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Two-Years Follow-Up in a Multidrug-Resistant HIV-1-Infected Woman Treated with Ibalizumab

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Abstract

Diarrhoea is a common and diverse aetiology problem in HIV infected patients that can cause deterioration in the quality of life, malnutrition and failure of antiretroviral therapy (ART). Ibalizumab (IBA), a humanized monoclonal antibody that binds to domain 2 of CD4 T lymphocytes receptor, has been recently approved for treating adults infected with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen. This case reports the usage of IBA in combination with ART regimen for a 53-years old woman with multidrug-resistant HIV-1 infection, who started with uncontrolled chronic diarrhoea simultaneously with ART failure. Conclusion: Intravenous IBA, in combination with optimized ART provided a significant viral load reduction and improved the patient clinical outcomes and quality of life over a period of two years.

Keywords: HIV-1; Diarrhoea; Ibalizumab; Antiretroviral therapy; Multidrug-resistant

List of abbreviations: AIDS: Acquired Immunodeficiency Syndrome; ART: Antiretroviral Therapy; CHAIN: Collaborative HIV and Anti-HIV Drug Resistance Network; EMA: European Medicines Agency; FDA: Food and Drug Administration; HIV: Human Immunodeficiency Virus

Introduction

The scale-up of antiretroviral therapy (ART) has reduced human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) related deaths and prevented new HIV infections [1].

The number of patients undergoing ART has dramatically increased over the last decade [2]. Despite this fact, only 59% of all people living with HIV had suppressed viral loads [2]. One major hindrance to the effectiveness of ART is drug resistance, as it limits the number of effective drugs, increases the potential for onward transmission and compromises survival [3,4].

Drug resistance to ART may be acquired or may be present prior to ART initiation. This increase in acquired drug resistance, which is associated with virological failure and treatment changes, is mainly due to the dramatic increase in ART usage and/or to poor treatment adherence [5]. In fact, HIV-infected individuals failing first-line highly active ART regimens are reported to have 50 to 97% of non-nucleoside analogue reverse transcriptase inhibitors resistance worldwide [6]. Moreover, this increased prevalence in acquired drug resistance may be also associated with transmitted drug resistance in newly infected individuals [5].

Drug resistance prior to ART represents an important health problem [6], since these patients have a higher risk of treatment discontinuation due to failure and to develop new drug resistant strains [7]. Pre-treatment drug resistance may be due to infection with a drug resistant viral strain or due to prior exposure to antiretroviral treatment, for example, for the prevention of mother-to-child transmission of HIV [8]. The prevalence of prior drug resistance may vary across countries, being as high as 25% in some countries [9]. This issue may be related with the fact that pre-treatment non-nucleoside reverse transcriptase drug class (NNRTI) resistance is higher than expected, due to the low genetic barrier of these drugs [9].

Ibalizumab (IBA) (Trogarzo®; Theratechnologies Inc. Montreal, Canada) is a humanized monoclonal antibody that binds to domain 2 of CD4 T lymphocytes receptor [10]. It was recently approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of adults infected with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen [10-12].

Up to now, clinical data about the efficacy of IBA in multidrug-resistant HIV-1-infected people is limited [13,14]. This paper is going to report a case of multidrug-resistant HIV-1-infected woman, who started with an episode of uncontrolled chronic diarrhoea that underwent IBA treatment in combination with optimized background therapy.

Case report

Fifty-three years old Spanish woman diagnosed of HIV-1 in 1993, heavily treated with more than 25 antiretrovirals and with resistance to 3-drug classes.

In August 2016, the patient started with liquid stools (more than 15/24 hours) without vomiting, fever and/or abdominal pain. The patient did not refer either change in diet or travels outside Spain, or changes in ART or adherence. In addition, over the last two months, the patient started with psoriatic dermatologic lesions and psoriatic nail involvement, which was associated with a clinical picture of psoriatic arthritis.

