World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4254/wjh.v6.i4.226

World J Hepatol 2014 April 27; 6(4): 226-229
ISSN 1948-5182 (online)

To treat or not to treat the "immunotolerant phase" of hepatitis B infection: A tunnel of controversy

Mohamed A Mekky

Mohamed A Mekky, Department of Tropical Medicine and Gastroenterology, Assiut University Hospital, Assiut 71111, Egypt
Author contributions: Mekky MA designed the work and wrote the paper.
Correspondence to: Mohamed A Mekky, MD, PhD, Department of Tropical Medicine and Gastroenterology, Assiut University Hospital, Assiut 71111, Egypt. doc_mekky0000@yahoo.com
Telephone: +2-88-4710955 Fax: +2-88-2343308
Received: September 15, 2013 Revised: December 8, 2013
Accepted: February 20, 2014
Published online: April 27, 2014

A thorough review of the updated published reports was carried out and a merge of the various management options, with a special point of view of the author, is stated.

Mekky MA. To treat or not to treat the "immunotolerant phase" of hepatitis B infection: A tunnel of controversy. *World J Hepatol* 2014; 6(4): 226-229 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i4/226.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i4.226

Abstract

Hepatitis B virus (HBV) infection is a global public health problem, with an estimated 350 million people worldwide chronically infected and approximately 500000 who die annually from HBV-related liver diseases. Management of chronic HBV is challenging and waves of guidelines emerge every year. One of the hottest topics and a matter of debate is the management of patients in their early immunotolerant phase of infection. With the lack of evidence, dealing with this particular subset of patients creates a great conflict with opposing views. In this review, the author highlights the pros and cons of these views and proposes a reasonable solution to resolve this dilemma.

Key words: Liver biopsy; Hepatitis B Virus; Immunotolerant phase; Polymerase chain reaction; Nucleotide analogue

Core tip: In this mini review, the author discusses the management dilemma of this peculiar subset of patients suffering from chronic hepatitis B in the immunotolerant phase. As already known, the immunotolerant phase of hepatitis B virus may last for a long period and hence there may be a potential for subtle liver damage.

INTRODUCTION

Hepatitis B virus (HBV) infection is a global public health problem, with an estimated 350 million people chronically infected worldwide. Fifteen to forty percent of these individuals will develop serious sequelae during their lifetime, with greater evolution to cirrhosis or hepatocellular carcinoma (HCC). The estimated 5-year rate of progression from chronic hepatitis B (CHB) to cirrhosis was estimated to be 12%-20% and the 5-year cumulative risk of developing HCC was also estimated to be between 10%-17% in patients with cirrhosis. These figures vary from country to country according to the disease endemicity and prevalence[1-3]. The natural history of CHB is complex and described to run through different immunological phases that may overlap. In its early phases, HBV infection is characterized by minimal liver damage on liver biopsy, a high level of HBV replication and positivity for HBe-antigen (HBeAg). These patients are asymptomatic and have normal levels of serum alanine aminotransferase (ALT). This phase is described as the "immunotolerant phase"[3,4].

Managing these patients creates a great conflict with two opposing views. One view is optimistic, conservative and relies upon the long-term course of benignity of the disease. They adopt the view of "leave the patient alone on close follow up". On the other hand, the other view is

pessimistic and relies upon the great risk of cancer development, even without cirrhosis. This latter view adopts the view of "to treat the patient and why wait". Between these two views, there are no real evidence based guidelines.

In this review, an extensive online research for English reviews and articles that tackle this subject by using the key words "immunotolerant", "HBV" and "management" was carried out. The author highlights the pros and cons of all views regarding the management strategies of this subject and makes a reasonable proposed solution for this dilemma.

