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Prevention of Hepatitis-B Reactivation During Immunosuppressive Therapy, Chemotherapy, Treatment with Biological Agents and After Organ Transplantation

Al-Ashgar HI[1], Khan QM[1], Abalkhail F[1], Khathlan A[2], Albenmousa, A[3], Maghfoor I[1], Ali Usman AS[1], Omrani A[1], Aljedai HA[1], Sanai F[4], Alquaiz M[1] and Peedikayil MC[1*]

[1]King Faisal Specialist Hospital & Research Center, Riyadh, SA

[2]King Fahad Medical City, Riyadh, SA

[3]Armed Force Hospital, Riyadh, SA

[4]National Guard Hospital, Jeddah, SA

[*]Corresponding author:

Musthafa Chalikandy Peedikayil,
Department of Medicine (MBC-46), King Faisal Specialist Hospital & Research Center, P.O.Box 3354, Riyadh, 11211, Saudi Arabia

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1. Introduction

Hepatitis B virus (HBV) is a major health problem worldwide. It is estimated that one in 3 persons have been exposed to HBV and around 400 million have chronic HBV.[1, 2] In Saudi Arabia the prevalence of HBV markers before implementation of HBV immunization (1990) was reported to be 50% for a single marker and 8.3% for HBsAg. [3, 4] The prevalence of HBsAg positivity in Saudis has dropped significantly since the implementation of HBV vaccination in 1990 to 0.05 and 0.22 in children and adults respectively. Among patients who are positive for HBsAg, only 26% are HBeAg positive. [3 ,4] In other words more than 70% of Saudi patients who are positive for HBsAg have precore (PC) or basal core promoter (BCP) mutants.

Hepatitis B virus reactivation (HBVr) is a serious disorder with high morbidity and mortality that may complicate chemotherapy (CT), immunosuppressive (IS) or a variety of expanding biological agents (BA). Therapy for solid tumors including trans-arterial chemoembolization (TACE) for hepatocellular cancer has been associated with HBVr. [5-15] Amongst a cohort of oncology patients from Asia with solid tumors, chronic hepatitis B (CHB) was documented in 12% of patients. Of those 20% experienced HBVr after (CT) [15,16].

HBVr has been reported in patients receiving (BA) for inflammatory bowel disease, rheumatological diseases, dermatological disorders, autoimmune disorders and several other diseases. HBV reactivation rate with these agents ranges from 5-40% [17-27]. A meta-analysis of 15 studies involving 578 patients exposed to rituximab gave a pooled risk estimation of HBV reactivation of 6.3% [28].

Solid organ transplantation and hematopoietic stem cell transplant (HSCT) carry high risk for HBVr. Hepatitis B reactivation has been observed in HBsAg positive patients, and HBsAg negative/anti-HBc positive patients who received HSCT with some fatalities [29-30]. HBVr in autologous and allogeneic stem cell transplantation at 2 years were 66% and 81% respectively. The high rate of HBVr in HSCT is most likley related to the pre-transplant conditioning (CT), post-transplant immunosuppression and the potentially protracted immunodeficient state while engraftment takes place [31].

The risk of HBVr depends on the HBV status, the therapy being used and host factors. The risk of HBVr can be classified into high risk >10%, moderate risk (1-10%) and low risk (<1%)2 see (Table 1). Patients who are HBsAg positive and/ or Anti HBcAb positive have very high incidence of HBVr ~ 50% with significant morbidity and mortality [32-33]. This warrants screening patients falling into the high and moderate risk groups for HBsAg and anti HBcAb before

commencing therapy. There is no enough data to assess the possible protective effect of anti HBsAb, and its presence or absence should not affect the decision to start HBV prophylaxis [34].

The high prevalence of HBV worldwide meant that a significant number of patients will receive organs from HBV exposed donors. Furthermore, there are potential recipients who either have chronic HBV or had been exposed to HBV in the past with one or more positive marker for HBV [35]. This problem is more likely to be seen in renal transplant recipients because of the higher prevalence of HBV among dialysis patients. HBsAg positive patients are at increased risk of progression of the disease and HBVr with its sequelae after transplantation. Furthermore, there is a negative effect on both patient and graft survival in HBsAg positive patients compared with HBsAg negative recipients [36-37]. Liver transplant recipients are at higher risk of HBV transmission compared to other solid organ transplantations [38].

