JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW™
eViralHepatitis Review
Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by educational grants from Gilead Sciences, Inc. and Vertex Pharmaceuticals

eViralHepatitis Review
VOLUME 2, ISSUE 9

REACTIVATION OF HEPATITIS B VIRUS INFECTION

In this Issue...

Hepatitis B virus (HBV) reactivation occurs when there is a loss of immune control, leading to a recurrence of or abrupt rise in HBV replication in a previously inactive chronic carrier. Clinically, reactivation can range from asymptomatic hepatitis to fulminant liver failure. The risk for HBV reactivation is likely dependent on a patient's baseline degree of immune control, as well as on the strength and duration of the immunosuppression used. The severity of liver disease–that is, the degree of liver fibrosis prior to undergoing chemotherapy–probably plays a role in how well a patient can tolerate HBV reactivation. Prophylactic treatment with antiviral therapy can be lifesaving in individuals experiencing HBV reactivation. The treatment approach in certain clinical situations is clear–for example, initiating prophylactic therapy in a patient positive for hepatitis B surface antigen (HBsAg) who has lymphoma and is undergoing rituximab-containing chemotherapy. As the use of immunosuppressive regimens expands and the underlying hepatitis B viral state becomes better defined, however, many clinical situations arise for which the benefit of prophylactic therapy is unknown.

In this issue, we review recent publications that describe the diverse clinical settings in which HBV reactivation can occur, the risk for reactivation in patients with resolved and occult HBV infection, and the success of different treatment approaches.

LEARNING OBJECTIVES

After completing this activity, the participant will demonstrate the ability to:

- Summarize the wide range of clinical settings in which the risk for hepatitis B virus (HBV) reactivation should be considered
- Describe the risk for HBV reactivation in hepatitis B surface antigen (HBsAg)-negative patients
- Evaluate the success of various treatment regimens and approaches to preventing HBV reactivation

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

IMPORTANT CME/CE INFORMATION ▼ Program Begins Below

ACCREDITATION STATEMENTS
Physicians
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the

STATEMENT OF RESPONSIBILITY
The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

INTENDED AUDIENCE
This activity has been developed for hepatologists, primary care physicians, infectious disease specialists, nurses, nurse practitioners, and others involved in the care of patients with viral hepatitis.

PLANNER DISCLOSURE
As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of the Johns Hopkins University School of

Program Information
CME/CE Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Internet CME Policy
Planner Disclosures
Disclaimer Statement

Length of Activity
1.0 hour Physicians
1.0 contact hour Nurses

Launch Date
September 6, 2012

Expiration Date
September 5, 2013

TO ACCESS THE POST-TEST

Step 1.
Review the CE Information and study the educational content.

Step 2.
Click the post-test link at the end of the newsletter.

Step 3.
Follow the instructions to access a post-test.

American Nurses Credentialing Center's Commission on Accreditation.

The Institute for Johns Hopkins Nursing and the American Nurses Credentialing Center do not endorse the use of any commercial products discussed or displayed in conjunction with this educational activity.

CREDIT DESIGNATIONS

Physicians

eNewsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of *1.0 AMA PRA Category1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses

eNewsletter: This 1 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each newsletter carries a maximum of 1 contact hour or a total of 7 contact hours for the 7 newsletters in this program.

Podcast: This 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour or a total of 2.5 contact hours for the 5 podcasts in this program.

SUCCESSFUL COMPLETION

To successfully complete this activity, participants must read the content, and then link to the Johns Hopkins University School of Medicine's website or the Institute for Johns Hopkins Nursing's website to complete the post-test and evaluation. Once you receive a passing grade, you can access and print your certificate of credit.

NOTE: If you have already registered for other Hopkins CME programs on their prospective websites simply enter the requested information when prompted.

There are no prerequisites for this activity.

This activity is supported by an educational grant from Gilead Sciences, Inc. and Vertex Pharmaceuticals.

LAUNCH DATE

January 31, 2012; activities expire 2 years from the date of publication.

STATEMENT OF NEED;

Central ideas emerged from our needs assessment. In order to provide optimal treatment to patients with viral hepatitis

Clinicians do not effectively identify their patients at risk for, or infected with, HBV

Clinicians lack the ability to interpret positive HBV screening and do not adequately counsel their patients re: their HBV status (for treatment or vaccination)

Clinicians do not properly treat, monitor, or refer their patients with viral hepatitis and moreover, they lack awareness of current treatments and emerging research

Clinicians require more evidence on tailoring HCV treatments to manage treatment side effects more effectively

Clinicians require more evidence-based information to manage antiviral treatment more effectively in co-infected patients

INTERNET CME POLICY

The Office of Continuing Medical Education (CME) at the Johns Hopkins University School of Medicine is committed to protecting the privacy of its members and customers. The Johns Hopkins University SOM maintains its Internet site as an information resource and service for physicians, other health professionals, and the public.

