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Case Report

Immunovirologic Discordant Response in Patient Beginning Antiretroviral Therapy

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Abstract

This is a case report of a patient seen at a Specialized Care Service in which the author worked in 2013 and 2014. The patient started with Highly Active Antiretroviral Therapy (HAART) and the response to treatment was an increase in the CD4 count accompanied by an increase in viral load (VL-/CD4+). Genotyping revealed resistance mutations to Efavirenz. Viral and patient factors that may lead to a discordant immunovirologic response are discussed. The subject is of great importance as the risk of mortality is high in the population that presents a discordant immunovirologic response when starting HAART.

Keywords: Immunovirologic; Discordant response; Genotyping

Introduction

AIDS remains a major global public health problem. According to the World Health Organization (WHO), by the end of 2019, almost 33 million deaths from the disease had occurred, while there were about 38 million people living with HIV at that time [1].

However, mortality has decreased considerably due to the advent of Highly Active Antiretroviral Therapy (HAART) in the 1990s, the early diagnosis of HIV infection, the reinforcement of the importance of adherence to treatment, the inclusion of genotyping as a treatment aid tool, and prevention of clinical complications resulting from treatment.

Highly Active Antiretroviral Therapy (HAART) against HIV aims to suppress viral replication to undetectable levels and, consequently, an increase in CD4 lymphocytes in the blood may occur.

The discussion of the case presented in this article will require some definitions about the concept of discordant immunovirologic response, which will be seen in Material & Methods.

Material and Methods

As a result of HAART, no detectable viral load is represented by VL+, and incomplete response or lack of response by VL-. As the cellular immune response, CD4+ means increase in immunity and CD4-, no response or even worsening of immunity. Concordant responses (VL+/CD4+ or VL-/CD4-) have well-defined prognosis.

The time elapsed from the start date of HAART (December 14, 2012) to request the second test for viral load and CD4 count (April 11, 2013) was 4 months, however the literature on the subject mentions a time of 6 months or even longer [2-4].

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Survey of medical records of all patients treated at the Specialized Care Service of Uruguaiana City Hall, Rio Grande do Sul state, Brazil, until July 2014.

Results

Male patient, born on January 17, 1985, was admitted to Specialized Care Service at Uruguaiana, RS, Brazil, on November 29, 2012, with complaints of weight loss, loss of appetite, persistent cough and fatigue. An anti-HIV test was conducted on the same date and the result was positive. He was married; however he had unprotected extramarital affairs. He had denied drug use and blood transfusions. Initial laboratory tests: non-reactive anti-HCV, non-reactive HBsAg, two non-reactive serology for syphilis; PPD non-reactive; toxoplasmosis IgM and IgG non-reactives, hematocrit was 28.6% and hemoglobin was 9.8 g%. Due to the anti-HIV positive, a CD4 count was requested on the same date, which resulted in 91/mm^3.

Tenofovir, Lamivudine and Efavirenz were started on December 6, 2012, date on which a new blood sample was requested for CD4 count and, this time, also viral load. The results of these exams are shown in the graph (December 14, 2012) (Figure 1). On April 11, 2013, a new sample was taken, whose results were not seen immediately.

Subsequently, given the discordant CD4 and viral load results of December 14, 2012 (baseline) and April 11, 2013, a new blood sample was requested whose results are also shown in the graph (July 27, 2013).

In a consultation held on September 24, 2013, the patient was asymptomatic and reported to be using HAART correctly.

Due to the discordant responses between viral load and CD4 count (April 11, 2013 and July 27, 2013) and the correct adherence to HAART, genotyping was requested, which showed on December 2, 2013:

- Sensitivity to TDF, TDF + 3TC; Etravirine (ETV), Atazanavir plus Ritonavir (ATV/r), Darunavir plus Ritonavir (DRV/r), Fosamprenavir plus Ritonavir (FPV/r), Indinavir plus Ritonavir (IDV/r), Lopinavir plus Ritonavir (LPV/r) and Tipranavir plus Ritonavir (TPV/r);

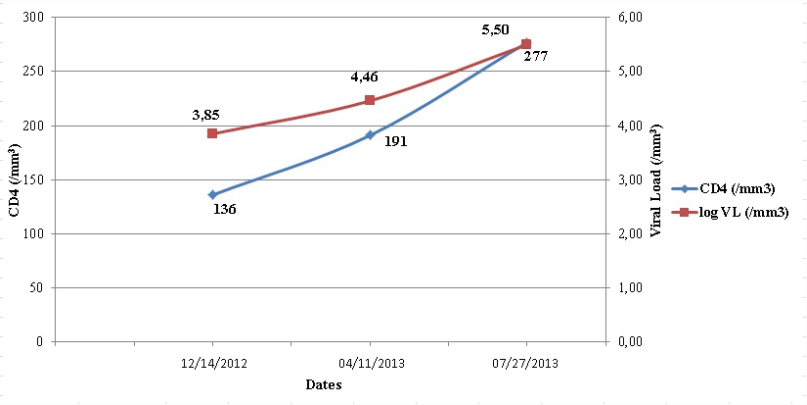

Figure 1: Graph- CD4 and viral load (log) results.

