Successful use of Eltrombopag in a patient with refractory HIV-associated immune thrombocytopenic purpura

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Abstract

Immune Thrombocytopenic Purpura (ITP) is not uncommon in patients with Human Immunodeficiency Virus (HIV) infection. This entity can be recurrent to standard therapy, which includes corticosteroids, intravenous immunoglobulins (IVIG) and highly active antiretroviral therapy (HAART). In immunocompetent patients with ITP, Eltrombopag, a thrombopoetin receptor agonist (TRA), has proven to be save and useful for increasing platelet counts and for treating patients with Hepatitis C virus (HCV) associated thrombocytopenia that need an interferon-based therapy. Safety and efficacy data with the use of TRAs in HIV-associated ITP are scarce, being a non-authorized indication. We report our one-year experience with Eltrombopag for treating a severe and refractory HIV-associated ITP.

Introduction

Thrombocytopenia has been associated with HIV since the beginning of the AIDS epidemic [1,2]. Immune thrombocytopenia purpura (ITP) was a relatively common abnormality, which was seen in as many as 30% of infected patients especially before the HAART era [3-5]. Nowadays, HIV-associated ITP has reduced the incidence to 3-5% [6,7]. Both, decreased production of platelets and increased destruction have been proposed as mechanisms of thrombocytopenia. Two different clinical situations may be seen in HIV-associated ITP: patients with advanced AIDS in which thrombocytopenia is a manifestation of bone marrow suppression and patients without significant T-cell depletion in whom thrombocytopenia develops likely as an immune phenomenon. In HIV-associated ITP, the standard treatments for classical ITP (corticosteroids, IVIG, splenectomy, danazol, Anti-D, dapsone and splenic radiation) have all been employed with varying degrees of success, being the highest response rates achieved in the HAART era [8]. When platelet counts remain persistently below 20×10^9/L despite therapies, patients retain a significantly increased risk of bleeding complications [9].

Eltrombopag, one of the TRAs, was granted approval for the treatment of refractory ITP after the failure of first line therapy, being effective in a high percentage of cases. Therapy with Eltrombopag for refractory HIV-associated ITP has not been sufficiently studied or reported. We report our successful use of Eltrombopag in a patient with HIV-associated ITP who was refractory to standard treatments.

Case report

A 61-year-old male with a history of morbid obesity, hypertension, coronary artery disease and dyslipidemia, was diagnosed of HIV infection in 2005. He was started on HAART (Abacavir, Lamivudine and Efavirenz), and 6 months after beginning, a non-detectable viral load and CD4 count over 500 cells/mm³ were both achieved.

In January 2006, he presented with multiple cervical, axillary, abdominal lymphadenopathies and splenomegaly, being diagnosed of Follicular Non-Hodgkin Lymphoma (NHL), grade I, stage IIIA, FLIPI 1. He achieved a complete response (CR) after 8 cycles of Rituximab, Cyclophosphamide, Vincristine and Prednisone, following annual controls in the Hematology department.

In July 2014, while remaining on continuous CR of the NHL, the patient was admitted because of acute generalized petechias on trunk and extremities and hemorrhagic blisters in the oral mucosa. Analytical results at the initial evaluation included hemoglobin 12 g/dl, hematocrit 37%, MCV 97.2 fL, WBC 7.4×10^9/L (neutrophils 5.4×10^9/L, lymphocyte 0.87×10^9/L), and platelets 2×10^9/L. The patient's chemistry and liver function tests were within normal limits. Additional testing revealed undetectable HIV viral load and CD4 count of 574 cell/mm³.

Bone Marrow biopsy showed adequate trilineage hematopoiesis and increased megakaryopoiesis in keeping with a peripheral destructive an etiology for the thrombocytopenia.