Medicine Office of Continuing Medical (OCME) to require signed disclosure of the existence of financial relationships with industry from any individual in a position to control content of a CME activity sponsored by OCME. Members of the Planning Committee are required to disclose all relationships, regardless of their relevance to the activity content. Faculty are required to disclose only those relationships that are relevant to their specific presentations. The following relationships have been reported for this activity:

- **Mark S. Sulkowski, MD,** has disclosed that he has served as a consultant for Abbott, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck, Novartis, Pfizer, Roche, and Vertex Pharmaceuticals. He also has received grants and research support from, Abbott, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol Myers-Squibb, Gilead, Janssen, Merck, and Roche, and Vertex Pharmaceuticals.
- **Raymond T. Chung, MD,** has disclosed that he has received grants/research support from Gilead, Pfizer, Roche/Genentech, Merck, and Romark.

No other planners have indicated that they have any financial interests or relationships with a commercial entity.

Guest Authors Disclosures

CONFIDENTIALITY DISCLAIMER FOR CONFERENCE ATTENDEES

I certify that I am attending a Johns Hopkins University School of Medicine CME activity for accredited training and/or educational purposes.

I understand that while I am attending in this capacity, I may be exposed to "protected health information," as that term is defined and used in Hopkins policies and in the federal HIPAA privacy regulations (the Privacy Regulations). Protected health information is information about a person's health or treatment that identifies the person.

I pledge and agree to use and disclose any of this protected health information only for the training and/or educational purposes of my visit and to keep the information confidential.

I understand that I may direct to the Johns Hopkins Privacy Officer any questions I have about my obligations under this Confidentiality Pledge or under any of the Hopkins policies and procedures and applicable laws and regulations related to confidentiality. The contact information is Johns Hopkins Privacy Officer, telephone: 410-735-6509, e-mail: HIPAA@jhmi.edu.

"The Office of Continuing Medical Education at The Johns Hopkins University School of Medicine, as provider of this activity, has relayed information with the CME attendees/participants and certifies that the visitor is attending for training, education and/or observation purposes only."

For CME Questions, please contact the CME Office at (410) 955-2959 or e-mail cmenet@jhmi.edu.

For CME Certificates, please call (410) 502-9634.

Johns Hopkins University School of Medicine
Office of Continuing Medical Education
Turner 20/720 Rutland Avenue
Baltimore, Maryland 21205-2195

Reviewed and Approved by
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP/7 or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K or better modem, Windows Media Player 9.0 or later, 128 MB of RAM, sound card and speakers, Adobe Acrobat Reader, storage, Internet connectivity, and minimum connection speed.

Monitor settings: High color at 800 x 600 pixels.

Continuing Medical Education at the Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in an Internet-based CME program. Your information will never be given to anyone outside of the Johns Hopkins University School of Medicine program. CME collects only the information necessary to provide you with the services that you request.

DISCLAIMER STATEMENT
The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of the Johns Hopkins University School of Medicine name implies review of educational format design and approach. Please review the complete prescribing information for specific drugs or combinations of drugs, including indications, contraindications, warnings, and adverse effects, before administering pharmacologic therapy to patients.

THIS ISSUE

Program Directors

Mark S. Sulkowski, MD
Professor of Medicine
Medical Director
Viral Hepatitis Center
Divisions of Infectious Disease
and Gastroenterology/Hepatology
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Raymond T. Chung, MD
Associate Professor of Medicine
Director of Hepatology,
Medicine Services
Harvard Medical School
Vice Chief of Gastroenterology
Massachusetts General Hospital
Boston, Massachusetts

Julie McArthur, MS, CRNP
Adult Nurse Practitioner
Division of Infectious Disease
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

GUESTS AUTHORS OF THE MONTH

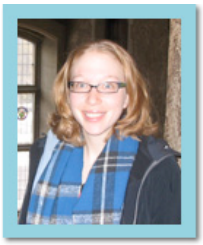
Commentary:

David Wong, MD
Assistant Professor of Medicine
University Health Network
University of Toronto
Toronto, Ontario, Canada

Guest Faculty Disclosures

No faculty members have indicated that they have any financial interests or relationships with a commercial entity whose products or services are relevant to the content of their presentations.

