were above the target level (150 ng/mL) in all patients. On a presumptive basis, the pharmacokinetic exposure of the raltegravir dose of 400 mg once daily seen in our patients in association with atazanavir/ritonavir might be sufficient to provide adequate antiretroviral coverage in an induction–maintenance strategy; should this drug combination prove to be successful in a clinical study, it would enable a reduction in both N/NtRTI-related toxicity and drug expenditure.

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# Rare case of rilpivirine-induced severe allergic hepatitis

**Yasir Ahmed[1], Wajid Siddiqui[1], Caroline B. Enoch[2], Helmut Albrecht[1] and P. Brandon Bookstaver[2]***

*[1]Department of Internal Medicine, Division of Infectious Diseases, University of South Carolina School of Medicine, Columbia, SC 29203, USA; [2]Department of Clinical Pharmacy and Outcomes Sciences, South Carolina College of Pharmacy, University of South Carolina, Columbia, SC 29205, USA*

*Corresponding author. Tel: +1-803-777-4786; Fax: +1-803-777-2820; E-mail: bookstaver@sccp.sc.edu

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Sir,

Drug-induced allergic hepatitis is a rare, liver-specific inflammatory reaction caused by hypersensitivity to a particular medication that may be associated with serious clinical implications.[1] Several medications, including antiretrovirals (ARVs) and, most notably, non-nucleoside reverse transcriptase inhibitors (NNRTIs), have been implicated as a cause of both drug-induced allergic hepatitis and hypersensitivity reactions.[2,3] Second-generation ARVs appear less likely to be associated with life-threatening hepatotoxicity compared with earlier counterparts; however, expanding clinical use of newer NNRTIs, such as rilpivirine, requires prudent post-marketing evaluation. To our knowledge, here we present the first case of a probable rilpivirine-induced acute allergic hepatitis.

A 28-year-old African-American man with longstanding AIDS and treatment non-adherence presented with nausea, vomiting, fever and generalized weakness for 2–3 days. The patient denied recent infectious contact or unusual ingestion including aspirin, acetaminophen or toxic mushrooms. The CD4 count was 17 cells/mm$^3$ and the HIV viral load was 262 774 copies/mL 2 weeks prior to admission. The patient had previously been diagnosed with disseminated *Mycobacterium avium-intracellulare* complex (d-MAC) infection 1 year earlier. The current ARV regimen included 300/200 mg of tenofovir/emtricitabine daily,

**Table 1.** Timeline of pertinent laboratory markers

| | AST (15–37[a]) | ALT (12–78[a]) | ALP (35–136[a]) | BUN (2.9–8.2[b]) | Cr (53–106[c]) |
|---|---|---|---|---|---|
| Prior to admission[d] | 35 | 20 | NA | 6.4 | 106 |
| Hospital day 1 | 5931 | 1516 | 293 | 13.9 | 221 |
| Hospital day 3 | 1713 | 775 | 110 | 18.6 | 247.5 |
| Hospital day 5 | 846 | 614 | 195 | 14.2 | 141.4 |
| Hospital day 10 | 116 | 170 | 178 | 5.7 | 88.4 |
| Hospital day 16 | 63 | 107 | 157 | 5.7 | 97.2 |
| Post-discharge[e] | 40 | 24 | 134 | 6.1 | 97.2 |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, serum creatinine; NA, not available.
[a]Normal reference range in U/L.
[b]Normal reference range in mmol/L.
[c]Normal reference range in μmol/L.
[d]Eight weeks prior to admission.
[e]Two weeks post-discharge.

300 mg of zidovudine twice daily and 400 mg of raltegravir twice daily. Due to non-adherence, ARV therapy had been simplified to the once-daily combination tablet 300/200/25 mg of tenofovir/emtricitabine/rilpivirine, which was initiated 4 days prior to admission. Other past medical history included hypertension, congestive heart failure and mild pericardial effusion. Concurrent medications on admission include atovaquone, ethambutol, azithromycin, carvedilol and amlodipine.