Active immunization of all patients with organ failure is the first step in prevention of HBV. However, the potency of the vaccine is low in dialyzed patients (70%) and even lower in renal transplant recipients (30%). Use of higher doses of vaccine was advised to improve efficacy. The aim is to achieve Anti-HBs titer above 10 iu/l [39-42].

HbsAg positive Patients who are for organ transplantation other than the liver require full assessment of the liver disease including staging with non-invasive means or liver biopsy to decide if they require double grafts. HBsAg positive patient who received solid organ transplant are at a higher risk for hepatocellular carcinoma (HCC) and should be monitored according to the approved guidelines for HCC surveillance. Because of the shortage of organs, donors with positive Anti HBcAb are accepted despite the risk of HBVr [43-46]. The risk of De novo hepatitis B from HBsAg negative/ HBcAb positive donor is high in liver transplant recipients and negligible with other organs.

The risk of de novo HBV infection occurs in upto 18% of previously vaccinated recipients and 4% of recipients with natural immunity [42]. The risk of de novo hepatitis B from HBcAb positive donor was reduced from 58% to 11% and from 18% to 2% in non-immune and previously vaccinated recipients respectively by combination of HBIG/lamivudine [42,47]. Use of organs from HBsAg positive donors should be individualized.

2. Hepatitis B Reactivation (HBVR)

(HBVr) is characterized by one log10 rise in the level of HBV DNA above the baseline in those who had positive HBV-DNA prior to therapy, reappearance of HBV-DNA in previously negative patients or reverse seroconversion of HBsAg. The rise in HBV-DNA precedes the elevation in ALT by days to weeks. Flare up hepatitis is defined by at least 2 fold rise above the upper limit of normal or above the baseline ALT level. If untreated the relapse is quite severe and can lead to acute liver failure and even death. Mortality of such relapses ranges between 4-41% and can be as high as 40% despite treatment with lamivudine if severe hepatic injury is present [48-52].

The mechanism for HBVr is not fully understood albeit related to the altered immune status of the patient. Loss of immunological control over the virus results in viral replication and the subsequent recovery of the immune system starts the process of viral elimination and destruction of the hepatocyte by pathogen associated molecular pattern (PAMP) and possibly apoptosis. Furthermore, there are agent specific mechanisms that may participate in HBVr. Glucocorticoids stimulates the viral glucocorticoid responsive element and induce viral transcription.48,53 TNF-a, stimulates an important antiviral pathway, the APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) proteins. This is responsible for degradation of cccDNA. Use of anti-TNF blocks this pathway and set ccc-DNA free for transcription. B-cell depleting agents suppress the B-cell and block the humoral immune response with loss of neutralizing antibodies and disrupting yet unclear B-cell viral suppressive effects independent of the antibodies. Histone deacetylase inhibitors, by reversing the deacetylation and making certain acetylated histones available for the ccc-NBA minichromosome complexes causing gene expression and HBV replication [2,54,55].

Both Randomized control trials (RCT) and several meta-analysis have shown that prophylaxis use of nucleos(t)ide analogues (NAs) significantly reduced the risk of HBVr, associated acute liver failure, mortality and avoided the interruption of Immunosuppressive medications [10,56-68]. Entecavir was shown to be superior to lamivudine in preventing HBVr [64-66]. So, only NAs with high efficacy and high genetic barrier for resistance should be used for the prevention of HBVr. Currently we have three medications that possess high efficacy and high barrier to resistance (Tenofovir Disoproxil Fumarate (TDF), Tenofovir Alafenamide Fumarate (TAF) and Entecavir (ETV) [67]. Because of the high resistance with Lamivudine, its use may be limited to short course prophylaxis.

The use of hepatitis B immunoglobulin (HBIG) in liver transplantation for prevention of HBVr has decreased with the advent of the highly effective (NAs). Some centers have stopped using (HBIG) passive immunization [5,69].

Despite the awareness of the HBVr among healthcare providers, there are still new cases appearing in the literature and faced in clinical practice [5,69]. This may in part be related to the increasing numbers and expanded use of new cytotoxic and immunomodulatory agents. Therefore, clear guidelines on the prevention of HBVr should be available to all physicians involved in treating such patients. The medications used in hepatitis B prophylaxis, their doses, main side effects are included in (Table 2). The renal dose adjustment is detailed in (Table 3).