IMMUNOTOLERANT PHASE: CHARACTERISTICS AND IMMUNOLOGICAL INSIGHT

The natural history of HBV infection is perplexing and its net result is an interplay between the viral replication and the host immune response. After primary infection, an immunotolerant phase characterized by a very high rate of viral replication but without liver injury takes place. The mechanism of this tolerance is not yet fully understood[5]. These patients are infected early in life through vertical or early horizontal infection. Such infection most often occurs in areas with high rates of endemic infection, low rates of maternal screening, and lack of widely available neonatal prophylaxis with HBV vaccine and hepatitis B immunoglobulin[6,7].

It is believed that before birth, HBeAg acts as a "tolerogen viral protein" in the fetus, and thus virus specific T-cells undergo deletion. This phase lasts from weeks to years, depending on the age at acquisition. After years/decades, this tolerance is somehow ruptured and the immune attack against infected hepatocytes to clear them begins, causing liver damage. During this "immune clearance phase", ALT levels increase and HBV DNA levels begin to decrease. Immune attacks of infected hepatocytes result in HBeAg seroconversion and this seroconversion is usually associated with sustained remission of liver disease. Selection pressures for the virus come from either competition between viral variants, which are different in their replicative efficiency, and the host immune activity[8-10].

It was found that the majority of young children who presented in the immunotolerant phase have either minimal chronic hepatitis or, more commonly, non-specific reactive hepatitis, in spite of persistently normal ALT activity[11-13].

Wang *et al*[14] studied seven patients (age range between 7-25 years) by follow up for at least 17 years with serial sampling for ALT activity and viral load. They concluded that the interplay between viral replication and host immunity explains the pattern of HBV dynamics within the host during the early stages of infection. That is, without immune selection, competition between peers increases the viral load and decreases the nucleotide diversity; in contrast, host immunity accelerates viral evolution and decreases copy numbers but increases diversity. The fully infected liver can yield between 10^9 to 10^{10} viruses per milliliter of serum, a level of production that would be expected to persist if infection were benign and the host were truly immunotolerant. Virus titers in adolescent and young adult carriers in the immunotolerant phase of infection tend to be lower, ranging from 10^7 to 10^9 copies per milliliter[15,16]. Some studies explain the declining of virus titers during the time in the immunotolerant phase by a low but persistent immune destruction of infected cells by the cytotoxic T-cell, leading to an adaptive immune response over time[14].

IMMUNOTOLERANT PHASE: MANAGEMENT OPTIONS AND DEBATES

Of particular concern is the fact that until now there is no drug therapy that is actually effective in achieving a sustained response against HBV in the immunotolerant phase[17].

The currently approved treatment options for chronic HBV infection are interferon and nucleoside analogues (NA). Interferon acts primarily as an immunomodulatory agent, while NAs have essentially antiviral effects. According to current consensus and guideline statements, treatment candidates are patients with active liver disease characterized by persistently elevated ALT levels and detectable HBV DNA (10^5 copy/mL) by most commercial assays, irrespective of their HBeAg/Ab status. These statements also concluded that HBeAg-negative inactive carriers do not need any treatment because of the absence of viral replication and liver injury. Also, patients in the immunotolerant phase should be followed up without treatment[18,19].

However, and in the light of the Risk Evaluation of Viremia Elevation and Associated Liver Disease study, a baseline high HBV DNA level was associated with a significant risk of hepatocellular carcinoma[20]. These results led to the debate on whether a HBV infected person with normal liver enzymes, unremarkable liver histology, but with a detectable level of HBV DNA (high or low regardless the cutoff), should be treated with antiviral drugs or not[20,21].

As a rule, most of the current guidelines recommend that patients with moderate/severe inflammation or bridging fibrosis/cirrhosis must be treated. Also, they recommend liver biopsy for the grey zone of patients who do not meet the typical criteria, have a detectable level of HBV DNA and/or fluctuating or persistently elevated ALT. The presence of significant inflammation or bridging fibrosis/cirrhosis is an indication for treatment[22,23].

Hence, and in the light of the previous statements, we can assume that there are two options regarding the management of the immunotolerant phase; the "why wait" view and the "close follow up" view.

