

Two case reports of severe myocarditis associated with the initiation of dolutegravir treatment in HIV patients

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Abstract

Rationale: The integrase inhibitor dolutegravir is now recommended as first-line treatment for HIV. A single case of myocarditis after treatment with dolutegravir was reported in the FLAMINGO trial. We present here 2 cases of severe myocarditis that occurred shortly after the initiation of dolutegravir treatment.

Patients concerns: The first case is a 45-year-old female who developed severe congestive heart failure and died, weeks after the initiation of dolutegravir treatment (for simplification of her antiretroviral regimen). The second case was a 51-year-old male who presented with effort dyspnea 3 weeks after the initiation of dolutegravir treatment and was later diagnosed as severe congestive heart failure. The treatment was changed and the patient survived, but he still suffers from severe heart failure with functional impairment.

Diagnosis and Outcome: Patient 1 died, patient 2 suffers from severe heart failure.

Lessons: We discuss here the possible relationship between the initiation of dolutegravir treatment and the development of lymphocytic myocarditis in our patients, and we suggest a possible mechanism.

Abbreviations: ART = antiretroviral therapy, AST = aspartate aminotransferase, CD4 = cluster of differentiation 4, CMV = cytomegalovirus, CPK = creatinine phosphokinase, DNA = deoxyribonucleic acid, DTG = dolutegravir, ECMO = extracorporeal membrane oxygenation, GMS = Grocott-Gomori methenamine silver stain, HIV = human immunodeficiency virus, HLA = human leukocyte antigen, HSV = Herpes simplex virus, IRIS = immune reconstitution inflammatory syndrome, LAD = left anterior descending, LDH = lactate dehydrogenase, LDL = lower detection limit, MRI = magnetic resonance imaging, NZBXW F1 = first-generation offspring of New Zealand Black and New Zealand White mice, PAS = periodic acid-Schiff, RT = reverse transcriptase, Trex-1 = three prime repair exonuclease-1, VL = viral load.

Keywords: dolutegravir, HIV treatment, myocarditis

1. Introduction

The integrase inhibitor dolutegravir (DTG) was approved on August 2013 by the US Food and Drug Administration (FDA) for the treatment of HIV infection.^[1] Several studies reported the efficacy of DTG (in combination of abacavir/lamivudine or tenofovir/emtricitabine) in the treatment of naïve and treatment-experienced HIV patients.^[2,3] DTG was shown to be safe and well-tolerated by the patients.^[2] In addition, DTG has a good lipid profile and limited pharmacological interactions with other

drugs.^[4] Currently, DTG is recommended as a first-line drug for HIV treatment.^[5] We present here 2 cases of severe myocarditis occurred shortly after the initiation of DTG treatment. This report was approved by the ethics committee of Kaplan Medical Center. We discuss the possible relationship between DTG and the development of myocarditis.

1.1. Case 1

A 45-year-old female was diagnosed with HIV 5 years ago during an investigation for mild thrombocytopenia. She did not smoke, had no hypertension, diabetes mellitus, or hyperlipidemia. There was no family history of any cardiovascular disease. The patient was treated for 10 years with levothyroxine (100 mcg/d) for hypothyroidism. At the time of diagnosis, her CD4 cell count was 49 cells/mL and the viral load (VL) was 1,936,182 copies/mL. Antiretroviral treatment (ART) with efavirenz and emtricitabine/tenofovir was initiated with a good virological (LDL) and immunological (CD4 213 cells/mL) response. Because of depression, her treatment was switched to lopinavir/ritonavir and emtricitabine/tenofovir. The later treatment caused diarrhea and therefore the treatment regimen was changed 3 years ago to raltegravir and emtricitabine/tenofovir. During the past 3 years, the patient felt good without any clinical complication or hospitalizations. Her CD4 cell counts were stable (350–420 cells/mL) with undetectable VL (LDL). The patient wanted to simplify her ART to a single tablet regimen; therefore, after a negative HLA-B5701 test, Triumeq (abacavir/lamivudine and dolutegra-

