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Case Report

Pharmacology Section

Hypersensitivity Reaction Associated with Abacavir Therapy in an Indian HIV Patient – A Case Report

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ABSTRACT

The most important and unique adverse effect of abacavir (ABC) is fatal hypersensitivity reaction (HSR). The objective of this report is to describe a case of ABC induced HSR that occurred in an Indian HIV patient during treatment. Although this adverse effect is not uncommon, it is perhaps underreported or has never been reported so far in an Indian case scenario. A 44-year-old known case of HIV-1 was admitted in view of his worsening condition and very low CD4 cell counts 3 cells/μL. He was on anti-retroviral therapy since three years but not regular. On the basis of treatment failure, non-compliance and progressive low CD4 counts, the anti HIV regime was switched over to abacavir 600 mg+ atazanavir/ ritonavir 300mg/100mg Two weeks after ABC therapy he presented with maculopapular rash, headache and signs of hepatic damage (serum AST, ALP and ALT increased to 3-4 fold) suggestive of hypersensitivity reaction. As we know discontinuation of the drug is the ultimate litmus test to confirm diagnosis of drug induced adverse reaction. We did confirm ABC induced HSR by de-challenge wherein, rash disappeared within 2-3 days and LFT came back to normal within 5 days. However, no rechallenge was done. HSR was more in favour of ABC because atazanavir failed to produce any similar reaction after re-challenge.

Keywords: De-challenge, Hepatic damage, Maculopapular rash, Underreported

CASE REPORT

A 44-year-old male, known case of HIV-1 on treatment since three years came to the hospital in December 2013. Patient was immediately admitted and found to be in a debilitated state with very low CD4 count- 3 cells/μL (as on 19/12/2013). Past history revealed that in 2010 he had presented with complaints of fever and weight loss for one month. On examination, he had generalised erythema, oral candidiasis and genital herpetic lesions. On being investigated he was diagnosed to have HIV-1 and CD4 count was 20 cells/μL. He was a chronic alcoholic since 15 years. No other opportunistic infections were present. HBsAg, TPRH and VDRL were negative. He was started with tab. tenofovir disoproxil fumarate 300 mg + lamivudine 300 mg + efavirenz 600 mg combination regime and tab co-trimoxazole160 mg /400 mg prophylaxis. He was noncompliant taking on and off medications. Repeated CD4 counts analysed were low 90, 40, 31, 17 and 3 cells/ μL on 13/01/2011, 12/08/2011, 17/04/2012, 04/10/2013 and 19/12/2013 respectively. In view of low CD4 counts and non-adherence of anti-retroviral therapy he was switched over to tab. abacavir 300 mg BD + atazanavir/ ritonavir 300 mg /100 mg on 05/02/2014. However, co-trimoxazole was continued. One week later, patient started developing red raised lesions on the back associated with itching. No vesiculation or oozing was present. Two weeks after ABC therapy he presented to the hospital with complaints of easy fatigability, decreased appetite,headache, vomiting, abdominal pain, and rash over the back. There was no history of fever, myalgia, arthralgia, oedema, pharyngitis, cough, paraesthesia etc. On clinical examination maculopapular exfoliative rash was found over the back region (20% of body), the vitals were stable and there was no hepatomegaly. Investigations revealed low blood counts with deranged liver function tests. In view of these adverse effects, abacavir + atazanavir/ ritonavir and co-trimoxazole were stopped. Patient was diagnosed as ABC induced HSR and cotrimoxazole induced pancytopenia.

Patient was treated symptomatically with tablet levocetrizine. LFT reports showed improvement [Table/Fig-1] and rash subsided within 2-3 d after stopping ABC. In view of drug intolerance [Table/Fig-1,2] and progressive decline in CD4 cells, the anti HIV regime was changed strategically to tablet tenofovir/emtricitabine 300 mg /200 mg +tablet atazanavir/ritonavir 300 mg /100 mg, tablet co-trimoxazole was replaced by tablet dapsone 100 mg/day to prevent pneumocystis pneumonia.

DISCUSSION

Abacavir (ABC) is the only approved antiretroviral (HIV-1) which belongs to synthetic carbocyclic guanosine analog group. Use of abacavir in combination with three antiretrovirals can be part of a successful salvage therapy. “ABC hypersensitivity reaction occurs in 2.3–9% of adults and children with some differences by ethnicity. The clinical diagnostic criteria for ABC hypersensitivity require at least two symptoms of fever, rash, nausea, vomiting, headache, lethargy, myalgia, arthralgia or gastrointestinal symptoms and 93% of cases show this reaction within 6 week (median time 11d) after commencement and resolving within 72h of withdrawal of the drug” [1]. Less common manifestations include respiratory symptoms, paraesthesia, oedema, renal or hepatic failure and anaphylaxis. The cause is a genetically mediated immune response linked to both the HLA-B*5701 locus and the M493T allele in the heat-shock locus HSP70-Hom. The latter gene is implicated in antigen presentation, and this haplotype is associated with aberrant TNF-α release after exposure of human lymphocytes to abacavir ex vivo. This is one of the strongest pharmacogenetic associations ever described [2].