At that time, she was on treatment with fixed combination of emtricitabine + tenofovir once daily; darunavir once daily and ritonavir once daily. Additionally, patient received fixed combination 160 mg trimethoprim / 800 mg sulfamethoxazole every other day (Table 1). In the next months we performed an exhaustive medical study, she experienced an important weight lost (15 kg in two years) and loss of appetite, and finally, in December 2018, the patient had a stage C3 HIV infection (Defined as a CD4+ cell count lower than 200, the percent of CD4+ cells is less than 14% of all lymphocytes, or an AIDS-related condition is present) with resistance to 3 drug classes and ART failure (at this moment we analysed the HIV genotype and based on the Stanford Univer-

sity HIV Drug Resistance database [15] we found high resistance to nevirapine; intermediate resistance to efavirenz, rilpivirine, and etravirine; possible resistance to azidothymidine and stavudine; and also, historical resistance to protease inhibitors that was found in other genotype studies performed throughout her evolution); oesophageal candidiasis; multifactorial macrocytic anaemia; leukopenia due to severe lymphopenia (associated to HIV); psoriatic arthritis (controlled) and onychopathy (uncontrolled); HIV-associated chronic diarrhoea with malabsorption; and severe mixed malnutrition syndrome with multivitamin deficiencies.

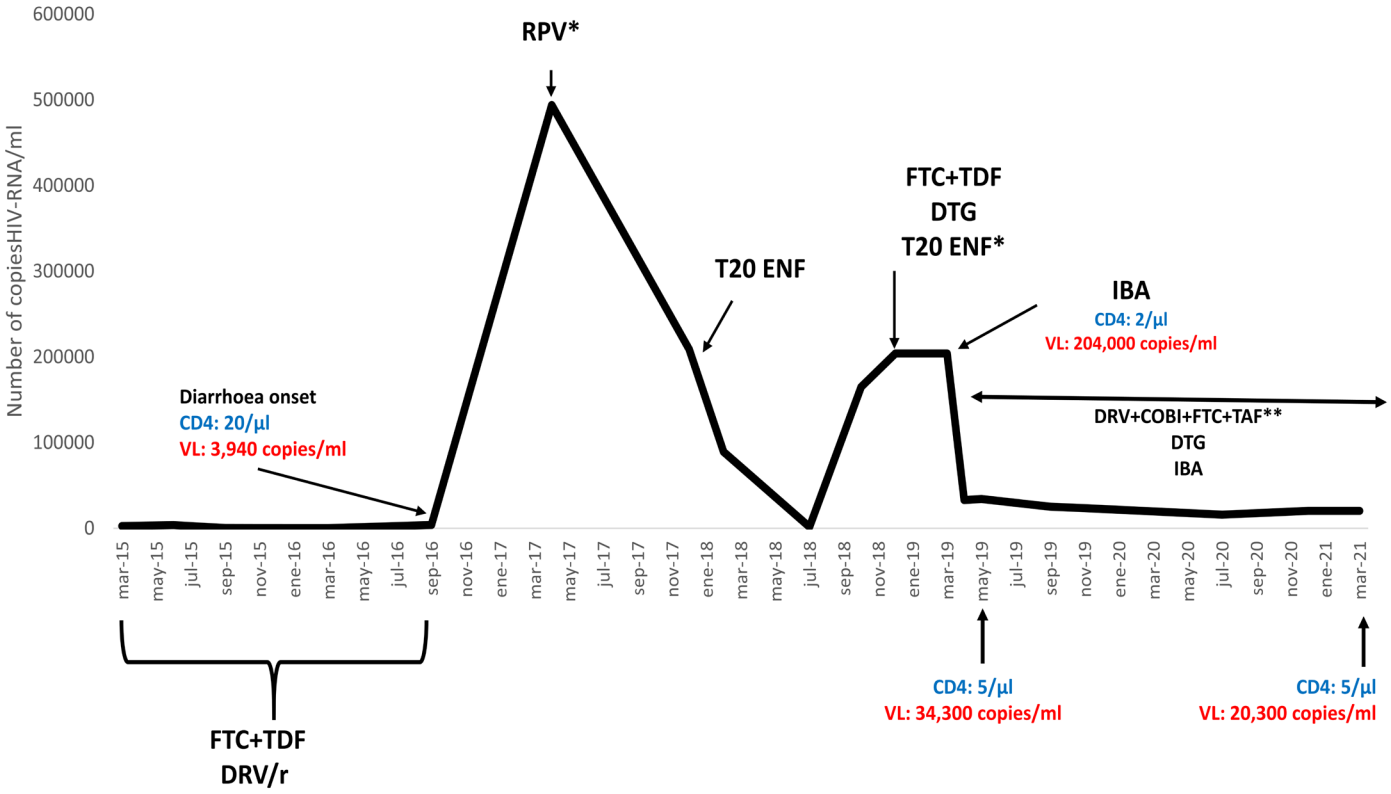
Data	Clinical features
March 2015	• Chronic hepatitis C treated with direct-acting antivirals and sustained viral response. • Various opportunistic infections: oral and/or oesophageal candidiasis, pneumonia. • High-grade intravulvar neoplasia (VIN-III) (simple vulvectomy in April 2014). • Maximum value of CD4: 200/µl. • VL ranging from 1,000 copies/ml to 3,000 copies/ml. • Resistance to reverse transcriptase inhibitors, nucleosides analogues and non-nucleosides analogues, and protease inhibitors. Sensitive to tenofovir.
