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Hypersensitivity reaction (HSR) in a subject HLA-B*5701 negative switching to a Dolutegravir/Abacavir/Lamivudine regimen: case report and brief review of the literature

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ABSTRACT:

Hypersensitivity reactions to antiretroviral drugs, and especially dolutegravir, can happen seldomly. Though they are rare, it is of utmost importance to early identify signs and symptoms characterizing a hypersensitivity reaction in a patient with no known allergy or predisposition.

A 41-year-old female patient switched to a dolutegravir/abacavir/lamivudine regimen because of osteoporosis. This regimen was chosen because it has a low toxicity on the bone. Hypersensitivity reaction was not promptly recognized because of a negative HLA-B*5701 test. We present this case and a brief review of relevant similar cases in literature.

Keywords: Hypersensitivity, HIV, Dolutegravir, Antiretroviral therapy, ART.

INTRODUCTION

After the beginning of different antiretroviral regimens, hypersensitivity reactions (HSR) can arise. They are more frequently observed during the first weeks of treatment. Generally, they are nonfatal and regress after treatment interruption. Unluckily, most of these syndromes are not predictable except for HLA-B*5701 associated abacavir HSR. The aim of this report is to describe a case of HSR occurred in an Italian HIV+ HLA-B*5701 negative patient after a therapeutic switch to a Dolutegravir (DTG) + Abacavir (ABC) + Lamivudine (3TC) fixed dose combination regimen.

CASE REPORT

A 41-year-old Caucasian woman affected by a known HIV-1 infection was admitted to the emergency department on the 2nd August 2016. She also suffered from Graves' disease since 2008. In September 2015 she was diagnosed with HIV infection (CDC class A2): at that time, $CD4^+$ T-cell count was 433 cell/µL (36%), and HIV-RNA plasma viral load (pVL) was 11,656 cps/mL. HLA-B*5701 test resulted negative.

On October 2015, an antiretroviral therapy with a fixed-dose combination of Efavirenz 600 mg + Emtricitabine 200 mg + Tenofovir disoproxil fumarate 245 mg (EFV/FTC/TDF) was started. Repeated $CD4^+$ T-cell count showed a progressive increase until 689 cells/µL on March 2016. HIV-RNA viral load was undetectable (< 20 cps/mL) since December 2015. In July 2016 she was diagnosed with osteoporosis (DEXA BMD T-score: -3,4 g/cm2). Therefore, the previous treatment was switched to a single tablet regimen (STR) with DTG/ABC/3TC 50/600/300 mg.

Ten days later, she referred to the emergency room of our hospital complaining of fever, nausea, asthenia, headache and arthralgia lasting for 2 days. She denied the concomitant use of other medications. Her labora-

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tory test showed thrombocytopenia and leukopenia (WBC 2,860 cells/μL, neutrophils 89%, PLTS 127,000 cell/μL), an increased high-sensitivity C reactive protein (hs-CRP) value (1.76 mg/dl), hypertransaminasemia (aspartate aminotransferase, AST, 100 IU/L; alanine aminotransferase, ALT, 63 IU/L), increased γ-glutamyl transferase (γGT, 136 IU/L) and lactate dehydrogenase (LDH, 454 IU/L); renal function and coagulation markers were deemed as normal.

On admission, body temperature was 39.3°C, blood pressure 80/60 mmHg. She was underweight (BMI 16.4) and showed tachycardia and cervical micro-lymphadenopathy. Cultures of peripheral blood for bacteria or fungi were performed, resulting negative. Serologies for hepatitis B and C, Epstein Barr virus (IgM), Cytomegalovirus (IgM and antigens), Toxoplasmosis (IgM), Cryptococcus (antigens), Leishmania (antibody by IFA test) and tumor markers (CEA, Ca 19-9, Ca 125, Ca 15-3, Alpha-fetoprotein and human Chorionic Gonadotropin) were negative. A CT scan of the thorax revealed an axillary and pre-tracheal micro-lymphadenopathy.

cART with DTG/ABC/3TC was continued. Suspecting sepsis, an empiric intravenous antibiotic treatment with Piperacillin/Tazobactam (4/0.5 g tris in die, tid) and Levofloxacin (500 mg quondam die, qd) was started, with no benefit. Three days after the admission, a non-itchy erythematous-macular skin rash appeared, spreading from the upper trunk to the neck and face. The following day the patient also developed further decrease of WBC (lowest value 1,700 cells/μL), PLTS (lowest value 105,000 cells/μL), and increase of transaminases (AST highest value was 888 IU/L, ALT highest value was 559 IU/L), γGT (highest value 1,041 IU/L) and LDH (highest value 2,390 IU/L). A peripheral blood smear analysis was negative and WBC count was normal. A bone marrow biopsy showed a mild hematopoietic cell hyperplasia with no sign of lymphomatous process. All her medications, including cART, were then discontinued. During the following days the patient's conditions improved. She was afebrile, in better general conditions, referring pain reduction.

On the 6th day of her admission, after the reintroduction of cART with DTG/ABC/3TC, a recrudescence of the symptoms with nausea, arthralgia, hyperpyrexia and rash was observed. The cART was definitely stopped, with progressive improvement of the patient's symptoms and laboratory abnormalities. After the discharge, HLA-B*5701 testing was repeated and confirmed to be negative. One month later she began a new cART with raltegravir and etravirine. At the moment, she does not refer of any side effects. The adverse reaction was promptly reported to the Italian Medicines Agency.