Our case report underscores the importance of recognizing ABC induced HSR. The case presented with clinical features like rash, headache, abdominal pain, malaise and signs of hepatic damage. Rash onset occurred between 5-7 days after initiation of therapy and was resolved within 2-3 day of ABC withdrawal. However, no re-challenge was done. In this case, ABC was started without skin patch testing at the same time as atazanavir. An atazanavir HSR cannot be entirely excluded; has been reported in 1% to 6% of HIV patients [3]. However, atazanavir did not produce any skin reactions after re-challenge. Co-trimoxazole causing hypersensitivity was completely ruled out because no such reactions were reported in the past while he was on co-trimoxazole for three years before ABC therapy. This argues in favour of ABC as the cause of rash. We used the RegiSCAR scoring system to classify our case as Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) or

Date	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	AST(IU/L)	ALT(IU/L)	ALP(U/L)
18/12/2013	0.3	0.1	32	18	187
26/2/2014	2.8	1.9	294	171	453
3/3/2014	0.4	0.2	35	62	300

[Table/Fig-1]: Liver function tests (LFT), *AST- Aspartate amino transferase, ALT- alanine aminotransferase, ALP- alkaline liver phosphatase*

Date	Hemoglobin(g/dl)	Hematocrit(%)	Total WBC(cells/µl)	Platelet (lakh/µl)
18/12/2013	10.2	30.8	8100 (N-38.3%, L-11.3%, B-0.8%, E-0.1%)	3.67
05/02/2014 (Day of starting abacavir)	9.9	30.4	7300 (N-62%, L – 27%M- 2%, E-4%)	2.68
26/02/2014 (Day of stopping abacavir)	8.1	23.8	900 (N-61%, L- 8%M-4%, E- 4%)	1.28
02/03/2014	6.7	19.9	1100 (N-60%, L-33%, M-3%, E-3%)	1.47
10/03/2014	7.6	22.7	2400 (N- 32%, L- 28%, M- 31%, E- 3%)	2.77

[Table/Fig-2]: Blood parameters before and after abacavir therapy., *N-Neutrophil, L-Lymphocyte, B- Basophil, M-Monocyte and E- Eosinophil*

drug hypersensitivity syndrome. RegiSCAR constitutes a European registry of severe cutaneous adverse reaction (SCAR).“In this line, the RegiSCAR’s scoring system has been designed to grade DRESS cases as “no,” “possible,” “probable,” or “definite” case. According to this our case scored 2 and graded as “possible” not a “definitive”one” [4]. The vast majority of cases were classified as either definite or probable cases of DRESS however, 10% of reported cases were not scored as DRESS according to the RegiSCAR system [4].

In one white population, the combination of these two markers (HLA-B*5701 locus and M493T allele) occurred in 94.4% of cases and <0.5% of controls for a positive predictive value of 93.8% and a negative predictive value of 99.5%. ABC should not be given to those with the HLA-B*5701 genotype; in all others, the risk of true hypersensitivity is essentially zero [5]. A meta-analysis of 25 clinical studies involving 5248 participants showed that ethnic origin might influence ABC hypersensitivity, with a lower risk associated with the Black race [6]. The highest prevalence 11% was found in Indian ethnic groups in northern Thailand, while among East Asian populations including Chinese, Korean, and Japanese, HLA-B*5701 prevalence was relatively low (0-0.3%). Caucasians in North America,UK, Spain, and Australia have a prevalence of the HLA-B*5701 allele of 6.5%-10% [7]. Martin et al., further explored the association between HLA-B*5701 and abacavir-induced HSR in a larger Western Australian cohort, and found that 94.4% (17/18) of patients who were clinically diagnosed with abacavir induced HSR (hypersensitivity reaction) carried an HLA-B*5701 allele while only 1.7% (4 of 230 subjects) of the HSR-free control group carried it [8]. More recent data using patch testing has shown that HLA-B*5701 as a marker for ABC hypersensitivity has 100% sensitivity in both US White and Black patients suggesting that the test should be used irrespective of race [1].

Case reports of the familial occurrence of ABC hypersensitivity were early clues for a genetic basis for this syndrome. Since that time, an enormous amount of progress has been made in this area with HLA-B*5701 genotyping now being used pre-prescription in most settings, and indeed this represents the best example of translational pharmacogenetics defined to date. Observational data from several clinics have shown that the use of the test reduces the incidence of hypersensitivity, and a change in the drug label with testing is now either mandatory or recommended in different countries. About 50% of antiretroviral hypersensitivity cases resolve spontaneously despite continuation of therapy. However, unlike many HSR/syndromes, this condition worsens with continued abacavir treatment. ABC can never be restarted or rechallenged once discontinued for hypersensitivity because reintroduction of the drug leads to rapid recurrence of severe symptoms, accompanied by hypotension, a shock like state, and possibly death”. The reported mortality rate of restarting ABC in sensitive individuals is 4% [2].

LIMITATION OF THE STUDY

No skin biopsy suggesting DRESS, no liver biopsy, no abacavir dermal patch test, no antinuclear antibody testing, no blood culture and no photographs of the skin rash were taken.

CONCLUSION

To date, there are few published cases describing ABC associated HSR in Indian HIV population. Clinicians prescribing ABC should be aware of this potential adverse effect, such that it may be recognized and managed in a timely manner. All the HIV patients who will be treated with ABC along with other anti-retroviral drugs should be screened with both HLA-B*5701 and ABC patch test, so that practice of phamacogenetics could be translated into personalized safe medicine.

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