Unlabeled/Unapproved Uses
The authors have indicated that there will be references to unlabeled or unapproved uses of lamivudine, entecavir, and tenofovir for HBsAg negative/HBcAb positive/HBsAb



Aviva Leber, MD
Gastroenterology Fellow
University Health Network
University of Toronto
Toronto, Ontario, Canada

negative patients undergoing significant immunosuppression.

Program Directors' Disclosures

COMMENTARY

It is estimated that approximately 350 million people worldwide are chronically infected with hepatitis B virus (HBV).[1] Many of these chronically infected people have sufficient immunity to maintain low-level viremia, and inactive disease[2] is associated with an excellent prognosis.[3] HBV reactivation weakens immune control, which leads to rising HBV DNA levels and subsequent liver injury, as indicated by elevated liver enzymes. Clinically, HBV reactivation can range from asymptomatic disease to liver failure.[4] Mortality from HBV reactivation has consistently been shown to be about 10%–a rate that is higher than that associated with spontaneous flares.[4] In the first cohort study on the subject, published in 1991, Lok and colleagues demonstrated a reactivation rate of 48% in patients positive for hepatitis B surface antigen (HBsAg) who were treated for lymphoma.[5] Advancements have been made since that time, including the successful use of prophylactic therapy; however, many unanswered questions remain.

Although the concept of HBV reactivation is clear, the definition and clinical evaluation vary significantly. The studies reviewed in this issue all define different parameters for HBV reactivation, rendering study comparison and interpretation difficult. Furthermore, clinically relevant endpoints, such as disruption of chemotherapy and clinical hepatitis, are not consistently evaluated as primary endpoints. Until a consensus has been reached on a clinically relevant definition of HBV reactivation, it will be difficult to transfer knowledge gained from clinical studies to clinical practice.

The risk for HBV reactivation is determined by host factors (HBsAg/antibody to hepatitis B surface antigen [anti-HBs]/antibody to hepatitis B core antigen [anti-HBc] status); viral factors (HBV DNA level); and degree of immunosuppression (underlying disease, treatment regimen). The articles reviewed in this issue emphasize the broad range of clinical situations in which HBV reactivation can occur. Kim and associates (reviewed in this newsletter) demonstrated that HBV reactivation occurs in HBsAg-positive, immunocompetent respirology patients who ingest chronic systemic corticosteroids. Tamori and coworkers (reviewed in this issue) demonstrated HBV reactivation with the use of low-dose methotrexate (MTX) in patients with rheumatoid arthritis. HBV reactivation, therefore, can occur with the use of low-dose immunosuppression. Although the cost-effectiveness has not been proved in all settings,[6] the US Centers for Disease Control and Prevention currently recommends universal screening for chronic HBV infection in patients receiving any form of immunosuppressive therapy.[7] Unfortunately, recent studies have shown that only a fraction of the oncology patients in the United States are screened.[8]

The serologic status of an HBV infection is also an important factor for reactivation. It has been well established that HBsAg-positive carriers have a higher risk for reactivation compared with persons who are HBsAg-negative/anti-HBc-positive.4 The risk profile and appropriate treatment regimen is unclear in patients who are negative for HBsAg. The studies by Koo and colleagues and Tamori and associates (both reviewed in this issue) reconfirm the low risk for reactivation among patients who are HBsAg-negative with varying disease states and are receiving different immunosuppressive regimens. The presence of hepatitis B surface antibody (HBsAb) appears to be protective, particularly in those with high titers. Unfortunately, these studies did not separate cases of occult HBV (HBsAg-negative/positive HBV DNA) from resolved HBV (HBsAg-negative/negative HBV DNA). The risk profiles may be substantially different in these two patient groups and thus require further evaluation.

Randomized, controlled trials (RCTs) have demonstrated the efficacy of prophylactic therapy with lamivudine. A trial in Taiwan by Hsu and collaborators showed that treatment with prophylactic lamivudine was superior to lamivudine administered after liver enzyme

elevation developed; however, cases of HBV reactivation were still reported with prophylactic therapy.9 With lamivudine resistance being a key factor in the failure of prophylactic therapy, newer and more potent antiviral agents have been developed. The study by Li and associates (reviewed in this issue) suggests that entecavir (and likely tenofovir) is more effective than lamivudine in preventing HBV reactivation. RCTs are needed to demonstrate the superiority of these more potent agents.

In a prospective cohort study reviewed in this newsletter, Tsai and colleagues explored the possibility of using deferred preemptive lamivudine therapy in HBsAg-positive patients undergoing breast cancer treatment. Although deferred preemptive treatment was successfully used in this study and possibly more cost-effective than prophylactic lamivudine, we would be hesitant to use the approach in routine clinical practice. All antiviral agents act slowly, taking several weeks to lower HBV DNA levels. Antiviral agents, therefore, will not salvage patients with fulminant hepatitis. Previous RCTs demonstrated the risk associated with the deferred preemptive approach in patients with lymphoma.[9,10] Deferred preemptive therapy, in combination with vigilant HBV DNA monitoring, may play a role in a defined population, but additional studies are warranted before that approach is implemented.

