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EDITORIAL

Expanding indications for chronic hepatitis B treatment: Is it really desirable to treat everyone?

Fabiola Di Dato, Raffaele Iorio

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Abstract

Chronic viral hepatitis causes an increased risk of progressive liver disease and hepatocellular carcinoma. On the wave of the World Health Organization's goal to reduce new cases and deaths from hepatitis B and C by 2030, there is an increasing call to expand the indications for treatment of chronic hepatitis B. Currently, the main goal of treatment is to achieve a functional cure due to the inability of current drugs to completely eradicate the virus. There are still many discrepancies between available guidelines in terms of eligibility for treatment as well as an uncertainty about the appropriate treatment duration. This editorial addresses key questions about the topic and whether indications for treatment should be expanded.

Key Words: Hepatitis B virus; Interferon; Nucleos(t)ide analogues; Functional cure; Children

Core Tip: There is a growing trend to expand the indications for the treatment of chronic hepatitis B. Starting from the concept that current therapies for chronic hepatitis B are unable to completely eradicate hepatitis B virus infection, this editorial critically analyzes the long-term efficacy of the available therapies and the rationale for an extension of current indications.

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INTRODUCTION

In 2016, the World Health Organization set the goal of reducing the global incidence of new cases of hepatitis B and C by 90% and deaths from these two viruses by 65% by 2030[1]. It is well known that patients with chronic viral hepatitis are at increased risk of progressive liver disease and hepatocellular carcinoma (HCC). Over the last few decades, different treatments [first based on interferons and then on nucleos(t)ides analogues (NAs)] have become available for chronic hepatitis B (CHB); the efficacy rates have been variable but none have achieved complete eradication of hepatitis B virus (HBV)[2]. As such, over the last decade the treatment of choice has become long-term administration of NAs with a high barrier to resistance[3].

Currently, the main indications for CHB treatment in adults and children are cirrhosis or active hepatitis. According to available guidelines, the decision to initiate treatment is based on a combined evaluation of HBV-DNA serum levels, alanine aminotransferase concentrations, hepatitis B e antigen status, stage of liver disease, a family history of HCC, and concomitance of HIV infection or other liver diseases[4]. However, there are discrepancies in terms of eligibility for treatment, ranging from conservative (see the European Association for the Study of the Liver guidelines) to interventionist positions (see the American Association of the Study of Liver Diseases and Asian Pacific Association for the Study of the Liver guidelines)[5-7]. Although available treatments are unable to completely eradicate HBV infection, there is a growing trend to broaden the indications for treatment in order to reduce the rates of progression to cirrhosis and HCC and to increase long-term survival.

These hot-topic questions were the subject of a review by Broquetas *et al*[2] and a Letter to the Editor by Bao *et al*[8] recently published in the *World Journal of Gastroenterology*. In particular, Bao *et al*[8] proclaimed the urgent need to extend treatment criteria to improve both the cost-effectiveness and survival of patients with CHB[8].

SHOULD THE INDICATIONS FOR HBV TREATMENT BE EXPANDED?

While there is no doubt about the ability of antiviral therapy in chronic hepatitis C to permanently eradicate the virus, it is equally certain that current antiviral therapies for CHB do not achieve lasting virological eradication in most cases. Since HBV infection is incurable due to the persistence of covalently closed circular DNA in hepatocytes, integration of HBV-DNA into host cell genomes, and HBV-induced defective innate and cellular immune responses, the real advisable goal of therapy has become functional cure (loss of hepatitis B surface antigen and undetectable HBV-DNA in serum)[3]. This limited goal rather than complete eradication of the infection is indicative of the current dissatisfaction with available treatments and the desire to reset therapeutic strategies[9].

In 2022, representatives from academia, industry, regulatory agencies, and patient advocacy groups came together to reach a consensus on CHB treatment endpoints, to update the primary and alternative endpoints, and to revise the functional cure definition (from undetected levels of HBV-DNA in 2019 to levels lower than the lower limit of quantification in 2022)[10]. This indicates the limited effectiveness of the current therapies. These elements must be carefully weighed before considering a possible expansion of the indications for CHB treatment.