DISCUSSION

Our case describes nonfatal serious adverse events associated to a DTG/ABC/3TC regimen. DTG and ABC safety sheets reports about the possibility of HSR and suggest stopping the treatment as soon as HSR is suspected[1,2]. It is not easy to discriminate which drug was associated to HSR. Our patient was HLA-B*5701 negative and the test was confirmed on a new sample after the discharge. Hypersensitivity events have been described in < 1% of subjects beginning DTG based therapy during clinical trials[1]. Although several cases were confounded by use of other co-suspect agents, one compelling case of severe HSR was observed in the absence of confounding factors and was attributed to DTG. Another case of worsening hypersensitivity with DTG re-challenge provides corroborative evidence of this risk.

Rash events, regardless of causality and of all grades, were observed in 5-7% subjects in a Phase 3 trial[3]. Majority of rash events were of mild to moderate severity and did not result in drug discontinuation. No cases of serious skin reactions, other than those presenting as part of HSR, were observed in the clinical development program.

In clinical trials, 3 treatment-naive subjects had DTG-related non-fatal SAEs: one of them with cardiac arrhythmia and the other 2 with hypersensitivity. About these last 2 cases, one (4529 SPRING-2) was a subject randomized to DTG/ABC/3TC who developed fever, rash, body aches, hypertransaminasemia and jaundice. Because of negative HLA-B*5701 testing and negative skin patch testing, the investigator assessed the event as hypersensitivity most likely related to DTG and not to ABC. The other SAE-drug hypersensitivity case regarded a randomized to DTG/ABC/3TC subject (6929 SINGLE) who developed swollen and scratchy throat, diarrhea and fever. This case also tested negative for HLA-B*57014.

In treatment experienced INSTI-naïve population, 2 subjects experienced DTG-related non-fatal SAEs: hepatoxicity in a male with previously diagnosed hepatitis B, and an acute renal failure in conjunction with symptomatic myositis[4].

Phase IIIb, open-label, international, multi-center ARIA study compared DTG/ABC/3TC regimen with ritonavir-boosted atazanavir (ATV-r)/TDF/FTC in 495 treatment-naïve HIV women. Drug-related AEs reported in the DTG/ABC/3TC arm included nausea (31 individuals, 13%), diarrhea (12, 5%), headache (5, 2%) and dyspepsia (4, 2%)[5].

An ABC-HSR also cannot be excluded: hypersensitivity reactions were associated with ABC in approximately 5-8% of patients during the first 6 weeks of treatment with some differences by ethnicity. The frequency of the major histocompatibility complex class I allele, HLA-B*5701, significantly correlates with risk of ABC hypersensitivity[6]. Screening for HLA*B-5701 and subsequent avoidance of ABC use in patients with this allele eliminated immunologically confirmed HSRs and significantly reduced the incidence of clinically suspected HSRs: presence of HLAB*5701, HLA-DR7, and HLA-DQ3 had a positive predictive value for hypersensitivity of 100%, and a negative predictive value of 97%[7,8]. An assessment of the symptoms of abacavir HSRs reported in the PREDICT-1 study indicated that subjects with immunologically confirmed abacavir HSRs were more likely to develop symptoms from at least 3 categories of organ and involving fever[9].

In literature, there are few cases of ABC-HSR in HLA*B5701 negative patients. Recent marketing authorization holder trials, which prospectively screened for the HLA-B*5701 allele and excluded subjects testing positive, more accurately reflect experience and reporting rates in clinical practice.

ASSERT Study reported that 6 out of 192 patients in the ABC/3TC arm had a clinically suspected ABC-HSR. All subjects reported a rash, 2 reported fever, 2 constitutional symptoms, gastrointestinal or respiratory events, and 2 subjects just rash. All subjects diagnosed with a clinically suspected HSR fully recovered from the event[10].

In ARIES study, 4 individuals (0.8%) were diagnosed with clinically suspected ABC-HSR during the first 2 weeks from therapy initiation. However, all 4 individuals reported rash as part of HSR: the first presented just with rash, one plus fever, constitutional symptoms and chest pains, another one plus fever, cough, gastrointestinal symptoms and constitutional symptoms, and the last one plus fever. Not all individuals met the case definition of HSR. ABC skin patch test results were negative for all of them[11].

In ASSURE study, only one out of 199 exposed subjects to ABC/3TC+ATV had a suspected reversible ABC hypersensitivity, but symptoms are not described[12]. SINGLE study reported 9 participants considered by the investigator to have had a serious adverse event related to DTG/ABC/3TC regimen: only one (<1%) in this group had a suspected drug hypersensitivity[13].

In conclusion, considering the increasing number of patients that will be treated with DTG and DTG/ABC/3TC based regimen also in order to the new ART treatment guidelines, (DHHS, EACS, SIMIT, GESIDA) we highlight the importance of active watch on possible HSR onset, though extremely rare, in patients with HLA B*5701 negative test, and a rapid and definitive interruption of the regimen at the onset of suggestive symptoms[14-17].

Conflict of Interest:
The authors declare that they have no conflict of interests.

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