In our clinical practice, prophylaxis is given to all patients receiving immunosuppression who are HBsAg-positive or have detectable HBV DNA levels. Prophylaxis is not administered to patients with resolved HBV who are HBsAb-positive (titer >10 IU/mL). In patients with resolved HBV but negative HBsAb titers, antiviral prophylaxis is given to those receiving profound immunosuppression, such as rituximab; deferred preemptive therapy is never used in such patients. Entecavir and tenofovir are preferred because of minimal resistance and the low risk for treatment failure.

In conclusion, many more patients are at risk for HBV reactivation than initially appreciated. Further prospective, randomized trials are needed to better define at-risk patient populations and guide effective treatment regimens.

Commentary References

1. Alter MJ. Epidemiology of hepatitis B in Europe and worldwide. *J Hepatol.* 2003;39(suppl 1):S64-S69. http://www.ncbi.nlm.nih.gov/pubmed/14708680
2. Ganem D, Prince AM. Hepatitis B virus infection – natural history and clinical consequences. *N Engl J Med*. 2004;350(11):1118-1129 http://www.ncbi.nlm.nih.gov/pubmed/15014185
3. de Franchis R, Meucci G, Vecchi M, et al. The natural history of asymptomatic hepatitis B surface antigen carriers. *Ann Intern Med*. 1993;118(3):191-194. http://www.ncbi.nlm.nih.gov/pubmed/8417636
4. Hoofnagle JH. Reactivation of hepatitis B. *Hepatology*. 2009;49(5 suppl):S156-S165. http://www.ncbi.nlm.nih.gov/pubmed/19399803
5. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology. 1991;100(1):182-188 http://www.ncbi.nlm.nih.gov/pubmed/1983820
6. Day FL, Karnon J, Rischin D. Cost-effectiveness of universal hepatitis B virus screening in patients beginning chemotherapy for solid tumors. *J Clin Oncol*. 2011;29(24):3270-3277. http://www.ncbi.nlm.nih.gov/pubmed/21788556
7. Weinbaum CM, Williams I, Mast EE, et al; Centers for Disease Control and Prevention (CDC). Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep. 2008;57(RR-8):1-20. http://www.ncbi.nlm.nih.gov/pubmed/18802412
8. Khokhar OS, Farhadi A, McGrail L, Lewis JH. Oncologists and hepatitis B: a survey to determine current level of awareness and practice of antiviral prophylaxis to prevent reactivation. *Chemotherapy*. 2009;55(2):69-75. http://www.ncbi.nlm.nih.gov/pubmed/19077421
9. Hsu C, Hsiung CA, Su I-J, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. Hepatology. 2008;47(3):844-853. http://www.ncbi.nlm.nih.gov/pubmed/18302293
10. Lau GK, Yiu HH, Fong DY, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. *Gastroenterology*. 2003;125(6):1742-1749. http://www.ncbi.nlm.nih.gov/pubmed/14724827

back to top

HBV REACTIVATION ASSOCIATED WITH THE USE OF SYSTEMIC CORTICOSTEROIDS

Kim TW, Kim MN, Kwon JW, et al. **Risk of hepatitis B virus reactivation in patients with asthma or chronic obstructive pulmonary disease treated with corticosteroids.** *Respirology*. 2010;15(7):1092-1097

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

 View journal abstract  View full article

Corticosteroids are commonly used for treating numerous medical conditions. It is well recognized that adding corticosteroids to intensive immunosuppressive regimens used to treat hematologic malignancies and autoimmune diseases increases the risk for HBV reactivation and clinical (even fulminant) hepatitis. The risk for HBV reactivation is dependent on viral factors, host factors, and the treatment regimen used; therefore, it is not possible to generalize the published risk for corticosteroids to all clinical situations.

This retrospective study by Kim and colleagues evaluated the risk for biochemical and viral HBV reactivation in patients with chronic obstructive pulmonary disease (COPD) or asthma who were receiving corticosteroid therapy. Patients were followed at two large tertiary care hospitals in South Korea between 1997 and 2007. To qualify for inclusion, patients had to be HBsAg-positive, antiviral therapy-naive, and have a history of corticosteroid (inhaled or systemic) use during the study period. Patients were excluded from the analysis if they had other risk factors for HBV reactivation, namely, hematopoietic stem cell or solid organ transplantation, use of systemic chemotherapy or other immunosuppressive agents, or transarterial chemoembolization or liver irradiation.

