavir 300 mg + lamivudine (3TC 150 mg) – suspended for low compliance; in 2006 fosamprenavir (telzir) + truvada (emtricitabine 200mg/tenofovir desoxopril fumarate 250 mg) – suspended for drug intolerance).

In October 2011, she started raltegravir (issentress) + nevirapina (viramune) with low compliance. At time of admission in our Department of Infectious Diseases laboratory analysis are: AST 19 IU/ml (reference range, 1-36 IU/l), ALT 23 IU/ml (reference range, 1-36 IU/l), total bilirubin 0.4 mg/dl, triglycerides 252 mg/dl, total cholesterol 269 mg/dl, HDL cholesterol 59 mg/dl, creatinine 0.70 mg/dl, glycaemia 82 mg/dl without history of insulin resistance, hypocomplementemia. Her multidrug-resistance profile at baseline for a new antiretroviral treatment is (test TRUGENE HIV-1): protease inhibitor mutations V82A, L90M, L10V, K20R, L33F, M36I, M46I, G48V, I54T, L63P, A71V, V77I, V82I, I84V. High level resistance to 3TC, AZT, d4T, FTC. The patient after HCV diagnoses (1995) has been eleven years with signs and symptoms of hepatic diseases and abnormal hematological and viroimmunological parameters.

In October 2011 chronic active hepatitis has been diagnosed after hepatic Biopsy-Stadium II A1 Metavir and Fibroscan 9. In this moment without the DAA, the choice for this patient has been Pregintron80 mg + rebetol 1000 mg for 12 months with SVR after therapy but with a severe increase of cardiovascular disease (abnormal ECG, body mass index, diastolic blood pressure and blood testing (C-reactive protein, fibrinogen, triglycerides, total cholesterol, high-density and low-density lipoprotein cholesterol, fasting glucose).

In January 2012 she started to antiretroviral therapy with Maraviroc + Truvada (emtricitabine 200 mg) + tenofovir disoxopril fumarate 250 mg) attended clinic regularly and reported good treatment adherence with limited side effects. During subsequent follow up and after seven years of Maraviroc therapy our patient has been maintaining good clinical conditions (no recurrent HCV and no progression of cardiovascular disease) with an optimal compliance to HAART regimen and limit side effects. In December 2018 biochemical, hematological and viroinmunological parameters have demonstrated a good response to Maraviroc, good compliance without, drugs resistance and side effects: CD4 T-cell count of 1225 cell/mm^3 and undetectable plasma HIV RNA concentration (detection limit 50 copies/ml), total bilirubin 0.50 mg/dl, triglycerides 153 mg/dl, total cholesterol 279 mg/dl, HDL cholesterol 52 mg/dl, creatinine 0.80 mg, glycemia 73 mg/dl ALT concentration to 22 IU/l and AST 17 IU/l (reference range, 1-36 IU/l) and clinic and blood parameters of cardiovascular disease have decreased (normal diastolic blood pressure, C-reactive protein, fibrinogen)

Currently, after a long Maraviroc experienced-seven years-laboratory examination and objective examination reveals a very important reduction hepatic signs and symptoms with fibroscan F0 and an increased rate of platelet (July 2018 208000 cell/mm^3, January 2019 292000 cell/mm^3), AST 14 IU/I, ALT 16 IU/l (reference range, 1-36 IU/l). In February 2019: CD4 T-cell count of 626 cell/mm^3 and undetectable plasma HIV RNA concentration (detection limit 50 copies/ml), AST 17 IU/ml, ALT 19 IU/ml, total bilirubin 0.5 mg/dl, triglycerides 132 mg/dl, total cholesterol 200 mg/dl, HDL cholesterol 72 mg/dl, creatinine 0.85 mg, glycemia 81 mg/dl. This case demonstrates that MARAVIROC in combination with TRUVADA in a patient with a complicate history of antiretroviral therapy and anti-HCV drugs was effective in suppressing the viral load of a highly treatment experienced patient with HIV-1with very limited side effects. In treatment experienced and multidrug resistance patients with HIV-1 infection coinfected, MARAVIROC has been shown to have maximum benefit when introduced with at least one other active new antiviral agent and has been observed a limit side effects.