The "why wait" view adopts the option to treat all patients with a persistently high level of viral replication regardless of the phase of infection and relying only on the presence of detectable DNA levels. They rely on the

high risk of cancer/cirrhosis development, considering the infection as not totally benign[24]. Therefore, earlier treatment intervention may be beneficial in preventing disease progression. A recently published study aimed to break this tolerance in children by treating a group of HBV-infected children in the immunotolerant phase with lamivudine and interferon and comparing them to an untreated group. They reported a cure rate in more than one-fifth of the studied cohort, a figure that is still primitive and not high[25].

On the opposing side, another strong option exists and adopts the view of "wait and observe". This view relies on some evidence. The first is the evidence of the benign long term course of the immunotolerant phase[26]. The second is the pooled results of poor response to antiviral therapy in this unique phase, which hardly reaches 19%[27]. The third is the proved emerging resistance on long term therapy[28]. The last is a heavy cost burden of treatment.

Wong *et al*[29] studied the risk of liver fibrosis progression in HBeAg-positive patients at different phases by recruiting two hundred and forty-seven HBeAg-positive patients without advanced fibrosis at baseline. They found that liver fibrosis progression is uncommon in HBeAg-positive patients and hence their results enforce the follow-up strategy.

As is known, the degree of fibrosis or inflammation on liver biopsy cannot be predicted by the level of HBV-DNA and ALT is also considered an imperfect surrogate marker for liver disease[30]. Therefore, without evidence of normal liver histology, the definition of immunotolerant disease depends mainly on the persistence of a normal ALT level as a major determinant. Nevertheless and unfortunately, the definition of a "normal" ALT level has been redefined several times and was subjected to a strong debate. The study of Prati *et al*[31] modified the normal upper limit for ALT to be 30 IU/mL for men and 19 IU/mL for women. Re-introducing these relatively low figures will endorse many more patients under the umbrella of raised ALT levels.

The most appropriate way to make this miss clear cut is to perform a liver biopsy. However, there are still some unanswered questions; *e.g.*, what is the optimal timing of liver biopsy during the natural history of this phase, how many times and at what intervals should it be done, which drug is the best to start with, *etc.*

The use of therapeutic vaccines may also help to break the tolerance. In spite of its preliminary application, the published results of the study of Buchmann *et al*[32] carry a great hope for a wide future applicability. They evaluated the potential use of a novel vaccine formulation, comprising particulate hepatitis B surface and core antigen and the saponin-based adjuvant, for its ability to stimulate T and B cell responses in C57BL/6 mice. Their results were promising and future intense research in this subject is deemed to be mandatory.

CONCLUSION

The immunotolerant phase of chronic HBV is a challenging problem, with an increasing awareness of its occurrence, especially in endemic areas. More intense studies are required for a better delineation of the pathogenesis and whether it is better is to break the tolerance or to wait for the natural clearance. Until then, the most suitable solution is to perform liver biopsy to stand on solid ground in choosing the best option, to wait or to interfere.

ACKNOWLEDGMENTS

We are thankful to Dr. Helal F Hetta, (PhD), Department of Internal Medicine, Division of Digestive Diseases, University of Cincinnati, 231 Albert B. Sabin Way, Cincinnati, OH, for his assistance with manuscript preparation and English language editing.

