not being significantly associated with SVR (OR 3.00, 95% CI 0.56–16.01, P=0.191) (Table 1). The qPCR and RFLP analyses disagreed in two cases (7.7%), where the rs8099917 genotype was determined by RFLP to be TT and qPCR indicated that it was TG. We arbitrarily considered the qPCR results to be the gold standard for analysis.

The prevalence of IL28B CC (rs12979860) in European patients was 46.9% and for TT (rs8099917) the prevalence was 51.5%, whereas in the present study, the frequencies were 34.6% and 53.8%, respectively. Moreover, there was no statistical correlation between the TT IL28B (rs8099917) genotype and SVR, possibly due to the modest influence of this SNP and/or the small sample size.

To our knowledge, this is the first study evaluating the prevalence of IL28B SNPs in a Latin-American population. The analysis presented here was limited due to the low statistical power associated with the small sample size. Nevertheless, we observed a significant association between the IL28B CC genotype and SVR in Brazilian patients coinfected with HIV, as has been shown in case studies in Western Europe.7,9

References


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Hepatitis B reactivation despite entecavir prophylaxis in a patient with chronic lymphocytic leukaemia receiving bendamustine

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Sir,

Several lines of evidence have shown that the occurrence of hepatitis B virus (HBV) reactivation is greatly reduced by the identification of high-risk patients and the use of prophylactic antiviral therapy.1 Although the occurrence of HBV reactivation depends on HBV-DNA levels, the risk is also strongly linked to immunosuppressive drugs used as part of chemotherapeutic regimens. Bendamustine is a well-known chemotherapeutic agent with both alkylating and purine-like properties that has been recently used for the treatment of chronic lymphocytic leukaemia (CLL). Herein we report the case of a CLL patient with HBV infection [hepatitis B surface antigen (HBsAg) positive/HBV-DNA negative] who developed HBV reactivation during bendamustine therapy and prophylactic use of entecavir.

A patient, diagnosed with CLL, was considered for chemotherapy with bendamustine (160 mg on days 1 and 2 every 4 weeks). Informed consent was obtained from the patient. The patient did not have serological testing for HBV. Thus, before starting chemotherapy, we performed serological screening for HBV infection and the results were the following: HBsAg positive, hepatitis B e antigen (HBeAg) positive, anti-hepatitis B core antibody (HBC) positive and anti-hepatitis B surface antibody (HBS) negative. HBV-DNA was undetectable (<12 IU/mL) (Cobas Roche TaqMan assay, Roche Diagnostics, Meylan, France). Liver enzymes were in the normal range. A pre-emptive antiviral therapy with entecavir (0.5 mg/day) was started. After the first cycle of bendamustine,
the patient showed a virological breakthrough characterized by an increase in HBV-DNA (1.28×10^6 IU/mL) and in liver enzymes [alanine aminotransferase (ALT) = 73 IU/L and aspartate aminotransferase (AST) = 44 IU/L]. The antiviral treatment was well tolerated and there was no evidence of inadequate adherence. HBV genotype D1 was detected with a lack of mutations in the surface antigen. Serotyping and mutations were assessed by sequencing HBV after PCR amplification. Serum HBV-DNA was extracted using a commercially available kit (QIAamp DNA Blood Mini Kit; Qiagen, Inc., Chatsworth, CA, USA). HBV sequencing was performed on the automated ABI Prism 3100 Genetic Analyzer using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Warrington, UK). To define the HBV genotype, sequences were compared with ≥30 GenBank reference sequences. Hepatitis D virus (HDV), hepatitis C virus (HCV) and other hepatotropic virus coinfections were also excluded. Chemotherapy with bendamustine was stopped and the antiviral treatment was intensified by increasing the dose of entecavir to 1 mg and adding tenofovir disoproxil fumarate at a dose of 300 mg/day. One month after the beginning of combined antiviral treatment, liver enzymes decreased to normal values and the HBV-DNA level was 9×10^3 IU/mL. After 5 months of therapy HBV-DNA became undetectable and the patient restarted chemotherapy. Up to 11 months after starting antiviral drugs, combined anti-HBV treatment was well tolerated.

In the literature there is only one report regarding the prophylactic use of entecavir in two HBV-infected patients undergoing chemotherapy for lymphoma. In both cases, no evidence of HBV reactivation was seen. The management of HBV reactivation under treatment for lympho-proliferative disease still remains a critical issue. The usefulness of the pre-emptive antiviral therapy with lamivudine in this particular group of patients is widely accepted. Entecavir is characterized by a higher genetic barrier and greater efficacy in the treatment of chronic hepatitis, and, until now, viral breakthrough in active HBsAg carriers undergoing chemotherapy for lympho-proliferative disease has not been reported. However, the case reported herein and the recent chemotherapy for lympho-proliferative disease has not been reported. The case reported herein and the recent observation showing that entecavir is associated with mortality in patients with HBV reactivation by increasing lactic acidosis and encephalopathy strongly suggest a note of caution in the use of entecavir as pre-emptive therapy. Indeed, to date, this indication is supported by only one published case report, while studies on the efficacy of entecavir are focused on the treatment of HBV reactivation in large B-cell lymphoma patients.

Another interesting finding of the present case is that viral breakthrough occurred in the absence of viral mutations. This finding parallels that of another CLL case, who received entecavir for HBV reactivation. Altogether, these observations may suggest that viral breakthrough may also be due to a putative mechanism of ‘immunological escape’, a condition that may favour an uncontrolled viral replication that the drug is not able to prevent. In the present case the high degree of immune system impairment, characteristic of CLL, and the immunosuppression induced by bendamustine may support this latter hypothesis.

The HBV reactivation that occurred in our patient was successfully controlled both by increasing the dose of entecavir and by adding tenofovir, another new nucleoside/nucleotide analogue (NUC) with a higher genetic barrier. This case report highlights that: (i) a viral breakthrough may occur during pre-emptive therapy with entecavir and close monitoring for HBV reactivation is mandatory for these patients; (ii) bendamustine should also be considered as a drug at high risk of HBV reactivation; and (iii) since the new NUCs are more expensive than lamivudine and their long-term safety is less well defined, future large prospective controlled studies are needed to address their use as first-line prophylactic therapy in the haematological setting.

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References