September 2016	• Liquid stools (more than 15/24 hours). • No vomiting, fever, and/or abdominal pain. • Loss of appetite and subsequent important lost weight (15 kg in two years). • Treatment with: ○ Fixed combination of emtricitabine + tenofovir once daily; darunavir once daily; and ritonavir once daily. ○ Fixed combination 160 mg trimethoprim / 800 mg sulfamethoxazole on intermittent days. • Negative stool cultures, including Campylobacter. • Negative parasites, including Giardia and Cryptosporidium. • Digestive endoscopy + biopsy: nonspecific results with negative cultures. • CD4: 20/µl; VL: 3940 copies/ml. • CT scan: Without significant findings. Normal thyroid scan. • Ritonavir was withdrawn (as possible cause of diarrhoea). Cobicistat was introduced. • Dolutegravir was added (CD4: 37/µl; VL: 430 copies/ml)
April 2017	• VL: 430,000 copies/ml. • Rilpivirine was added, but no significant changes in VL were observed and was consequently withdrawn.
January 2018	• Enfuvirtide was added (CD4: 6/µl and VL: 2,650 copies/ml). • Slight improvement of diarrhoea. • Intense asthenia.
December 2018	• CD4: 2/µl and VL: 204,000 copies/ml. • Resistance study: ○ High level to Nevirapine. ○ Intermediate to: Efavirenz, Rilpivirine, and Etravirine. ○ Possible resistance to: Azidothymidine and stavudine. ○ Sensitive to: Integrase inhibitors and protease inhibitors (PI)(but historical resistance to PI).

VL: Viral load; CT scan: Computerized tomography scan

Table 1: Overview of the case report from March 2015 to December 2018

After gaining admission to an early access program, IBA loading dose (2000 mg) was intravenously (IV) administered on March 21, 2019; followed by maintenance dose of 800 mg of IBA every 14 days for the next 2 years, plus optimized background therapy (Darunavir+Cobicistat+Emtricitabine+tenofovir alafenamide and Dolutegravir).