In this study, HBV reactivation was defined as a combination of: (1) hepatitis, which was defined as a ≥&3-fold increase in alanine aminotransferase (ALT) level that exceeded the reference range (>58 U/mL) or an absolute increase in ALT to >100 U/mL (regardless of baseline value); (2) rise in viral load, which was defined as an increase in serum HBV DNA level to $>10^4$ IU/mL. HBV reactivation was confirmed by a hepatologist.

Patients were evaluated based on their corticosteroid regimen. Treatment consisted of inhaled corticosteroids (ICS) or systemic corticosteroids (SCS). Patients in the SCS group were further substratified according to the strength of the dose (>20 mg/day vs. <20 mg/day) and duration of therapy (intermittent vs. continuous for ≥3 consecutive months).

One hundred ninety-eight patients were included in the analysis, 126 of whom were treated with ICS and 72 of whom were treated with SCS. At baseline, age, gender, and hepatitis B e antigen (HBeAg) status did not differ significantly between the two groups. The majority of patients were HBeAg-positive despite an older average age of 55 years, perhaps because of prior exposure to steroids and thus relative immune suppression. However, HBeAg status was determined in only 35/72 (48%) of the cohort receiving systemic steroids. Reactivation occurred in a total of 12 patients: 4 of 126 (3.2%) in the ICS group and 8 of 72 (11.1%) in the SCS group. All patients were treated successfully with lamivudine, with no progression to liver failure or death. Overall, seven patients were HBeAg-positive and five patients were HBeAg-negative. A significantly higher rate of reactivation occurred in those receiving >20 mg of daily SCS (P=0.014) and in those who received continuous therapy for ≥3 months (P=0.048) compared to the ICS group.

It is difficult to draw firm conclusions from this study because of its retrospective design. Since the characterization of HBV was not determined for the majority of patients prior to receiving corticosteroid therapy, it is not possible to know if ALT elevations were due to the natural history of intermittently active HBV disease or to reactivation from immunosuppression. Nonetheless, this study is important because it broadens the clinical scope of illnesses and therapies that need to be considered when evaluating increases in the risk for HBV reactivation and identifies an area that warrants additional research.

back to top

HBV REACTIVATION IN PATIENTS WITH RHEUMATOID ARTHRITIS

Tamori A, Koike T, Goto H, et al. **Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts.** *J Gastroenterol*. 2011;46(4):556-564

Aggressive, early immunosuppressive therapy to prevent joint destruction is being adopted as first-line treatment for persons with rheumatoid arthritis (RA). Patients are treated with disease-modifying antirheumatic drugs (eg, MTX), biologic therapy (eg, infliximab), or both for prolonged, often lifelong, treatment courses. Case reports of HBV reactivation during treatment courses for RA have been published[1,2] for both HBsAg-positive and HBsAg-negative carriers. Recent prospective studies, however, have shown inconsistent results regarding the risk for reactivation in HBsAg-negative patients. The aim of the current study by Tamori and associates was to clarify the prevalence of HBV reactivation among RA patients receiving long-term immunosuppressive therapy.

This prospective cohort study followed 50 patients with RA from a single center in Japan between 2007 and 2009. The mean observation period was 23 months. Patients were included in the analysis if they were receiving immunosuppressive therapy (biologics or nonbiologics) and were positive for hepatitis B core antibody (HBcAb) with no other known liver disease. Before receiving immunosuppressive therapy, patients were tested for their HBsAg, HBsAb, and HBV DNA status. Those with HBV DNA levels >2.1 log copies/mL (126 copies/mL) were treated with prophylactic entecavir (0.5 mg/day). Patients were monitored every two to three months with repeat HBV DNA testing.

Study outcomes were defined as follows: (1) hepatitis flares were defined as ALT >400 IU/L (10x the upper limit of normal [ULN]); (2) HBV reactivation was defined as a 1-log copy/mL increase in HBV DNA or an HBV DNA level >2.1 log copies/mL–essentially anyone with a positive HBV DNA result. Of the 50 patients enrolled, five were HBsAg-positive and 45 were HBsAg-negative. The mean patient age was 59 years, and there was a strong female predominance. In the HBsAg-positive group, all patients were HBeAg-negative, and three patients were treated prophylactically with entecavir because of a positive baseline HBV DNA (highest level, 4.2 log copies/mL). The other two patients in the HBsAg-positive group were treated with MTX and eventually required therapy, at 14 and 19 months, respectively, for elevated HBV DNA levels, with the highest level at 3 log copies/mL. Both of these patients responded to antiviral therapy without any ensuing hepatitis flares.