Furthermore, unlike chronic hepatitis C where the treatment with new antivirals has a defined duration, the length of therapy for CHB is still a matter of debate. Most people who start hepatitis B treatment must continue it for life to maintain the block of viral replication thus subjecting patients with the high costs of long-term therapy. Indeed, virological relapse is common upon withdrawal of treatment, and the risk of hepatic decompensation after withdrawal is real[11].

The relationships between levels of viral replication and the determination of liver damage are very intriguing in hepatitis B. In fact, patients, such as vertically infected children who present the highest levels of viremia, usually have no signs of liver damage (the so-called immunotolerance phase). In contrast, liver damage often occurs in phases in which viral replication declines and the organism recognizes the virus as non-self[2]. Despite this paradigm that is exhibited in the background of all available guidelines on the topic, the idea that the control of viral replication translates into a positive impact on the reduction of inflammation and liver fibrosis is increasingly strengthened[5-7]. However, the benefit of the treatments used is often based on surrogate parameters rather than mortality/survival percentages. In addition, if there had been a clear benefit in treated patients compared to untreated ones, the indications for therapy would have rapidly expanded in the same way as what happened for hepatitis C.

Much of the reasoning from Bao *et al*[8] to support the expansion of treatment indications comes from a modeling and economic impact analysis that demonstrated that expanding the treatment criteria could reduce HBV-related mortality rates and improve cost-effectiveness[12,13]. As already mentioned, there are studies that have demonstrated an advantage of the treatment, but other positions cannot be ignored. CHB patients included in therapeutic trials are heterogeneous for a series of parameters such as patient age, duration of infection, disease phase, geographical origin, genetic background, virological characteristics, disease severity, and comorbidities, all of which influence the evolution of the disease and complicate the interpretation of results regarding the effectiveness of treatments[9].

Furthermore, the tendency to mainly publish studies with favorable results should not be overlooked[14]. As for the favorable repercussion of treatment on the risk of HCC, there is substantial agreement on the positive impact of antiviral treatment, but controversies and open questions remain[15]. In addition, expanding treatment would also mean treating all children with CHB. Would this imply long-term therapy for these young patients with a long life expectancy? At what cost? It should not be ignored that studies with long observation periods of treated children compared to untreated children have not highlighted major differences in terms of complications and mortality over a period of 24-29 years[16, 17]. The other pediatric studies that demonstrated an advantage of the treatment focused heavily on obtaining laboratory

objectives rather than the risk of complications from cirrhosis and HCC and duration of survival[18,19]. Thus, as often happens, we run the risk of applying evidence carried out in adulthood to children and therefore medicalizing a group of subjects who may not have significant complications in the long term.

CONCLUSION

It would be desirable to define whether the time has already come to expand the therapeutic indications of antivirals with their current cost/effectiveness ratio or whether it is better to wait for new integrated therapeutic strategies that also include immunomodulators aimed at restoring immune functions depleted in CHB patients.