Informed Consent

He is participating in the NIA study, an Italian cohort study on patients taking new antiretroviral inhibitors (raltegravir). He gave written informed consent to participate in this study.

Discussion

The goals of therapy are the prolonged suppression of viral levels to less than detection limits (<50 copies/mL for Amplicor assay, <75 copies/mL for VERSANT assay, and <80 copies/mL for NucliSens assay), with the aim to restore and preserve immunologic function, improve quality of life, and avoid HIV-associated morbility and mortality. Treatment success needs strict lifelong drug adherence and Maraviroc in patients with a long history of antiretroviral therapy, side effects and resistance has a high potency and long half-life, allowing single-pill dosing.

Maraviroc is only effective against CCR5-tropic virus, which predominates throughout infection but is more common in patients at the early asymptomatic stage of infection. It is not known how quickly resistance may develop to maraviroc in clinical practice. Current evidence supports the continued development of maraviroc as a potentially useful, alternative treatment for the management of HIV infection. Use of maraviroc did not increase hepatotoxicity in this patient with HCV therapy with Pregintron 80 mg + rebetol 1000 for 12 months. Our patient, experienced and multidrug resistant with active chronic hepatitis has never stopped Maraviroc along seven years of antiretroviral therapy and therefore has not developed another resistance.

Preliminary evidence indicates that maraviroc is likely to provide an alternative therapy for treatment-experienced and coinfected patients, and for treatment-naïve patients who are newly infected with drug-resistant virus. However, improvements in efficacy or short- and long-term side effects for maraviroc compared with currently available regimens in treatment-naïve patients could positively impact on it use in this patient population provided that its use does not promote the selection of X4 HIV

and more rapid disease progression. Approximately 50-60% of treatment-experienced patients and 80-85% of treatment-naïve patients are infected with the CCR5-tropic virus only. A viral tropism test (Monogram Biosciences, San Francisco, CA, USA) is available to determine the probability of successful treatment, but the cost and turnaround time (3-5 weeks). In summary, long term maraviroc therapy, meets an unmet need for a well-tolerated drug that reduces viral load with limit side adverse events in a HIV-1 experienced patient with preexisting class resistance and HCV therapy.

Current evidence supports the continued development of maraviroc as a potentially useful, alternative treatment for the management of HIV infection in patients coinfected. Its favorable toxicity profile makes the drug attractive for consideration in other clinical situations, including patients with earlier stages of disease, cardiovascular risk and viral hepatitis coinfection. Further investigation regarding possible beneficial effects of maraviroc on liver fibrosis may be warranted.

Competing Interest's Declaration

Authors have not received any reimbursement, fees, funding or salary from organizations that may gain or lose financially from the publication of this manuscript, either now or in the future. They do not hold any stocks or shares in such organizations. Authors do not hold (and neither are applying for) any patents relating to the content of the manuscript. They have not received any reimbursement, fees, funding or salary from organizations that hold or have applied for patents relating to the content of the manuscript. Authors have no other financial competing interests, and neither have any non-financial competing interests to declare in relation to this manuscript.

Authors' Contributions

Liliana Elena Weimer participated in the drafting of the manuscript. Lucia Brescini contributed to the design and conception of the study, acquisition of data, analysis and interpretation of data; she also contributed to drafting the manuscript and approved the final draft. Oscar Cirioni and Gianluca Morroni; contributed to drafting the manuscript. Andrea Giacometti. participated in the study design and performed the statistical analysis. Liliana Elena Weimer contributed to drafting the abstract. Liliana Elena Weimer and Lucia Brescini participated in the acquisition, analysis and interpretation of data, helped in drafting the abstract and interpretation of data, participated in drafting the manuscript. BF contributed to the design of the study.

Conflicts of Interest

The authors do not have a commercial or other association that might pose a conflict of interest.

Financial Support: None

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