In the HBsAg-negative group, 36 of 45 patients were HBsAb-positive. HBV reactivation occurred in one patient after 10 months of receiving low-dose MTX therapy. The female patient was 73 years old, with a serologic profile consistent with resolved infection: seroconversion to HBsAg-negative status in 1993; HBsAb barely positive, with a titer of 9.9 mIU/mL; HBV DNA <2.1 log copies/mL. During MTX treatment, the patient's HBsAb became negative, her HBV DNA level rose to 4.7 log copies/mL, and her HBsAg became positive after 10 months of therapy. She was treated with entecavir and experienced a subsequent hepatitis flare, which eventually resolved. The patient continued taking MTX throughout her treatment course. Even in those without HBV reactivation, HBsAb titers decreased during treatment in the majority of patients in whom the titers had been <800 mIU/mL before immunosuppression. The clinical significance of this is not clear, as reactivation did not occur in any of the patients within the two years of follow-up.

This study supports the high risk for reactivation in HBsAg-positive carriers treated for RA, regardless of the type of immunosuppressive therapy selected. A preemptive, but not prophylactic, approach appeared effective in HBsAg-positive patients with low baseline HBV DNA levels. The risk for HBV reactivation in HBsAg-negative patients was low in this study, occurring in 1 patient with only mild immunosuppression and preceded by a loss of HBsAb. The role of monitoring HBsAb titers is unclear and warrants further investigation.

Commentary References

1. Verhelst X, Orlent H, Colle I et al. Subfulminant hepatitis B during treatment with adalimumab in a patient with a rheumatoid arthritis and chronic hepatitis B. *Eur J Gastroenterol Hepatol* 2010;22:494-99. http://www.ncbi.nlm.nih.gov/pubmed/20306568
2. Gwak GY, Koh KC, Kim HY. Fatal hepatic failure associated with hepatitis B virus reactivation in hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. Clin Exp Rheumatol 2007;25:888-9. http://www.ncbi.nlm.nih.gov/pubmed/18173926

back to top

RISK FOR HBV REACTIVATION IN HBSAG-NEGATIVE PATIENTS WITH LYMPHOMA

Koo YX, Tay M, Teh YE, et al. **Risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen negative/hepatitis B core antibody positive patients receiving rituximab-containing combination chemotherapy without routine antiviral prophylaxis.** *Ann Hematol*. 2011;90(10):1219-1223

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View full article

The role of prophylactic antiviral therapy in patients with HBsAg-negative/HBcAb-positive HBV infection is unclear. Studies consistently demonstrate that the risk for reactivation is substantially lower in these patients, compared with their HBsAg-positive counterparts. Currently, guidelines from the American Association for the Study of Liver Diseases do not recommend the routine use of prophylactic antiviral agents in patients who are HBsAg-negative/HBcAb-positive. However, patients who are HBsAg-negative/HBcAb-positive are a heterogeneous group. The risk for reactivation may be increased in those with detectable HBV DNA levels and in those who are HBsAb-positive.

Koo and colleagues set out to clarify the risk for HBV reactivation in a high-risk patient population (underlying lymphoma and receiving a rituximab-containing treatment regimen) who were HBsAg-negative/HBcAb-positive, as well as to identify risk factors for reactivation in these patients. Sixty-two patients were enrolled in this retrospective cohort study and were treated between 2006 and 2009. Patients were included in the study if they were antiviral treatment-naive.

Definition of the study outcomes was as follows:

1. Hepatitis severity graded according to World Health Organization criteria
    1. Grade 1: 1.25 x ULN to 2.5 x ULN
    2. Grade 2: >2.5 x ULN to 5.0 x ULN
    3. Grade 3: >5.0 x ULN to 10.0 x ULN
    4. Grade 4: >10.0 x ULN
2. HBV reactivation if reappearance of HBsAg associated with a rise in HBV DNA levels

Baseline characteristics of the patients revealed a median age of 67 years, with a slight male predominance. The majority of the patients were of Chinese ethnicity. A total of 62 patients were followed in the study. Forty-six of the 62 patients were evaluated for the presence of HBsAb, 33 of which were positive; none of the 36 patients assessed for HBV DNA levels had detectable HBV DNA (the sensitivity of the underlying assay used was not documented).

The rate of reactivation was 3% (two of 62 patients). Both of the patients experiencing HBV reactivation were HBsAb-negative. Unfortunately, the baseline HBV DNA levels of both patients were not known. Both of these patients were elderly and had advanced lymphoma (Ann Arbor stage 3). Additionally, both of the patients experienced reactivation after receiving the six cycles of primary chemotherapy; one of the two patients experienced reactivation during maintenance therapy with rituximab. One patient was treated with lamivudine but died from HBV reactivation; one patient was not treated but recovered from the hepatitis flare.