FOOTNOTES

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REFERENCES

1 **World Health Organization**. Hepatitis. 2020. [cited 4 February 2024]. Available from: https://www.who.int/health-topics/hepatitis/elimination-of-hepatitis-by-2030#tab=tab_1
2 **Broquetas T**, Carrión JA. Past, present, and future of long-term treatment for hepatitis B virus. *World J Gastroenterol* 2023; **29**: 3964-3983 [PMID: 37476586 DOI: 10.3748/wjg.v29.i25.3964]
3 **Leoni S**, Casabianca A, Biagioni B, Serio I. Viral hepatitis: Innovations and expectations. *World J Gastroenterol* 2022; **28**: 517-531 [PMID: 35316960 DOI: 10.3748/wjg.v28.i5.517]
4 **Indolfi G**, Easterbrook P, Dusheiko G, Siberry G, Chang MH, Thorne C, Bulterys M, Chan PL, El-Sayed MH, Giaquinto C, Jonas MM, Meyers T, Walsh N, Wirth S, Penazzato M. Hepatitis B virus infection in children and adolescents. *Lancet Gastroenterol Hepatol* 2019; **4**: 466-476 [PMID: 30982722 DOI: 10.1016/S2468-1253(19)30042-1]
5 **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 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]
6 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]
7 **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. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]
8 **Bao ZH**, Dai ZK, Tang HX. Antiviral treatment standards for hepatitis B: An urgent need for expansion. *World J Gastroenterol* 2024; **30**: 418-420 [PMID: 38313234 DOI: 10.3748/wjg.v30.i4.418]
9 **Pawlotsky JM**. New hepatitis B drug development disillusions: time to reset? *Lancet Gastroenterol Hepatol* 2023; **8**: 192-197 [PMID: 36343654 DOI: 10.1016/S2468-1253(22)00341-7]
10 **Ghany MG**, Buti M, Lampertico P, Lee HM; 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference Faculty. Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: Report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference. *J Hepatol* 2023; **79**: 1254-1269 [PMID: 37377088 DOI: 10.1016/j.jhep.2023.06.002]
11 **Hirode G**, Choi HSJ, Chen CH, Su TH, Seto WK, Van Hees S, Papatheodoridi M, Lens S, Wong G, Brakenhoff SM, Chien RN, Feld J, Sonneveld MJ, Chan HLY, Forns X, Papatheodoridis GV, Vanwolleghem T, Yuen MF, Hsu YC, Kao JH, Cornberg M, Hansen BE, Jeng WJ, Janssen HLA; RETRACT-B Study Group. Off-Therapy Response After Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B: An International, Multicenter, Multiethnic Cohort (RETRACT-B Study). *Gastroenterology* 2022; **162**: 757-771.e4 [PMID: 34762906 DOI: 10.1053/j.gastro.2021.11.002]
12 **Lim YS**, Ahn SH, Shim JJ, Razavi H, Razavi-Shearer D, Sinn DH. Impact of expanding hepatitis B treatment guidelines: A modelling and economic impact analysis. *Aliment Pharmacol Ther* 2022; **56**: 519-528 [PMID: 35614532 DOI: 10.1111/apt.17052]
13 **Zhang S**, Wang C, Liu B, Lu QB, Shang J, Zhou Y, Jia J, Xu X, Rao H, Han B, Zhao T, Chen L, Xie M, Cui J, Du J, Zeng J, Huang N, Liu Y, Zhang L, Zhuang H, Cui F. Cost-effectiveness of expanded antiviral treatment for chronic hepatitis B virus infection in China: an economic

evaluation. *Lancet Reg Health West Pac* 2023; **35**: 100738 [PMID: 37424693 DOI: 10.1016/j.lanwpc.2023.100738]

14 **Hopewell S**, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev* 2009; **2009**: MR000006 [PMID: 19160345 DOI: 10.1002/14651858.MR000006.pub3]

15 **Kim SK**, Fujii T, Kim SR, Nakai A, Lim YS, Hagiwara S, Kudo M. Hepatitis B Virus Treatment and Hepatocellular Carcinoma: Controversies and Approaches to Consensus. *Liver Cancer* 2022; **11**: 497-510 [PMID: 36589728 DOI: 10.1159/000525518]

16 **Iorio R**, Giannattasio A, Cirillo F, D' Alessandro L, Vegnente A. Long-term outcome in children with chronic hepatitis B: a 24-year observation period. *Clin Infect Dis* 2007; **45**: 943-949 [PMID: 17879906 DOI: 10.1086/521864]

17 **Bortolotti F**, Guido M, Bartolacci S, Cadrobbi P, Crivellaro C, Noventa F, Morsica G, Moriondo M, Gatta A. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. *Hepatology* 2006; **43**: 556-562 [PMID: 16496323 DOI: 10.1002/hep.21077]

18 **Jonas MM**, Lok AS, McMahon BJ, Brown RS Jr, Wong JB, Ahmed AT, Farah W, Mouchli MA, Singh S, Prokop LJ, Murad MH, Mohammed K. Antiviral therapy in management of chronic hepatitis B viral infection in children: A systematic review and meta-analysis. *Hepatology* 2016; **63**: 307-318 [PMID: 26566163 DOI: 10.1002/hep.28278]

19 **Zheng F**, Tan Z, Liang Z, Xiang W. Efficacy and Safety of Antiviral Therapy for Immune-tolerant Hepatitis B Viral Infection in Children: A Systematic Review and Meta-analysis. *Pediatr Infect Dis J* 2023; **42**: 942-948 [PMID: 37523508 DOI: 10.1097/INF.0000000000004057]

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