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EDITORIAL

Hepatitis B Reactivation or Hepatitis C Exacerbation in Patients with Hematological Malignancies

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Hepatitis B reactivation or hepatitis C exacerbation are critical clinical problems in patients with hematological malignancies undergoing immunosuppressive therapy or chemotherapy. Indeed, they can cause acute liver failure that may, in turn, delay or interrupt chemotherapy with a dramatic impact on cancer evolution.[1] Risk factors for hepatitis B virus (HBV) reactivation have been described in patients receiving chemotherapy, including male gender, older age, chemotherapy regimen (monoclonal antibodies such as rituximab, ofatumumab, obinutumumab) and hepatitis B status (presence of hepatitis B surface antigen [HBsAg] or of isolated antibodies directed against the HBV core protein [anti-HBc antibodies]).[2] Screening all patients with hematological malignancies for HBsAg and anti-HBc antibodies is thus key to prevent HBV reactivation.[3] International clinical practice guidelines recommend pre-emptive/prophylactic therapy in patients with hematological malignancies and HBV markers who receive chemotherapy.[3,4] Different strategies have been proposed according to the serum HBV markers present, but there is no consensus on the treatment of choice in the different settings.[3,4] Recently, grading of HBV reactivation was proposed to guide treatment decisions, based on the type of virological event (reverse seroconversion [i.e. seroreversion] or rise in HBV DNA), the severity of liver injury, and the consequences of immunosuppressive therapy.[5] In contrast to HBV reactivation, acute exacerbation of hepatitis C virus (HCV) infection has been poorly studied. It has been reported in 11% of cases in a recent study,[6] but pre-emptive/prophylactic treatment has not been studied and is not recommended by international clinical practice guidelines.[7]

In this issue of *Annals of Hepatology*, Guarino, *et al*. measured the incidence of hepatitis B reactivation and hepatitis C exacerbation in 322 patients with Hodgkin's (89.7%) or non-Hodgkin (10.3%) lymphoma undergoing chemotherapy. Forty-seven patients were found with HBV markers, including 34 patients (10.5%) with isolated anti-HBc antibodies and 13 patients (4%) with both HBsAg and anti-HBc antibodies. HBV reactivation occurred in 2 of them, 1 and 6 months after the end of chemotherapy, respectively. Both patients had non-Hodgkin lymphoma and were treated with R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone). One patient was anti-HBs and anti-HBc antibody-positive and did not receive lamivudine prophylaxis. He was treated with lamivudine at the time of reactivation and recovered within two months. The other patient had isolated anti-HBc antibodies and received lamivudine prophylaxis. At the time of reactivation, this patient was switched to tenofovir disoproxil fumarate (TDF) and recovered within a month. Both reactivations presented with detectable HBV DNA in serum (1,800 and 2,500 IU/mL, respectively) and elevated serum alanine aminotransferase level, over 10-fold the upper limit of normal values.

Lamivudine has been extensively used to treat chronic hepatitis B, based on its antiviral efficacy and safety profile, its affordable cost and its broad availability. However, sustained lamivudine administration is associated with the frequent selection of resistant HBV (24% and 70% after 1 and 5 years of treatment, respectively), which causes virologic breakthrough characterized by a return to baseline replication levels.[4] Pre-emptive or prophylactic administration of lamivudine was shown to reduce, but not eliminate, the risk of HBV reactivation in patients receiving immunosuppressive therapy.[8] In the study by Guarino, *et al.,* one of the two patients with HBV reactivation was on lamivudine prophylaxis. Similar findings have been reported in patients with lymphoma,[2] as well as in individuals with other types of malignancies such as breast cancer[9]

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and in hematopoietic stem cell transplant recipients.[10] Altogether, these findings suggest that lamivudine prophylaxis is suboptimal. Thus, recommendations for pre-emptive/prophylactic therapy of HBV reactivation must be updated. The second generation of nucleos(t)ide analogues, that includes entecavir and TDF, has been shown to be more potent and to have a substantially higher barrier to resistance than lamivudine or adefovir. Indeed, selection of resistant viruses occurred in only 1.2% of cases after 5 years of entecavir and in no case after 6 years of TDF therapy in patients with chronic hepatitis B.[4] Entecavir and TDF were reported to reduce the incidence of hepatitis, liver decompensation and treatment interruption in patients on chemotherapy.[11,12] Thus, entecavir or TDF must now be preferred as first-line pre-emptive/prophylactic HBV therapy in patients at risk of HBV reactivation receiving immunosuppressive therapy or chemotherapy. Their use will be favored by the fact these two drugs are now off-patent. Recently, tenofovir alafenamide (TAF), a phosphonate prodrug of TDF, has been approved in the US and Europe. TAF administration is associated with a lower risk of kidney toxicity or bone density changes than TDF, while displaying equivalent anti-HBV activity and a similarly high barrier to resistance.[13,14] The interest of TAF in pre-emptive/prophylactic treatment of HBV reactivation must now be evaluated.

Patients with isolated anti-HBc antibodies represent a special population in which no standard strategy has yet been established to prevent HBV reactivation. Two approaches have been proposed.[3, 4] The first one consists in pre-emptive therapy guided by serial monitoring of HBV DNA levels, with antiviral therapy being started as soon as HBV DNA becomes detectable. This strategy raises the issue of the ideal rhythm and duration of monitoring. An alternative approach is to start prophylactic antiviral therapy in all high-risk patients, such as those receiving rituximab-containing chemotherapy. This approach requires better identification of the risk factors of HBV reactivation. No consensus has been reached as to the best approach for this population of patients.