This study is limited by its small size and retrospective design. In general, the results support the belief that the risk for reactivation is low among those with resolved HBV (HBsAg-negative/HBcAb-positive), even in high-risk patient groups (ie, those with hematologic malignancy receiving rituximab-based therapy). This finding is consistent with those of previous studies.

The risk for reactivation in HBsAg-negative/HBcAb-positive patients, however, is likely not uniform. It is important to differentiate occult HBV infection (ie, HBsAg-negative/HBV DNA detectable) from resolved HBV infection (ie, HBsAg-negative/HBV DNA undetectable). Moreover, the presence of HBsAb appears to be protective, particularly if a patient's titers are high, and may help to further substratify patients with resolved HBV infection. Finally, although the risk for HBV reactivation is low, the consequences to an individual patient may be fatal. This further emphasizes the importance of identifying the HBsAg-negative carriers at highest risk as they would receive the greatest benefit from prophylactic antiviral therapy.

back to top

DEFERRED PREEMPTIVE THERAPEUTIC APPROACH FOR PREVENTION OF HBV REACTIVATION IN PATIENTS WITH SOLID TUMORS

Tsai SH, Dai MS, Yu JC, et al. **Preventing chemotherapy-induced hepatitis B reactivation in breast cancer patients: a prospective comparison of prophylactic versus deferred preemptive lamivudine.** *Support Care Cancer*. 2011;19(11):1779-1787.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View full article

The risk for HBV reactivation in patients with solid organ tumors undergoing chemotherapy is lower than that in chemotherapy-treated patients with hematologic malignancies. This is likely because there is less baseline host immune dysregulation and differences in the treatment regimens. In patients with hematologic cancers, prophylactic antiviral therapy is recommended; however, the treatment approach for those with solid malignancies is less clear. After a patient begins chemotherapy, an increase in viral replication generally occurs one to two weeks before clinical hepatitis develops.

The aim of this study by Tsai and coworkers was to explore a deferred preemptive lamivudine regimen, based on HBV DNA surveillance, vs. standard prophylactic lamivudine therapy to prevent chemotherapy-induced HBV in patients with breast cancer. The study consisted of two parts. The first part retrospectively compared the baseline host and viral factors in patients with underlying hematologic malignancies vs. those with breast cancer. The second part was a prospective cohort study that followed 45 patients from a single center in Taiwan. The deferred preemptive group (n=22) was followed with monthly HBV DNA titers while undergoing chemotherapy, and lamivudine treatment was initiated if a significant rise in HBV DNA levels was observed. The second group (n=23) received prophylactic lamivudine within seven days of chemotherapy initiation. Patients continued receiving antiviral therapy for four weeks post chemotherapy.

Definition of the study outcomes was:

1. Significant rise in HBV DNA levels was defined as
    1. 100-fold (2-log) increase from baseline
    2. If baseline HBV DNA $<10^5$ copies/mL, rise in HBV DNA to $>10^5$ copies/mL
    3. If baseline HBV DNA $>10^5$ copies/mL, 10-fold (1-log) increase from baseline
2. Hepatitis was defined as
    1. If baseline ALT was normal, ALT elevated to >2 x ULN
    2. If baseline ALT was abnormal, >1.5-fold increase from baseline

Eighty-one patients with hematologic malignancies were compared with 65 patients with breast cancer. Those with hematologic malignancies were more likely to have higher viral loads and to be HBeAg-positive before beginning chemotherapy. Baseline characteristics

were not well described for the 45 patients who participated in the cohort study. Of the 22 patients in the deferred preemptive group, 15 (68%) had elevated HBV DNA levels and were started on lamivudine therapy. Of these 15 patients, four developed biochemical hepatitis, and two of them required interruption of their chemotherapy. All four patients experienced complete resolution of their HBV infection with lamivudine therapy. Of the 23 patients who received prophylactic lamivudine, two developed hepatitis after completion of chemotherapy (while still on lamivudine) and one patient developed icteric hepatitis upon lamivudine withdrawal. All patients experienced complete resolution of their HBV infection. No deaths were reported in either treatment group. The total duration of antiviral therapy was shorter among patients in the deferred preemptive group than among those in the prophylactic treatment group.