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vir) was initiated. Two weeks later, she was admitted with low-grade fever, severe shortness of breath, and legs edema. Her creatine phosphokinase (CPK) was 345 units/L (normal range 10–190 units/L), aspartate aminotransferase (AST) 92 units/L (normal range 0–35 units/L), and her troponin T levels were 823 ng/L (normal range 0–14 ng/L). She was intubated and mechanically ventilated. Echocardiography revealed severe right and left ventricular systolic dysfunction with an estimated left ventricular ejection fraction of 20% to 25% (normal 60%). Computerized tomography was negative for pulmonary embolism, and cardiac catheterization revealed no coronary artery disease. To confirm the clinical diagnosis of severe myocarditis, an endomyocardial biopsy was done, demonstrating lymphocytic myocarditis with prominent myocyte necrosis. No granulomas, giant cells, or inclusion bodies associated with viral cytopathic effects were found. Immunostaining (CD20, CD3) demonstrated lymphoid aggregates composed of organized B and T-cell populations. Stains for cytomegalovirus (CMV), Herpes simplex virus (HSV), periodic acid–Schiff (PAS), and Grocott–Gomori methenamine silver stain (GMS) were all negative. Triumeq treatment was continued throughout her hospitalization. Despite treatment with antibiotics, dobutamine, and digoxin the patient's condition did not improve. Extracorporeal membrane oxygenation (ECMO) was initiated, but 3 weeks later, the patient had died.

1.2. Case 2

A 51-year-old male was diagnosed with HIV, acquired by heterosexual contacts, 12 years ago. For the past 5 years the patient had diabetes mellitus and was treated with metformin and aspirin. The patient did not smoke, and had no hypertension, hyperlipidemia, or a family history of cardiovascular disease. At the time of diagnosis, the patient had low CD4 cell counts (70 cells/mL) and a high VL (1,590,000 copies/mL). Treatment with efavirenz, epivir, and didanosine was recommended, but the patient did not take it on a regular basis. Six years ago, he restarted ART with efavirenz and emtricitabine/tenofovir (based on resistance assay) with a good virological response (LDL) and a slight immunological improvement (CD4 cell count was 100 cells/mL). Due to proteinuria, his antiretroviral regimen was changed to efavirenz and abacavir/epivir. The patient was treated with the later regimen for 3 years with a stable clinical, immunological (CD4 110 cells/mL), and virological response (VL-LDL). Due to sleep disturbances, efavirenz was changed to dolutegravir. Three weeks later, he complained of progressive exertional dyspnea. He was referred to cardiological evaluation, but missed his appointment. He continued to suffer from dyspnea, and 2 months later, he was hospitalized because of severe dyspnea and legs edema. Laboratory evaluation revealed elevated troponin T levels (138, normal range 0–14 ng/L), elevated lactate dehydrogenase (LDH) (886, normal range 185–480 units/L), and elevated aspartate aminotransferase (AST) (147, normal range 0–35 units/L). Echocardiography revealed severe left and right ventricular dysfunction (ejection fraction 20%; normal 60%). Computed tomography of the chest was negative for pulmonary emboli. Cardiac catheterization revealed stenosis of the distal left anterior descending (LAD) artery. Technetium (^{99m}Tc) scan of the heart showed a small antero-septal subendocardial infarction compatible with his distal LAD stenosis. Since the severity of his ventricular dysfunction was not proportional to the small antero-septal wall infarction, myocarditis was suspected. Indeed, cardiac magnetic resonance imaging (MRI) suggested the diagnosis of myocarditis that was further confirmed by endomyocardial

biopsy. The patient was treated with diuretics, the ART was changed to darunavir/ritonavir, epivir, and raltegravir, but he still suffers from severe heart failure.