In the study by Guarino, *et al.,* 8 patients (2.5%) were anti-HCV antibody-positive, and 2 of them (0.6%) were HCV RNA-positive, a result in keeping with the reported prevalence of HCV infection in patients with hematological malignancies. No exacerbation of hepatitis C was observed in this study. There is currently no recommendation to prevent HCV exacerbation in immunocompromised patients. New orally administered anti-HCV therapies are now available with high efficiency after 8 to 24 weeks of therapy.[7] Thus, prophylactic treatment is theoretically possible. The data by Guarino, *et al.* do not make it possible to conclude as to whether such an approach would be valuable. However, given the extraordinary efficacy of new anti-HCV therapies, early diagnosis and curative treatment of HCV infection before immunosuppressive therapy or chemotherapy is started appears as the most efficient strategy to prevent the complications associated with HCV exacerbation, provided that HCV treatment does not delay chemotherapy in patients who need to be urgently treated.

In conclusion, hepatitis B reactivation in patients with hematological malignancies is a relatively rare event that may have dramatic consequences. These consequences can be avoided by screening all candidates to chemotherapy and immunosuppressive therapy for HBsAg and anti-HBc antibodies prior to treatment initiation. Which patients should benefit from pre-emptive/prophylactic therapy of HBV reactivation remains debated. Lamivudine appears as suboptimal, whereas entecavir, TDF or TAF should be used as first-line drugs in this indication. The incidence and severity of hepatitis C exacerbation in patients undergoing immunosuppressive therapy remain poorly known. Further studies should explore the clinical consequences of such exacerbations in order to generate clear recommendations as to the optimal timing of therapy and drug regimen.

ABBREVIATIONS

- **anti-HBc antibodies:** antibodies directed against the HBV core protein.
- **HBV:** hepatitis B virus.
- **HBsAg:** hepatitis B surface antigen.
- **HCV:** hepatitis C virus.
- **TDF:** tenofovir disoproxil fumarate.
- **TAF:** tenofovir alafenamide.

CONFLICTS OF INTEREST

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REFERENCES

1. Castelli R, Ferraris L, Pantaleo G, Lambertenghi-Deliliers G, Cicardi M. High rate of hepatitis B viral breakthrough in elderly non-Hodgkin lymphomas patients treated with Rituximab based chemotherapy. *Dig Liver Dis* 2016; 48: 1394-7.
2. Ozoya OO, Sokol L, Dalia S. Hepatitis B Reactivation with novel agents in non-Hodgkin's lymphoma and prevention strategies. *J Clin Transl Hepatol* 2016; 4(2): 143-50.
3. Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration

warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? *Hepatology* 2015; 61(2): 703-11.
4. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012; 57(1): 167-85.
5. Visram A, Feld JJ. Defining and grading HBV reactivation. *Clinical Liver Disease* 2015; 5(2): 35-8.
6. Mahale P, Kontoyiannis DP, Chemaly RF, Jiang Y, Hwang JP, Davila M, Torres HA. Acute exacerbation and reactivation of chronic hepatitis C virus infection in cancer patients. *J Hepatol* 2012; 57: 1177-85.
7. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol* 2017; 66(1): 153-94.
8. Huang H, Li X, Zhu J, Ye S, Zhang H, Wang W, Wu X, et al. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. *JAMA* 2014; 312: 2521-30.
9. Liu Z, Jiang L, Liang G, Song E, Zheng Y, Gong C. Hepatitis B virus reactivation in breast cancer patients undergoing chemotherapy: a review and meta-analysis of prophylaxis management. *J Viral Hepat* 2017; 00: 1-12.doi: 10.1111/jvh.12672.
10. Cerva C, Colagrossi L, Maffongelli G, Salpini R, Di Carlo D, Malagnino V, Battisti A, et al. Persistent risk of HBV reactivation despite extensive lamivudine prophylaxis in haematopoietic stem cell transplant recipients who are anti-HBc-positive or HBV-negative recipients with an anti-HBc-positive donor. *Clin Microbiol Infect* 2016; 22: 946.e1-946.e8.
11. Tseng CM, Chen TB, Hsu YC, Chang CY, Lin JT, Mo LR. Comparative effectiveness of nucleos(t)ide analogues in chronic hepatitis B patients undergoing cytotoxic chemotherapy. *Asia Pac J Clin Oncol* 2016; 12(4): 421-9.
12. Zhang MY, Zhu GQ, Shi KQ, Zheng JN, Cheng Z, Zou ZL, Huang HH, et al. Systematic review with network meta-analysis: Comparative efficacy of oral nucleos(t)ide analogues for the prevention of chemotherapy-induced hepatitis B virus reactivation. *Oncotarget* 2016; 7: 30642-58.
13. De Clercq E. Tenofovir alafenamide (TAF) as the successor of tenofovir disoproxil fumarate (TDF). *Biochem Pharmacol* 2016; 119: 1-7.
14. Agarwal K, Fung SK, Nguyen TT, Cheng W, Sicard E, Ryder SD, Flaherty JF, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. *J Hepatol* 2015; 62: 533-40.

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