



In the Light of European Association for the Study of the Liver 2017: Terminology and Approach to Hepatitis B Virus Reactivation in Patients at High Risk

Avrupa Karaciğer Araştırmaları Derneği 2017 Işığında: Yüksek Riskli Hastalarda Hepatit B Virüsü Reaktivasyonuna Yaklaşım ve Terminoloji

Bircan KAYAASLAN, Rahmet GÜNER

Yıldırım Beyazıt University Faculty of Medicine, Atatürk Training and Research Hospital, Department of Infectious Disease and Clinical Microbiology, Ankara, Turkey

Keywords: Hepatitis B virus reactivation, terminology, prevention
Anahtar Kelimeler: Hepatit B virüsü reaktivasyonu, terminoloji, önleme

Kayaaslan B, Güner R. In the Light of European Association for the Study of the Liver 2017: Terminology and Approach to Hepatitis B Virus Reactivation in Patients at High Risk. Viral Hepat J. 2017;23:83-85.

Dear Editor,

Reactivation of hepatitis B virus (HBV) is a prevalent and important problem in transplant recipients receiving immunosuppressive treatment for prevention of organ rejection or in those who receive chemotherapy for lymphoma or leukemia (1). It is defined as a sudden increase in HBV replication in patients with inactive or resolved hepatitis B, in hepatitis B surface antigen (HBsAg) carriers and HBsAg-negative but anti-hepatitis B core (HBc)-positive patients (2). The current guidelines recommend HBV screening in patients who will receive cancer chemotherapy or immunosuppressive therapy and in those who are candidate for organ transplantation. All patients with active or inactive disease or resolved HBV infection are at risk for HBV reactivation in different degree depending on the type of immunosuppressive therapy. Treatment recommendations are based on the patients' risk group (1,3,4). Reddy et al. (4) have described the recommendation of the American Gastroenterological Association Institute systematically about prevention and treatment of HBV reactivation during immunosuppressive drug therapy in detail.

HBsAg, anti-HBs and anti-HBc total antibody should be screened prior to initiation of immunosuppressive treatment (5,6,7). There are some differences in the management of prevention of hepatitis B reactivation in the literature. We assume that these differences result from the confusion in nomenclature. In this report, we aimed to draw attention to the fact that there is a need for using standardized nomenclature and definition about recommended therapy for risky population.

In the literature, terms such as "prophylactic", "pre-emptive" and "therapeutic" antiviral therapy are used to describe recommended treatment option for prevention of HBV reactivation in patients infected with HBV who undergo immunosuppressive treatment. There is no enough description about the use of "prophylactic, pre-emptive and therapeutic antiviral therapy" terms in the current clinical guidelines for hepatitis B, although they contain recommendations for prevention of reactivation in this patient populations (5,6,7). The distinction between "prophylactic" and "pre-emptive" treatment has not been clearly understood in the European Association for the Study of the Liver (EASL) 2012

clinical practice guideline. "Pre-emptive treatment" has been recommended for HBsAg-positive patients during treatment and 12 months after discontinuation of therapy regardless of HBV DNA levels (8). The last updated EASL 2017 guideline does not use the term "pre-emptive treatment" in this patient population and recommends the use of nucleos(t)ide analogues (NAs) for prophylaxis and treatment. The guideline recommends pre-emptive treatment in HBsAg-negative, anti-HBc-positive patients with moderate or low-risk of HBV reactivation and describes the meaning of pre-emptive treatment. Initiation of prophylactic NAs in HBsAg-negative and anti-HBc-positive patients at high-risk for HBV reactivation has been remarked as recommendation of some experts in EASL 2012 guideline. EASL 2017 offers anti-HBV prophylaxis in these patient populations as guideline recommendation (6).

