Nucleoside Analogues and Mitochondrial Toxicity

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An evaluation of the US Food and Drug Administration’s Adverse Event Reporting System identified that patients coinfected with human immunodeficiency virus and chronic hepatitis C virus who were treated with a regimen of ribavirin and didanosine, with or without stavudine, were at increased risk for events associated with mitochondrial toxicity, including fatal hepatic failure, peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis. In response, the US product labels for didanosine and ribavirin have been revised to caution clinicians against coadministration of these drugs.

Cases suggestive of mitochondrial toxicity (MT), including cases of pancreatitis, lactic acidosis with liver failure, and hepatic steatosis, have been reported among patients coinfected with HIV and hepatitis C virus (HCV) who received treatment with ribavirin in combination with didanosine or in combination with didanosine and stavudine. The US Food and Drug Administration (FDA) was concerned that these reports might represent an important pattern of drug toxicity [1, 2].

The FDA’s Adverse Event Reporting System (AERS) was searched in May 2002 and again in November 2002 for all reports of adverse events in HIV and HCV–coinfected patients receiving therapy with ribavirin and any of the 7 approved nucleoside analogue reverse-transcriptase inhibitors (NRTIs): didanosine, stavudine, zidovudine, lamivudine, abacavir, zalcitabine, and tenofovir. A total of 221 reports were obtained, representing 85 unduplicated patients. Of these, 31 patients had cases that involved a total of 58 adverse events that were suggestive of MT, including pancreatitis and/or increased lipase levels (21 events), lactic acidosis and/or increased lactate levels (20 events), elevated liver function test values (8 events), hepatic steatosis (6 events), elevated creatinine kinase levels (1 event), neuropathy (1 event), and multiorgan failure (1 event).

Patients were primarily male (71%), with a mean age of 40.6 years (range, 30–54 years) and a mean weight of 66.1 kg (range, 52–100 kg). Nearlly 90% of the patients (27 of 31) had received didanosine, and 71% (22 of 31) had received stavudine; 20 of 27 patients had received both didanosine and stavudine. Use of the other NRTIs was very low. The mean durations of therapy for the NRTIs were as follows: didanosine, 20.8 months (range, 2 months–11 years); stavudine, 15.5 months (range, 2.5 months–4 years); lamivudine, 15.2 months (range, 6 months–4 years); and abacavir, 4.8 months (range, 2.5–8 months). Tenofovir was administered to 2 patients; one patient received it for 1 day and the other received it for 4 months. The mean duration of ribavirin therapy was 4.8 months (range, 7 weeks–9 months). Five patients died; all were receiving didanosine, 3 were receiving concomitant stavudine, and all had lactic acidosis. One patient had concomitant pancreatitis, and 1 patient had concomitant liver failure.

We found a significant increase in the risk of MT in patients who received concomitant ribavirin and didanosine (OR, 12.4; 95% CI, 3.785–40.846) or ribavirin with didanosine and stavudine (OR, 8.0; 95% CI, 2.94–21.884), compared with patients who received ribavirin in combination with other NRTIs (figure 1). No association was found between sex or body weight and the development of MT. There was also no association between the occurrence of MT and the use of protease inhibitors or nonnucleoside reverse-transcriptase inhibitors.

The relationship between NRTI plasma exposure and the efficacy or toxicity of the NRTI is generally not well defined, and identification of therapeutic or toxic thresholds is difficult to determine. NTRIs undergo phosphorylation to their active intracellular triphosphate moiety and the pathway to formation of the triphosphate is generally complex, with ≥1 saturable steps required. Because of these saturable steps, plasma concentrations and intracellular triphosphate concentrations generally do not correlate. In vitro data demonstrate that ribavirin can promote phosphorylation of didanosine towards its active metabolite, which likely explains the increased risk of MT.

Both zidovudine and stavudine are known causes of mitochondrial dysfunction, and ribavirin has been shown in vitro to antagonize phosphorylation to their active triphosphate forms [3, 4]. In addition, there appears to be an increased risk...
of MT in patients coinfected with HIV and HCV who receive stavudine [5]. We did not find a relationship between the use of zidovudine and cases of MT; this may be due to antagonism of phosphorylation. However, although the contribution of stavudine to the development of MT in our series is not clear, we hypothesize that, despite pressure against phosphorylation by ribavirin, sufficient levels of stavudine’s active intracellular triphosphate may indeed be present at concentrations sufficient to cause mitochondrial dysfunction.

AERS is a voluntary reporting system that is useful for identifying new types of adverse events. Because pancreatitis, lactic acidosis, and hepatic steatosis are described in the labeling of NRTIs, many clinicians no longer report such events. Thus, it is likely that our data are constrained by the under-reporting of events. Furthermore, because of the uncertainty regarding the total number of patients receiving therapy with ribavirin and didanosine, the true incidence of MT cannot be calculated. In addition, no data pertaining to clinical outcome were available; therefore, a relationship between the occurrence of MT in patients receiving NRTIs and antiviral activity could not be assessed.

Regardless, we conclude that coinfected patients treated with a regimen of ribavirin and didanosine, with or without stavudine, are at risk for MT, and we hypothesize that the MT events observed in these reports were likely related to ribavirin’s promotion of didanosine’s phosphorylation towards its active metabolite. On the basis of these data, the US prescribing information for all formulations of didanosine and for both currently approved ribavirin products has been revised to caution clinicians against coadministration of these agents. Additional investigations are needed to determine the correlation between plasma and intracellular concentrations of stavudine and the occurrence of MT.

References