REFERENCES

1 **Lee WM**. Hepatitis B virus infection. *N Engl J Med* 1997; **337**: 1733-1745 [PMID: 9392700]
2 **Beasley RP**. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 1988; **61**: 1942-1956 [PMID: 2834034]
3 **Shao J**, Wei L, Wang H, Sun Y, Zhang LF, Li J, Dong JQ. Relationship between hepatitis B virus DNA levels and liver histology in patients with chronic hepatitis B. *World J Gastroenterol* 2007; **13**: 2104-2107 [PMID: 17465456]
4 **Daniels G**. A century of human blood groups. *Wien Klin Wochenschr* 2001; **113**: 781-786 [PMID: 11732113]
5 **Ganem D**, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med* 2004; **350**: 1118-1129 [PMID: 15014185]
6 **McMahon BJ**. The natural history of chronic hepatitis B virus infection. *Hepatology* 2009; **49**: S45-S55 [PMID: 19399792 DOI: 10.1002/hep.22898]
7 **Dienstag JL**. Hepatitis B virus infection. *N Engl J Med* 2008; **359**: 1486-1500 [PMID: 18832247 DOI: 10.1056/NEJMra0801644]
8 **Hsu HY**, Chang MH, Hsieh KH, Lee CY, Lin HH, Hwang LH, Chen PJ, Chen DS. Cellular immune response to HBcAg in mother-to-infant transmission of hepatitis B virus. *Hepatology* 1992; **15**: 770-776 [PMID: 1568717]
9 **Hadziyannis SJ**, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2001; **34**: 617-624 [PMID: 11584355]
10 **Farci P**, Quinti I, Farci S, Alter HJ, Strazzera R, Palomba E, Coiana A, Cao D, Casadei AM, Ledda R, Iorio R, Vegnente A, Diaz G, Tovo PA. Evolution of hepatitis C viral quasispecies and hepatic injury in perinatally infected children followed prospectively. *Proc Natl Acad Sci USA* 2006; **103**: 8475-8480 [PMID: 16707577]
11 **Chang MH**, Hwang LY, Hsu HC, Lee CY, Beasley RP. Prospective study of asymptomatic HBsAg carrier children infected in the perinatal period: clinical and liver histologic studies. *Hepatology* 1988; **8**: 374-377 [PMID: 3356419]
12 **Chen DS**. Natural history of chronic hepatitis B virus infection: new light on an old story. *J Gastroenterol Hepatol* 1993; **8**: 470-475 [PMID: 8218997]
13 **Hsu HC**, Lin YH, Chang MH, Su IJ, Chen DS. Pathology of chronic hepatitis B virus infection in children: with special reference to the intrahepatic expression of hepatitis B virus antigens. *Hepatology* 1988; **8**: 378-382 [PMID: 3356420]
14 **Wang HY**, Chien MH, Huang HP, Chang HC, Wu CC, Chen PJ, Chang MH, Chen DS. Distinct hepatitis B virus dynamics in the immunotolerant and early immunoclearance phases. *J Virol* 2010; **84**: 3454-3463 [PMID: 20089644 DOI: 10.1128/