The Asian Pacific Association for the Study of the Liver (APASL) guideline on the management of hepatitis B infection recommends "prophylactic" antiviral therapy in HBsAg-positive cancer patients and in those who undergo solid organ transplantation or receive immunosuppressive agents for auto-immune and rheumatic diseases. The guideline recommends prospective follow-up of alanine aminotransferase (ALT) and HBV DNA testing in HBsAg-negative and anti-HBc-positive patients with undetectable serum HBV DNA who receive chemotherapy and/or immunosuppression, regardless of anti-HBs status and treatment with NA therapy upon confirmation of HBV reactivation before ALT elevation (7). This strategy was named as "pre-emptive" antiviral treatment in a literature review by Hwang and Lok (1) in which the most descriptive definition of recommended therapy for prevention of HBV reactivation have been made. They have proposed use of the term "preventive antiviral therapy" as antiviral therapy started when ALT and/or HBV DNA levels increase and there are no signs of jaundice or liver failure when antiviral therapy is initiated in patients receiving immunosuppressive therapy. The guideline of the American Society of Transplantation (AST) for viral hepatitis in solid organ transplantation does not recommend routine antiviral prophylaxis in patients with resolved hepatitis B infection (HBsAg-negative, anti-HBc-positive \pm anti-HBs-positive) who undergo immunosuppressive treatment. However, the AST recommends initiating "prophylactic antiviral treatment" in patients with increased risk for HBV reactivation (anti-HBc-positive alone or intense immunosuppression) or alternately monitoring HBV DNA and HBsAg level and initiating "pre-emptive antiviral treatment" if HBsAg becomes positive or if HBV DNA progressively rises (9). The meaning of the terms of "prophylactic" and "pre-emptive" antiviral treatment in the AST guideline are similar to those defined by Hwang and Lok (1). We think that it is better the current guidelines use this nomenclature and explain the meaning of the terms when they recommend an approach for the prevention of HBV reactivation.

A similar confusion is also available in a review about antiviral treatment in renal transplant patients written by Ridruejo (10). In the review, "antiviral treatment" has been recommended in patients with chronic hepatitis B and "prophylactic", "pre-emptive" or "salvage therapy" in inactive hepatitis B carriers based on HBV DNA level and hepatocellular histology. The meaning of the terms

is poorly understood. The other topic we want to point out is the contradictions in treatment recommendations in the review. Pre-emptive therapy is recommended in patients with HBV DNA ≤ 2000 IU/mL, while prophylactic antiviral therapy is recommended in HBV DNA-negative patients. We think that the recommendation on pre-emptive therapy is an imprudent approach especially in HBV DNA-positive organ transplant patients. The reviewer also recommends starting treatment at least 2 weeks before renal transplantation in those with HBV DNA ≤ 2000 IU/mL in the section of timing of initiation of treatment. This suggestion is not compatible with the definition of prophylactic and pre-emptive treatment.

The EASL 2017 guideline has corrected the terminology confusion in the previous version. The recommendations of the updated EASL 2017, AST guideline and the APASL guideline are parallels to approach to HBV reactivation in high-risk patients (6,7,9). In the light of the EASL 2017 guideline, prophylactic/pre-emptive (on-demand) and therapeutic approaches are standardized according to the patients' hepatitis B status and the type of immunosuppressive treatment (6). We think that this algorithm becomes a reasonable and non-confusing approach to HBV reactivation.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.K., R.G., Concept: R.G., B.K., Design: R.G., B.K., Data Collection or Processing: B.K., R.G., Analysis or Interpretation: B.K., R.G., Literature Search: B.K., R.G., Writing: B.K., R.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol.* 2014;11:209-219.
- Hoofnagle JH. Reactivation of hepatitis B. *Hepatology.* 2009;49(Suppl 5):156-165.
- Seetharam A, Perrillo R, Gish R. Immunosuppression in Patients with Chronic Hepatitis B. *Curr Hepatol Rep.* 2014;13:235-244.
- Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology.* 2015;148:215-219.
- Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50:661-662.
- European Association for the Study of the Liver. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67:370-398.
- Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao

- JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepato Int.* 2016;10:1-98.
8. European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol.* 2012;57:167-185.
 9. Levitsky J, Doucette K; AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. *Am J Transplant.* 2013;13(Suppl 4):147-168.
 10. Ridruejo E. Antiviral treatment for chronic hepatitis B in renal transplant patients. *World J Hepatol.* 2015;7:189-203.