Viral load decreased significantly from 204,000 copies/ml in March 2019 (IBA started) to 20,300 copies/ml in March 2021. The Figure 1 summarizes the viral load from March 2015 to March 2021.The total amount of lymphocytes increased from 0.24 x 10^3/ml in May 2019 to 0.45 x10^3/ml in September 2019. However, CD4 did not significantly change over the follow-up (2 CD4/µl in December 2018 and 5 CD4/µl in March 2021) (Table 2).



RPV: Rilpivirine; DRV: Darunavir; COBI: Cobicistat; FTC/TDF: Emtricitabine + tenofovir; DRV/r: Darunavir/ritonavir; T20 ENF: Enfuvirtide; DTG: Dolutegravir; IBA: Ibalizumab

*It was withdrawn later due to lack of effectiveness.

**800 mg/150 mg/200 mg/10 mg of DRV/COBI/FCT/TAF, respectively.

Ibalizumab: loading dose (2000 mg) was intravenously (IV) administered on March 21, 2019; followed by maintenance dose of 800 mg of ibalizumab every 14 days from April 4, 2019 to March 21, 2021.

Figure 1: Overview of the viral load from March 2015 to March 2021

Date	CD4 (Cells/µl)	Viral load (Copies/ml)	Weight (Kg)	Stools	
				Number	Nocturnal
March 21, 2019[1]	2	204,000	35.1	8-10	Yes
April 4, 2019[2]	N.A.	N.A.	37.0	8-9	yes
April 17, 2019[2]	4	33,000	36.6	6	No
April 30, 2019[2]	N.A.	N.A.	37.8	4-5	No
May 14, 2019[2]	5	34,300	38.0	5-6	No
May 29, 2019[2]	N.A.	N.A.	37.2	4-5	No
September 17, 2019[2]	5	25,200	37.5	2-3	No
November 19, 2019[2]	5	23,600	38.0	2-3	No
July 8, 2020[2]	5	15,900	37.5	2-3	No
December 23, 2020[2]	7	20,300	37.5	2-3	No
March 10,2021[2]	5	20,300	38.0	2-3	No

[1]Ibalizumab intravenous loading dose (2,000mg)

[2]Under maintenance dose of 800 mg of ibalizumab every 14 days

NA: Not available

Table 2: Overview of the case report clinical characteristics

Additionally, administration of IBA was associated with a significant decrease in the number of stools from 8-10/24 hours in March 2019 (before starting with IBA) to 2-3/24 hours in March 2021, as well as with a weight gain from 35.1 kg in march 2019 to 38.0 kg in March 2021 (Table 2) with improving in quality of life.

The patient suffered a new episode of Candida albicans esophagitis, successfully controlled with micafungin (it was resistant to all azole antifungal agents).

Discussion

HIV infection is currently considered as a global pandemic infecting millions of people and has contributed to a substantial mortality burden [2].

Hereby, we report the case of a 53-years old Spanish woman diagnosed with HIV-1 infection who presented with an episode of severe diarrhoea. Parasitology investigation of diarrheic stool sample was reported to be negative for Campylobacter infection; Cryptosporidium and Giardia lamblia.

Diarrhoea is a common problem in HIV infected patients that may cause malabsorption of medications and failure of ART, which is under-recognised as a cause of poor treatment adherence [15]. The aetiology of diarrhoea in HIV-infected patients is multifactorial. Although opportunistic infections are an obvious cause to consider, there are also many non-infectious causes, such as the HIV itself, HIV associated gastrointestinal malignancies, pancreatic disease, or the ART regime [15]. Diarrhea can appear due to the use of antimicrobials or as a side effect of ART [16]. Diarrhea may be associated with several of the therapies used in ART regimens, including nucleoside reverse-transcriptase inhibitors and nonnucleoside reverse-transcriptase inhibitors, protease inhibitors, and integrase inhibitors [17]. Protease inhibitors are the agents with the greatest association. Ritonavir in combination with lopinavir and fosamprenavir is one of the most often reported with up to 10% to 15% of patients using it affected [18].