The patient was initially treated with Prednisone 1 mg/kg daily plus IVIG 0,4 g/Kg for five consecutive days, without initially increasing in the platelet counts. After two weeks, platelets moderately improved to 37×10^9/L but spontaneously dropped to 22×10^9/L, being necessary to repeat a new course of IVIG while maintaining daily corticosteroids treatment. Over the next two months, a high dose of prednisone (100

mg per day) was impossible to reduce by continuous and difficult to control hyperglycemic episodes, and with a minimal platelets response (platelets count between $7 \times 10^9/L$ and $37 \times 10^9/L$). Splenectomy was considered but was avoided due to concern regarding potential infectious complications. After requesting patient's written informed consent, a compassionate use of TRAs was decided. Eltrombopag at a dose of 50 mg p.o daily was initiated as an alternative treatment for refractory HIV-related thrombocytopenia. After 4 weeks, platelets count rose to $485 \times 10^9/L$ allowing the progressive tapering of prednisone until its complete interruption. Currently, 6 months after starting on Eltrombopag, platelets counts are stable between 185 and $220 \times 10^9/L$, with 25 mg twice a week as the minimum effective dose, with no hepatotoxicity signs or history of thrombotic episodes.

Discussion

Thrombocytopenia (TP) is common in patients with HIV infection, reported in as many as 10-30% of patients and seen more often in IV drug users and advanced HIV infections even in post-HAART era [8].

The pathophysiology of HIV-associated ITP has not been fully elucidated but is likely somewhat different than that of classic ITP [10]. Severe T-cell depletion and consequent immune dysregulation occurs with HIV infection. In addition, megakaryocytes express HIV receptors CD4, CXCR4 and CCR5, and therefore, may be vulnerable to direct viral cytotoxicity, which ultimately could lead to a decrease in platelets formation [11]. Antiplatelet immune complexes are also present on platelets of HIV-infected patients and may be an important contributor to ITP pathogenesis [11].

The common treatments for classical ITP have been used with varying degrees of success and the highest response rates seen in the HAART era. Shortly after HAART became available, antiretrovirals were shown to be successful in treating ITP in a randomized trial of Zidovudine monotherapy [12]. Long-term treatment with corticosteroids, produce an initial rapid response but induce immunosuppression. IVIG do not have this risk but lack sustained effects. Splenectomy is reserved for resistant HIV-associated thrombocytopenia and is curative in 50 percent of patients [13].

Recently, Kowalczyk and colleagues, described 5 patients with refractory HIV-related ITP. These patients, unlike our patient, were diagnosed of HIV at the same time of the ITP symptoms appearance. All 5 patients had failed or relapsed after conventional treatment (corticosteroids and IVIG) and recovered the platelets counts after received TRAs. Our patient presented the ITP episode after 10 years on HAART, not being in relationship with HIV- progression, documented infection or daily medication changes. NHL relapsing disease was also excluded. As many reported cases, the initial therapy option was full-dose corticosteroids plus five days of IVIG without an adequate platelet response and severe secondary metabolic effects. After starting treatment with TRAs, our patient presented platelets count recovery.

TRAs have been granted approval for the treatment of refractory ITP. These agents are effective in between 59% to 88% of ITP cases, and loss of response while on continued therapy is uncommon [14,15]. Eltrombopag, an oral, non-peptide TRA that interacts with thrombopoietin receptor leading to JAK/STAT pathway signaling in megakaryocytes, has been well studied in several clinical trials evaluating their effectiveness in treating various subsets of patients with problematic ITP. However, these studies have not detailed its use and efficacy in the treatment of HIV-associated thrombocytopenia. For this kind of patients, there is a substantial need for additional treatment options beyond the traditional ITP therapies, as platelet

counts often remain inadequate despite multiple interventions. Side effects associated with TRAs are well documented. An increase in bone marrow reticulin fibrosis has been reported in 5% of patients, but to date there are no disconcerting signals to suggest that the marrow fibrosis is progressive or irreversible [16,17]. Eltrombopag, also carries a warning because of increased risk of hepatotoxicity. Additionally, portal vein thrombosis has been reported in patients with chronic liver disease, with an estimated risk of thrombosis around 5.5% [18].

While HIV-associated ITP remains an important clinical problem in the HAART era, the availability of Eltrombopag, gives medical providers additional treatment options. In conclusion, we want to stress that Eltrombopag may be useful for treating severe and refractory HIV-associated ITP patients. Although in our experience neither hepatotoxicity nor thrombotic events were observed, further experience is needed, to better determinate the effectiveness and the safety of Eltrombopag in the context of HIV-associated ITP.

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