This is an interesting study that explores the use of deferred preemptive therapy in a lower-risk group with underlying solid malignancies. The presumed benefit of this strategy is its cost- effectiveness, and it could theoretically help to reduce lamivudine resistance. The cost savings are lost, however, when the price of frequent HBV DNA testing is considered. The danger is that the response to antiviral therapy is slow, and it may not be able to prevent a flare (or even death) once a patient's HBV DNA level has begun to rise. This is particularly problematic in the many centers that do not have access to rapid HBV DNA results.

back to top

ENTECAVIR VS. LAMIVUDINE FOR THE PREVENTION OF HBV REACTIVATION IN PATIENTS WITH LYMPHOMA

Li HR, Huang JJ, Guo HQ, et al. **Comparison of entecavir and lamivudine in preventing hepatitis B reactivation in lymphoma patients during chemotherapy.** *J Viral Hepat*. 2011;18(12):877-883.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View full article

Chemotherapy indirectly leads to HBV reactivation through immunosuppression, resulting in loss of immune control and thus allowing for uncontrolled viral replication. Subsequent

immune recovery can induce a vigorous inflammatory response to HBV that leads to subclinical hepatitis or liver failure.

The benefit of antiviral prophylaxis for chronic HBV carriers has been recognized since the late- 1990s.[1] At that time, lamivudine was the only treatment available. Lamivudine is a potent antiviral agent, suppressing HBV DNA by approximately 3 to 4 logs.[2] Long-term use of lamivudine, however, is limited by the high risk for treatment failure attributable to resistance. Entecavir is a more potent and expensive antiviral agent that, on average, decreases HBV DNA levels by 7 to 8 logs.[2] Whether this increased potency is needed to prevent HBV reactivation is unclear.

The current study by Li and collaborators was designed to compare the efficacy of entecavir vs. lamivudine for preventing HBV reactivation in patients with lymphoma. This study retrospectively examined patients with malignant lymphoma from four hospitals in China between 2007 and 2009. To qualify for study inclusion, patients had to be HBsAg-positive, treatment-naive, and have normal liver function and normal liver enzymes. Patients were treated with either entecavir (0.5 mg/day) or lamivudine (100 mg/day), at the discretion of their physicians. Antiviral therapy was begun one week before initiating chemotherapy and ended six months after chemotherapy was stopped. Patients underwent biochemical evaluation of viral status and liver function before each cycle of chemotherapy and monthly during follow-up.

Definition of the study outcomes was: (1) hepatitis was defined as a ≥3-fold increase in ALT that exceeded the reference range (58 U/mL) or an absolute increase in ALT increase to >100 U/mL above baseline; (2) HBV reactivation was defined as a 10-fold (1-log) increase in HBV DNA from baseline or an absolute HBV DNA >105 (5 log) copies/mL; (3) secondary endpoints included chemotherapy disruption and mortality from liver failure.

One hundred twenty-three patients were included in the study, with 89 receiving lamivudine and 34 receiving entecavir. The baseline characteristics of the patients did not differ significantly, with a median viral load of 4 log copies/mL. Nonetheless, there was a risk for bias, as the physicians were not blinded when prescribing the antiviral agents.

In the lamivudine group, 18 patients experienced HBV reactivation and 11 patients developed HBV. One patient developed severe hepatic failure after the eighth cycle of a rituximab-cyclophosphamide/doxorubicin/vincristine/ prednisone (CHOP) regimen and died despite the addition of entecavir. This is not surprising, since it can take many weeks for any of the currently available antiviral agents to exert a significant clinical effect. The patient who died was found to be lamivudine-resistant because of the tyrosine-methionine-aspartate-aspartate (YMDD) mutation. Chemotherapy disruption occurred in 18 patients; however, it was unclear whether HBV reactivation was responsible in all these patients. In the entecavir group, four patients developed HBV reactivation but none had HBV-related hepatitis. No individual risk factor was found to be significantly associated with HBV-related hepatitis on logistic regression analysis.

This study demonstrates that HBV reactivation can occur despite prophylactic treatment with lamivudine or entecavir, but that entecavir has superior efficacy to lamivudine against HBV.

References

1. Lai CL, Chien RN, Leung NWY et al. **A one year trial of lamivudine for chronic hepatitis B.** *NEJM*. 1998;339:61-68. http://www.ncbi.nlm.nih.gov/pubmed/9654535
2. Sherman M, Shafran S, Burak K et al. Management of chronic hepatitis B: consensus guidelines. *Can J Gastroenterol 2007*; 21(Suppl C):5C-24C http://www.ncbi.nlm.nih.gov/pubmed/17568823

back to top

Presented by JHUSOM and IJHN in collaboration with DKBmed.

COMPLETE THE POST-TEST

Step 1.
Click on link to download instructions for the posttest and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST