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AUTHORS' REPLY

Current strategies in the management of hepatitis B virus reactivation

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We would like to thank Xing Li, Yan-Fang Xing, Qu Lin, Min Dong, Xiang-Bo Wan and Xiang-Yuan Wu for their correspondence on our Review (Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat. Rev. Clin. Oncol.* **9**, 156–166; 2012),[1] which raises some important issues (The treatment of severe hepatitis B virus reactivation after chemotherapy. *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2012.1-c1).[2] Their comments highlight some of our own concerns regarding the treatment of hepatitis B virus (HBV) reactivation. We agree that our Review focused primarily on prevention of HBV reactivation. Although rescue treatment for acute HBV reactivation is an important issue, its description was beyond the scope of our Review, which was written for an oncology audience. We sought to provide oncologists with information to improve the understanding of HBV (and hepatitis C virus) reactivation, with the hopes of lowering the risk of hepatic complications and improving the overall survival for patients with cancer. In our opinion, data on salvage therapy is better suited to journals focusing on hepatology or infectious diseases.

In their correspondence, Li *et al.*[2] referred to their series of 19 patients with lymphoma who were diagnosed and treated for hepatitis exacerbation following treatment with chemotherapy in combination with rituximab.[3] Not all patients in the study had hepatitis attributed to HBV reactivation. Five of the 19 patients had serum HBV DNA tests before each cycle of chemotherapy and received prophylactic lamivudine; these patients reached viral response. Two patients who had viral breakthroughs with lamivudine-induced YMDD mutations continued to receive prophylactic lamivudine and subsequently died of acute HBV exacerbation. Rescue antiviral strategies (monotherapy or combination therapy) did not influence the outcomes of these patients, probably because of delays in the initiation of antiviral therapy. However, rescue treatment shortened viral response times and seemed to improve the prognosis of patients with acute exacerbation of HBV. There is no mention in the manuscript on the type of salvage agents used to suppress viraemia.[3]

Treatment of acute HBV reactivation involves aggressive supportive therapy, discontinuation of chemotherapy and the use of antiviral agents.[4] Lamivudine can be effective in achieving clinical improvement and control of viral replication in acute HBV reactivation.[5] However, this drug can be less effective in the setting of hepatic decompensation, and there are serious concerns regarding the issue of resistance.[4] HBV reactivation has also been reported in patients on prophylactic lamivudine therapy and upon withdrawal of the drug.[4,6]

Viral resistance to nucleoside or nucleotide analogues during the long-term treatment of chronic HBV can be a major problem in patient management.[7] The best strategy for treating acute HBV reactivation in a patient who had been on lamivudine would be to add or switch to tenofovir.[8,9] For those patients who develop HBV reactivation (and have never received treatment with nucleoside analogues), entecavir and tenofovir are the drugs of choice given their potent antiviral effect and low levels of resistance.[10,11]

We must emphasize that rescue therapy should be determined by the pathways of antiviral resistance in chronic HBV. From a cross-resistance perspective, the five nucleoside and nucleotides analogues available to treat HBV infection have been placed, based on structural characteristics, into three groups: L-nucleosides (lamivudine and telbivudine), alkyl phosphonates (adefovir and tenofovir), and D-cyclopentanes (entecavir). The common mutations that confer resistance to lamivudine and telbivudine (that is, rtM204V/I and rtL180M) confer cross-resistance to other L-nucleosides and reduce sensitivity to entecavir but not to adefovir and tenofovir, which are the potential therapeutic options for patients with these mutations. Conversely, patients who are resistant to adefovir (that is, those bearing rtN236T mutations) and tenofovir generally remain sensitive to L-nucleosides and entecavir.[9] Primary resistance to tenofovir has not been confirmed at this point.[9] Of note, none of the 641 nucleoside-naive or nucleoside-treated patients developed HBV polymerase/reverse transcriptase mutations associated with tenofovir resistance after up to 144 weeks of exposure to tenofovir monotherapy.[7] Both the L-nucleosides and alkyl phosphonates also select for the mutation rtA181T/V, thereby making it a marker for multidrug resistance. Patients with this 'shared' mutation (rtA181T/V) can be rescued with entecavir. Multiple mutations (for example, rtS184G, rtS202G/I and rtM250I/V) in addition to those that confer resistance to lamivudine and telbivudine are required for high-level resistance to entecavir.[9] For patients who are resistant to entecavir, tenofovir can be added to their regimen.[9]

We thank Li *et al.*[2] for their interest in our Review and believe that their comments reflect the paucity of clinical studies involved in the treatment of HBV reactivation.

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Competing interests
H. A. Torres declares that he has acted as a consultant for Merck and Vertex. M. Davila declares no competing interests.

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