2. Discussion

The 2 patients here developed myocarditis shortly after the initiation of DTG treatment. The first patient was hospitalized with severe congestive heart failure 2 weeks after she was switched (for simplification of her ART) to 1 single tablet regimen of Triumeq (abacavir/lamivudine and DTG). As for the other patient, he started to complain of shortness of breath 3 weeks after the initiation of DTG, but did not attend any medical evaluation. Two months later, he was hospitalized with small antero-septal infarction and severe myocarditis with right and left ventricular failure.

Our first patient did not have any risk factor for heart disease (other than her HIV infection). She presented with clinical symptoms and signs of severe congestive heart failure, elevated levels of cardiac muscle enzymes, evidence of significant systolic ventricular dysfunction, and clear evidence of lymphocytic myocarditis by MRI and endomyocardial biopsy. The second patient had diabetes mellitus, which is a well-known risk factor for atherosclerotic cardiovascular disease. The fact that he was treated with abacavir for 3 years also may contribute to his antero-septal myocardial infarction.^[6] Nevertheless, the severity of the ventricular systolic dysfunction and the elevation of his troponin levels were disproportional to his small antero-septal myocardial infarction. Therefore, the patient underwent further evaluation by MRI scan and endomyocardial biopsy, which confirmed the diagnosis of lymphocytic myocarditis.

The main DTG associated adverse events reported in the DTG trials were diarrhea, nausea, headache, and naso-pharyngitis.^[1,2] However, the supplementary appendix to the FLAMINGO trial reported 1 case (out of 244 treated patients; 0.4%) of myocarditis in the DTG-treated group.^[4] No data are available regarding the backbone treatment of the patients (either tenofovir/emtricitabine or abacavir/lamivudine), the severity of the myocarditis, or the time period between DTG initiation and the development of the myocarditis.

It should be noted that our 2 patients were also treated by other medications that may be associated with development of heart disease. Thus, the first patient was treated with abacavir which was initiated at the same time of DTG. The second patient was treated for 3 years with abacavir.

The mechanism involved in the pathogenesis of the severe myocarditis in our 2 patients is not completely clear. Since the patients were, at the time of myocarditis, clinically stable with good virological response (LDL) and stable CD4 cell counts, the possibility of active HIV infection, opportunistic infection, or immune reconstitution inflammatory syndrome (IRIS), as the primary causes for myocarditis, are highly unlikely. The symptoms and signs of myocarditis developed, in both patients, 2 to 3 weeks after the initiation of DTG treatment; thus we cannot rule out the direct effect of DTG on the myocytes. Indeed, muscular toxicity/injury was previously reported in patients receiving raltegravir, which is another integrase inhibitor.^[7] Nevertheless, no muscular injury was reported after DTG treatment.^[8]

Dolutegravir, as an integrase inhibitor, prevents HIV DNA from integrating itself into the human genome,^[9] causing accumulation of preintegrating DNA.^[10] The accumulation of retroviral elements (caused by DTG) may resemble the effects of the retroviral elements accumulation in the three prime repair

exonuclease-1 (Trex-1)-deficient mice, which succumbed due to severe myocarditis. The enzyme Trex-1 is thought to degrade endogenous retroelements.^[11] Indeed, integrase inhibitors were shown to exacerbate murine lupus like disease in NZBxW F1 mice,^[12] probably by increasing the amounts of retroelements that can stimulate the innate immune syndrome.^[11,13] The possibility that our 2 patients had developed kind of Trex-1 pathway mutations (malfunction) cannot be excluded. Interestingly, reverse transcriptase (RT) inhibitors are shown to meliorate the myocarditis in Trex-1-deficient mice.^[14] Thus, the role of the other antiretroviral drugs (abacavir, lamivudine) is unlikely. The fact that in both cases the endomyocardial biopsy revealed lymphocytic myocarditis may support an immune mechanism (in response to the accumulation of retroviral elements) for the DTG-associated myocarditis.

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