- Intermediate susceptibility to Didanosine (ddI) and Zidovudine plus Lamivudine (ZDV/3TC);
- Resistance to Lamivudina (3TC), Abacavir (ABC), Zidovudina (ZDV), Stavudine (d4T), Nevirapine (NVP), Efavirenz (EFV).

Mutations shown: 67N, 70R, 184V, 211K, 214F, 219E, 103N, 225H, 13V, 15V, 41K, 63P, 77I. Polymorphisms shown: 38V, 67D, 70K, 122K, 123E, 135M, 162C, 200A, 202V, 219K, 228R / L, 245Q, 17D, 37N, 57K, 64V.

The antiretroviral regimen was modified to TDF + 3TC + LPV/r on December 5, 2013.

Discussion

Moore et al. [5], in 2005, cited that discordant responses (VL-/CD4+ or VL+/CD4-) had uncertain prognosis because there were too few studies. More recently, however, evaluating only the reconstitution of the CD4 lymphocyte count, Ali et al. [6], concluded that a poor cellular response can lead to worse outcomes.

It is known that 40% to 60% of patients have VL+/CD4+ response, 12% to 27.3% have VL-/CD4- and the remainder develops discordant response [5,7]. Discordant response may present as only immunologic improvement (5% to 18%) or as just virologic improvement (7% to 48%) [7,8]. An increased risk of AIDS-related events and mortality is associated with discordant response [7,9]. The prevalence of discordant immunovirologic responses depends on the criteria used to define the types of responses, the follow-up period and the type of patients (treatment-naïve or pretreated) [10].

The type of response (VL-/CD4+) presented by the patient in this case report was the less common in a sample of 1527 patients, with 11.7% of total [5]. Several factors may be involved in this discordant response, which can be classified into four groups [11], as shown at (Table 1).

There are two theories that attempt to explain the discordance in virologic failure [13]. The former suggests a direct effect of Protease Inhibitors (PI) on the survival of CD4 lymphocytes, modulating apoptosis of CD4 lymphocytes by HIV [10]. The latter refers to HIV strains resistant to any antiretroviral. A resistant virus has lower viral replication fitness, so the complete recovery of blood levels of CD4 lymphocytes becomes more difficult to happen [10,12,13]. The case presented case above there were two resistance mutations to Efavirenz. Despite this discordance can result in clinical benefit [13], a HAART with only two active drugs may result in immunologic failure [14].

The large number of described factors into the medical literature, possibly associated with the type of response VL-/CD4+, tell us that few things are known about the pathogenesis of discordant immunovirologic response [8].

Immunovirologic discordance as described in the case above was possibly due to viral Efavirenz resistance. The failure related to resistance to HAART treatment is associated with a high mortality rate [15].

Currently in developed countries, genotyping is included among the laboratory tests that are required to start the HAART [15]. However, the genotyping sensitivity decreases over time infection, because the resistance evaluation is made only on the prevalent viral population at the time of the test [15]. Nevertheless, the resistance prevalence to non-nucleoside inhibitors of reverse transcriptase in Brazil was 4.4% in recent study [16]. This same study reported that patients which partners are using antiretroviral have a 2.5 times higher risk of having viral mutation resistance strains. This suggests that the mutation was transmitted by HIV from their treating partners [15].

Conclusion

This article reinforces the need for strict monitoring of the immunovirologic response of patients who started HAART.

There are some factors related to HIV and to patients that can have a negative influence, either in reaching an undetectable viral load or in reaching the complete restoration of CD4 lymphocytes.

In the case in question, due to the correct use of antiretroviral medication and clinical improvement, there was a suspicion and subsequent confirmation of viral resistance to the drugs.

Early detection from this type of discordant imunovirologic response (VL-/CD4+) is very important. The incomplete suppression of viral replication may lead to acquisition of HIV drug resistance, to elevated morbidity and mortality, and does not contribute to reduce the risk of viral transmission. Although the case described here is from 2013, the topic remains very current in the literature.

Ethical Approval

Retrospective observational study. Ethical approval not required.

Table 1: Factors involved in discordant immunovirologic responses.

1. HIV related factors	
1.1. Level of viral replication	· baseline HIV RNA above 105 copies/ml [5,7]
1.2. HIV virulence	· HIV with reduced cytopathic effect (absence of tropism for CXCR4) [10,12]
	· HIV mutants with inability to replicate in human thymus [10,12]
2. Patient related factors	
2.1. Non-immunological factors	· history of drug adiction [5]
	· use of ZDV/3TC [5,7], ddI/d4T [5,7], ddI/3TC [5,7] or saquinavir [7]
	· regimens containing boosted PI with ritonavir [7]
	· anemia (hemoglobin below 10 g%) [9]
	· low adherence [2,5,7,10,16]
	· sexual transmission of HIV [2,7]
	· absence of clinical progression [7]
	· low amount of viral rebound during the first year after indetected viral load is reached [7]
	· younger age group (below 30 years old) or advanced age [7,9,16]
	· modified pharmacokinetics [10]
2.2. Immune response to infection	· regeneration of HIV-specific immune response similar to that of long-term non-progressors [12]
	· increase in half-life of CD4 lymphocytes [10,12]
	· baseline lower CD4 count [2,7,16]
	· limited α interferon production [2]
	· down-regulation of Interleucin-7 [2,16]

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