JVI.02164-09.]
15 **Lai M**, Hyatt BJ, Nasser I, Curry M, Afdhal NH. The clinical significance of persistently normal ALT in chronic hepatitis B infection. *J Hepatol* 2007; **47**: 760-767 [PMID: 17928090]
16 **Carey I**, D'Antiga L, Bansal S, Longhi MS, Ma Y, Mesa IR, Mieli-Vergani G, Vergani D. Immune and viral profile from tolerance to hepatitis B surface antigen clearance: a longitudinal study of vertically hepatitis B virus-infected children on combined therapy. *J Virol* 2011; **85**: 2416-2428 [PMID: 21147914 DOI: 10.1128/JVI.01449-10]
17 **Yalcin K**, Degertekin H, Yildiz F, Celik Y. Markers of disease activity in chronic hepatitis B virus infection. *Clin Invest Med* 2003; **26**: 27-34 [PMID: 12659467]
18 **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 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]
19 **Liaw YF**, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, Guan R, Lau GK, Locarnini S; Chronic Hepatitis B Guideline Working Party of the Asian-Pacific Association for the Study of the Liver.. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008; **2**: 263-283 [PMID: 19669255 DOI: 10.1007/s12072-008-9080-3]
20 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73 [PMID: 16391218]
21 **Chen CJ**, Yang HI, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *Hepatology* 2009; **49**: S72-S84 [PMID: 19399801 DOI: 10.1002/hep.22884]
22 **Iloeje UH**, Yang HI, Jen CL, Su J, Wang LY, You SL, Chen CJ. Risk and predictors of mortality associated with chronic hepatitis B infection. *Clin Gastroenterol Hepatol* 2007; **5**: 921-931 [PMID: 17678844]
23 **Sanai FM**, Babatin MA, Bzeizi KI, Alsohaibani F, Al-Hamoudi W, Alsaad KO, Al Mana H, Handoo FA, Al-Ashgar H, Alghamdi H, Ibrahim A, Aljumah A, Alalwan A, Altraif IH, Al-Hussaini H, Myers RP, Abdo AA. Accuracy of international guidelines for identifying significant fibrosis in hepatitis B e antigen--negative patients with chronic hepatitis. *Clin Gastroenterol Hepatol* 2013; **11**: 1493-1499.e2 [PMID: 23811251 DOI: 10.1016/j.cgh.2013.05.038]
24 **Zoulim F**, Mason WS. Reasons to consider earlier treatment of chronic HBV infections. *Gut* 2012; **61**: 333-336 [PMID: 22147510 DOI: 10.1136/gutjnl-2011-300937]
25 **Poddar U**, Yachha SK, Agarwal J, Krishnani N. Cure for immune-tolerant hepatitis B in children: is it an achievable target with sequential combo therapy with lamivudine and interferon? *J Viral Hepat* 2013; **20**: 311-316 [PMID: 23565612 DOI: 10.1111/jvh.12007]
26 **Dienstag JL**, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin M. A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med* 1995; **333**: 1657-1661 [PMID: 7477217]
27 **Lok AS**, Lai CL, Wu PC, Leung EK, Lam TS. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. *Gastroenterology* 1987; **92**: 1839-1843 [PMID: 3569757]
28 **Hongthanakorn C**, Chotiyaputta W, Oberhelman K, Fontana RJ, Marrero JA, Licari T, Lok AS. Virological breakthrough and resistance in patients with chronic hepatitis B receiving nucleos(t)ide analogues in clinical practice. *Hepatology* 2011; **53**: 1854-1863 [PMID: 21618260 DOI: 10.1002/hep.24318]
29 **Wong GL**, Chan HL, Yu Z, Chan HY, Tse CH, Wong VW. Liver fibrosis progression in chronic hepatitis B patients positive for hepatitis B e antigen: a prospective cohort study with paired transient elastography examination. *J Gastroenterol Hepatol* 2013; **28**: 1762-1769 [PMID: 23808759 DOI: 10.1111/jgh.12312]
30 **Hu KQ**, Schiff ER, Kowdley KV, Min AD, Shiffman ML, Lee WM, Goodman ZD, Dau LO, Peschell KJ, Fagan EA, Flaherty JF. Histologic evidence of active liver injury in chronic hepatitis B patients with normal range or minimally elevated alanine aminotransferase levels. *J Clin Gastroenterol* 2010; **44**: 510-516 [PMID: 20179614 DOI: 10.1097/MCG.0b013e3181d34c65]
31 **Prati D**, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, Vianello L, Zanuso F, Mozzi F, Milani S, Conte D, Colombo M, Sirchia G. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002; **137**: 1-10 [PMID: 12093239]
32 **Buchmann P**, Dembek C, Kuklick L, Jäger C, Tedjokusumo R, von Freyend MJ, Drebber U, Janowicz Z, Melber K, Protzer U. A novel therapeutic hepatitis B vaccine induces cellular and humoral immune responses and breaks tolerance in hepatitis B virus (HBV) transgenic mice. *Vaccine* 2013; **31**: 1197-1203 [PMID: 23306359 DOI: 10.1016/j.vaccine.2012.12.074]

P- Reviewers: Alavian SM, Quarleri J **S- Editor**: Gou SX
L- Editor: Roemmele A **E- Editor**: Wu HL

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com