Examination revealed a temperature of 39.2°C, heart rate of 102 beats/min, blood pressure of 107/63 mmHg and respiratory rate of 18 breaths/min. The patient was in mild distress, but systemic examination was otherwise unremarkable. Initial laboratory work-up showed $6.1\times10^9$/L white blood cells with 0% eosinophils, 92 g/L haemoglobin, $198\times10^9$/L platelets, 5931 U/L aspartate aminotransferase, 1516 U/L alanine aminotransferase, 293 U/L alkaline phosphatase, 1 mg/dL total bilirubin, 71 U/L γ-glutamyl transferase, 9 μmol/L serum ammonia, 13.9 mmol/L blood urea nitrogen and 221 μmol/L serum creatinine (baseline = 106 μmol/L). Of note, liver enzymes were normal (aspartate aminotransferase, 35 U/L and alanine aminotransferase, 20 U/L) 8 weeks prior to admission. A work-up was done to rule out common causes of acute hepatitis, including serum blood alcohol and acetaminophen concentrations, hepatitis A IgM and IgG, hepatitis B surface antigen, hepatitis C virus RNA viral load, serum creatine phosphokinase and a urine drug screen, all of which were unremarkable. Considering a possible drug hypersensitivity reaction to rilpivirine, ARV therapy was discontinued. On hospital day 3, the patient began to defervesce and liver enzymes began to normalize. Blood cultures, including acid-fast bacilli smears and cultures, remained negative.

The patient's liver enzymes improved rapidly and renal function completely normalized by hospital day 16 (Table 1), at which time d-MAC therapy and atovaquone prophylaxis for *Pneumocystis jiroveci* were reinitiated. Given the temporal relationship with the initiation of the updated ARV regimen and after ruling out other causes, a new ARV regimen was initiated, consisting of 300/200 mg of tenofovir/emtricitabine daily, 300 mg of atazanavir daily, 100 mg of ritonavir daily and 400 mg of raltegravir twice daily. At a 2 week follow-up visit, liver enzymes were completely normal.

Idiosyncratic adverse reactions in the liver fall within two categories: those resulting from an unusual metabolism of the drugs (i.e. overproduction of toxic metabolites in susceptible individuals), and those involving an immune-mediated hepatocyte attack triggered by the drug (e.g. allergic hepatitis). In the first type, the effects are dose dependent and may appear after the first administration of the substance. In the second form, the adverse effects are not dose dependent and usually become apparent after previous asymptomatic trials with the drug (e.g. period of sensitization).[4,5]

Drug-induced allergic hepatitis is a liver-specific hypersensitivity reaction to a particular medication. The mechanism by which this hepatic tissue specificity is determined is now beginning to be understood.[4,5] It is frequently associated with fever, rash and liver cell infiltration, usually occurring within the first 4–6 weeks of treatment.[1] Our patient presented with fever and increased liver enzymes ∼4 days after initiation of rilpivirine and no rash was noted. The acute kidney injury resolved with hydration and discontinuation of rilpivirine. According to the Naranjo scale for adverse drug reactions, the case scored 5, predicting a probable association with rilpivirine.[6] There were no other recent medication changes or additional agents known to cause allergic hepatic hypersensitivity reactions. With other causes of hepatitis ruled out, the concluding diagnosis was rilpivirine-induced acute allergic hepatitis.

Acute hepatitis leading to liver failure with a fatal outcome in the context of a hypersensitivity drug reaction has been reported with nevirapine and abacavir in HIV-infected patients. Maraviroc-induced hepatic hypersensitivity reactions have also been documented.[7–9] Rilpivirine, a second-generation NNRTI, was recently approved in the USA, Canada and Europe for use in combination therapy in HIV-1-infected treatment-naive adults. As prescribed in our patient, rilpivirine is coformulated with tenofovir disoproxil fumarate and emtricitabine in a single tablet for once-daily administration.[10] Safety data from the ECHO and THRIVE studies comparing rilpivirine versus efavirenz

in treatment-naive subjects demonstrated a low incidence of hepatic adverse events in both groups (rilpivirine, 5.5% versus efavirenz, 6.6%), with higher rates in patients coinfected with hepatitis B virus or hepatitis C virus than in those not coinfected (26.7% versus 4.1%, respectively).[10,11] No specific cases of allergic hepatitis were noted and no life-threatening hepatotoxicity associated with rilpivirine therapy has been published to date. Although unclear, it is possible that the risk of allergic hepatitis is heightened with a low CD4 count, as in our patient, or due to other host factors, such as race or gender.

Drug-induced liver injury is of concern due to its unpredictable nature and serious clinical implications. Most episodes of allergic hepatitis have a good clinical prognosis upon drug discontinuation. Since rilpivirine is a recently approved agent for HIV treatment, prudent post-marketing monitoring for serious allergic hepatitis and reporting of such events are required.

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