CASE REPORT

Abacavir-induced fulminant hepatic failure in a HIV/HCV co-infected patient

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SUMMARY

Abacavir hypersensitivity is a rare, yet significant adverse reaction that results in a spectrum of physical and laboratory abnormalities, and has been postulated to stem from a variety of aetiological factors. The major histocompatibility complex haplotype human leucocyte antigen (HLA)-B5701 is a significant risk factor in development of hypersensitivity reactions, yet only 55% of HLA-B5701+ individuals develop such reactions, suggesting a multifactorial aetiology. Nevertheless, prospective screening and avoidance of abacavir in these patients has limited adverse events. Within this spectrum of adverse events, abacavir-induced liver toxicity is exceedingly rare and reported events have ranged from mild elevations of aminotransferases to fulminant hepatic failure. We report the case of a 50-year-old Caucasian woman with a history significant for HIV, hepatitis C virus and a HLA-B5701+ status, transferred to our emergency department in a hypotensive state and found to have acute liver failure, acute renal failure and significant rhabdomyolysis following a change of highly active antiretroviral therapy regimen.

BACKGROUND

Abacavir hypersensitivity is a rare, yet significant adverse reaction that results in a spectrum of physical and laboratory abnormalities ranging from mild rash to hepatotoxicity, nephrotoxicity, disseminated intravascular coagulation and respiratory compromise, necessitating cessation and future avoidance of abacavir.^{1–8} Abacavir-induced hypersensitivity has been postulated to stem from mitochondrial toxicity,⁹ production of reactive metabolites,^{10 11} altered peptide repertoire presentation by major histocompatibility complex (MHC) I complexes^{12–14} and covalent haptenation of endogenous peptides.^{1 10 11} The MHC haplotype human leucocyte antigen (HLA)-B5701 is a significant risk factor in development of hypersensitivity reactions,^{2 3 15} and prospective screening and avoidance of abacavir in these patients, considered the current standard of care, has limited, but not eliminated, adverse events.^{16–18} While the overwhelming majority of individuals who develop abacavir hypersensitivity reactions are HLA-B5701+, only 55% of HLA-B5701+ individuals develop such reactions, suggesting a multifactorial aetiology.^{14 18} Furthermore, reactions have been shown to occur in individuals who are HLA-B5701–, albeit at a lower rate and at delayed time range compared to those with a HLA-B5701+ status.^{1–3 19 20}

Within this spectrum of adverse events, abacavir-induced liver toxicity is exceedingly rare, and reported events have ranged from mild elevations

in the enzymes aspartate (AST) and alanine aminotransferases (ALT),^{1 19–21} to fulminant hepatic failure typified by cytoarchitectural abnormalities and hepatocyte loss on liver biopsy.²⁰ Previously published case reports^{19 20} have focused on adverse reactions in HLA-B5701– individuals and have demonstrated delayed transaminase elevations months after initiating abacavir,^{19 20} even in viral hepatitis-infected patients.²⁰ Numerous reports have highlighted the temporal relationship between initiation of abacavir therapy and the onset of adverse reactions, and have attempted to elucidate the mechanisms underlying the onset of adverse events.^{1 14} Lucas *et al*¹⁴ have suggested that abacavir-induced hypersensitivity may result from: (1) rapid reactivation of pre-existing memory T cells, even in abacavir-naïve individuals, resulting in immediate sensitivity, (2) delayed reactivation of memory T cells, resulting in delayed reactions occurring 2–3 weeks after exposure or (3) de novo expansion of naïve CD8+ T cells.

CASE PRESENTATION

We report a case of a 50-year-old Caucasian woman with a medical history significant for HIV, hepatitis C virus (HCV) and a HLA-B5701+ status, transferred to our emergency department in a hypotensive state and found to have acute liver failure, acute renal failure and significant rhabdomyolysis. Four months prior to admission, the patient was started on highly active antiretroviral therapy antiviral medications Truvada (emtricitabine/tenofovir) and Tivicay (dolutegravir), which had been successful and well tolerated without any significant associated signs or symptoms. During that time, AST and ALT were 111 and 58 IU/L, respectively, with total and direct bilirubin levels of 0.5 and 0.25 mg/dL, respectively.

Three weeks prior to admission, the patient had been switched to Triumeq (abacavir/dolutegravir/lamivudine) for once daily medication dosing. Two weeks after switching, the patient began to develop progressive episodes of nausea, vomiting, diarrhoea, diffuse myalgia and near-syncope. On admission, the patient was found to be in acute liver failure, with progressive increases in AST and ALT to 1264 and 310 IU/L, respectively, acute renal failure, with blood urea nitrogen of 48 mg/dL and a creatinine of 3.05 mg/dL, and significant rhabdomyolysis (creatinine kinase (CK) 6896 IU/L). Prothrombin time (PT) and international normalised ratio (INR) were significantly elevated at 25.6 s and 2.3, respectively. Quantitative RNA PCR for HCV viral load revealed low viral numbers 2.8×10^6 IU/L.

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OUTCOME AND FOLLOW-UP

Triumeq was immediately discontinued and aggressive intravenous fluid hydration was started with a reduction of AST and ALT to 37 and 50 IU/L, respectively, within 8 days of discontinuation. Blood urea nitrogen and creatinine also normalised to 11 and 0.6 mg/dL, respectively, with similar reduction in CK levels to 199 IU/L by the fourth day of hospitalisation. Normalisation of PT and INR were similarly observed by the third day of hospitalisation, to 12.3 s and 1.1, respectively, and remained normal until discharge.

DISCUSSION

In summary, abacavir is a potent nucleoside reverse transcriptase inhibitor that has been shown to markedly reduce HIV1 viral loads and increase CD4+ T-cell numbers when utilised alone or in combination.⁸ While abacavir has a favourable dose-safety profile,⁸ and can be safely used in individuals with impaired renal function^{4 22} or in those utilising other medications or substances affecting liver metabolism (eg, alcohol dehydrogenase and cytochrome P450 enzymes),^{23 24} abacavir-induced hypersensitivity reactions are a significant adverse event, limiting its widespread use. Although the HLA-B*5701 haplotype has been shown to be associated with robust cytotoxic T-cell responses and slowed progression of HIV,^{3 25} it has also been shown to be strongly associated with the development of abacavir-induced hypersensitivity reactions, prompting prospective haplotype analyses and immediate drug cessation in cases suspicious for hypersensitivity. These reactions span a spectrum ranging from mild rash to severe systemic reactions, occur within hours to many months after the initiation of abacavir therapy, and force clinicians and patients to be aware of, and remain alert to, the adverse events associated with abacavir therapy.

Learning points

- ▶ Abacavir hypersensitivity is a rare reaction that often occurs in the setting of a positive human leucocyte antigen-B*5701 status.
- ▶ Abacavir-induced liver toxicity occurs along a continuum with adverse events ranging from mild elevations in the enzymes aspartate and alanine aminotransferases to fulminant hepatic failure.
- ▶ Prospective screening prior to the initiation of abacavir therapy aids in reducing, but not eliminating, hypersensitivity reactions.

Competing interests None declared.

Patient consent Obtained.

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