Although ritonavir was eliminated due to a possible cause of diarrhea, this did not solve the problem. On the other hand, Trimethoprim-Sulfamethoxazole prophylaxis may lead to antibiotic resistance and favor the appearance of Diarrhea [19].

As aforementioned in the introduction, drug resistance to ART may be acquired or may be present prior to ART initiation [5,6]. Its onset may be due to different causes including poor treatment adherence, poor absorption, varying pharmacokinetics, drug-drug interactions, inappropriate prescribing practices, interruption of drug supply, and low genetic barrier of some ARVs to resistance development, like, for example, some non-nucleosides, nucleoside analogs, and first-generation integrase inhibitors [20,21].

The onset of our case was associated with a significant increase in viral load (from 3,940 copies in September 2016 to 430,000 in April 2017) despite proven good adherence. These findings speak in favour of a malabsorption syndrome, which was hampering the effectiveness of ART.

In our patient, the initiation of IBA therapy was associated with a significant decrease in viral load. As compared to other ART, IBA offers some advantages, including its novel mechanism of action, no cross-resistance with others antiretroviral agents, low potential for toxicities and lower drug-drug interactions [10-12].

IBA inhibits HIV entry into the CD4 T cell, by binding to the CD4 T cell extracellular domain 2 at amino acid sites L96, P121, P122, and Q163 [22]. The binding mechanism of IBA induces steric hindrance, which prevents these conformational changes within the complex of the CD4 T cell and the HIV envelope gp120 [14,23].

Based on the results of clinical trials, therapeutic regimen with IBA includes a 2000 mg loading dose, administered IV, followed by IV 800 mg maintenance dose every 2 weeks [13,14].

Regarding resistance profile, our patient had resistance to nevirapine, efavirenz, rilpivirine and etravirine; historical resistance to protease inhibitors, and a possible resistance to azidothymidine and stavudine.

Nevertheless, the addition of IBA to her improved ART regimen provided positive clinical outcomes. Despite the significant improvement in both survival and quality of life that entailed the advent of ART, there are growing concerns about resistance to available therapies [3-5].

According to CoRIS register, the global percentage of resistance mutations was 7.8% (95% CI, 7.1% -8.5%) [24]. Moreover, in 2019-year in Spain, clinically relevant resistance to different ART in naïve patients was 0% to dolutegravir, bictegravir and darunavir; 1% for lamivudine/emtricitabine; 1.2% for tenofovir disoproxil fumarate/tenofovir alafenamide; 1.9% for abacavir and 2.6% for raltegravir [25]

These figures do not significantly differ from those reported by other European Registers (SPREAD; EuroCoord; CHAIN; and HIV-CASUAL) [26-28].

IBA demonstrated similar maximal percentage of inhibition regardless of baseline resistance to different antiretroviral agents [10,11]. Additionally, cross resistance has not been reported between IBA and other antiretroviral medications, including enfuvirtide and maraviroc [10-12]. Despite these advantageous pharmacokinetic parameters, resistance to IBA may occurs, as with all antiretroviral agents.

Although different factors, such as intravenous administration, poor visit adherence, unstable housing, or transportation barriers might hamper the optimal use of IBA, in our patient, intravenous administration may be considered an advantage as it prevents malabsorption syndrome.

Conclusions

Diarrhoea in HIV-infected patients is a common symptom that can cause deterioration in the quality of life, malnutrition and even systemic compromise. Although the aetiology of diarrhoea is diverse, reduction of viral load improves chronic diarrhoea in HIV-infected individuals.

In this multidrug-resistant HIV-1-infected woman, intravenous IBA in combination with optimized ART was able to significantly reduce the viral load and improved the patient clinical outcomes and quality of life over a period of two years.

Further studies are need to elucidate other clinical aspects, including other routes of administration, resistance or how to build an optimized ART regimen.

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Disclosure of potential conflicts of interest

None of the Co-authors have any conflict of interest to declare.

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