The grading of evidence and strength of recommendation is based on the following:

Table 1: Risk Stratification for Hbvr

Risk	Viral	Therapeutic Agent
High	HBsAg+	Stem cell and solid organ transplantation, Anthracylines (Doxorubicin, epirubicin), high dose steroids, Beta-cell depleting agents (rituximab, ofatumumab), Systemic chemotherapy, TACE, TNF inhibitors, cytokine and integrin Inhibitors
	HBsAg-ve HBcAb+	Stem cell and solid organ transplantation, Beta-cell depleting agents (rituximab, ofatumumab)
Moderate	HBsAg-ve HBcAb+	TNF inhibitors, cytokine and integrin Inhibitors
Low	Irrespective of HBV status	Azthioprine, 6-mercaptopurine, methotrexate, Direct acting anti hepatitis C agents, corticosteroids for < 1week, Intra-articular steroids,
Uncertain		Tyrosine kinase inhibitors

Table 2: Medications Used in The Prevention of Hepatitis B Reactivation

Medication	Dosing	Side Effects	Comments
Lamivudine (LAM)	100 mg orally daily	Cough, nausea, vomiting, myalgia, pancreatitis, neuropathy, diarrhea, rash	Use should be limited to short term prophylaxis, Pregnancy category B,Severe and fatal hepatitis after withdrawal reported
Entecavir (ETV)	0.5 and 1 mg orally daily	Fatigue, headache, dizziness, nausea, lactic acidosis, hepatomegaly with severe steatosis	Do not use in lamivudine experience patients, Pregnancy: category C,Severe and fatal hepatitis after withdrawal reported
Tenofovir disoproxil fumarate(TDF)	300 mg orally daily	Fatigue, diarrhea, nausea, neuropathy, lactic acidosis, rhabdomyolysis, renal impairment	Pregnancy: category B, Severe and fatal hepatitis after withdrawal reported
Tenofovir Alafenamide Fumarate (TAF)	25 mg orally daily	Headache, fatigue, abdominal pain, cough, high ALT, lactic acidosis	Use in patients with renal impairment, Pregnancy: no data, Severe and fatal hepatitis after withdrawal reported
HBV vaccine Engerix-B	20 mcg IM at 0,1 and 6 months	Pain, pruritic, erythema, fever, nodules, severe allergic reactions	Use double dose in case of failure or low response conditions
Hepatitis B immunoglobulins (HBIG)	High dose IV 10,000 IU, Low dose IV 3000-6000 IU, Low dose IM, SC 400-800 IU	Headache, erythema, myalgia, malaise	Coagulation disorders, Pregnancy: category C

Table 3: HBV Antiviral Dosing in Renal Impairment

Drug\ClCr	Lamivudine	Entecavir	TAF	TDF
> 50 ml/ min	100 mg daily	0.5 mg daily	No dose adjustment	300 mg daily
30- 49 ml/ min	100 mg Q 48 h	0.5 mg Q 48 h	No dose adjustment	300 mg Q 48 hr
10- 29 ml/ min	100 mg Q 72 h	0.5 mg Q 72 h	No data	300 mg Q 72- 96 h
< 10 ml/ min	100 mg Q week	0.5 mg Q week	No data	Hemodialysis: 300 mg Q week

2.1. Grade of Evidence

I Further research is unlikely to change confidence in the estimate of the clinical effect

II Further research may change confidence in the estimate of the clinical effect

III Further research is very likely to affect the confidence in the estimate of the clinical effect and it is based on opinion of respected authorities or descriptive epidemiology

2.2. Strength of Recommendations

1. Strong as judged by quality of the evidence, patient outcomes and cost

2. Weak due to uncertainty

3. Management of Patients Receiving Immunosuppressive, Chemotherapy or Biological Agents (Is/Ct/Ba)

3.1. Baseline Screening for Hepatitis B

Based on the high prevalence of positive Anti-HBc in Saudi patients, the severity of HBVr and the expanded use of biological and immunosuppressive medications that may result in HBVr in patients who are HBsAg positive or may have occult hepatitis B, there must be a strategy for screening, management and follow up [1,2, 67, 70-94].

1. All patients who are likely to receive an agent associated with high or moderate risk for HBVr (Table-I) should be screened for:

i. HBsAg, Anti-HBc (I-1)

ii. Anti-HBs quantification is an optional test (III-1)

2. Anti HBs status should not affect the decision for HBV prophylaxis in high-risk patients (see table-I (II-1)).

3. Patients who turned to be positive for HBsAg or Anti HBc should be screened for HBV-DNA in moderate and high-risk patients (III-1).

4. Patients treated with low-risk immunosuppressive therapy does not require screening (III-2).

3.2. Active Immunization

There is no available data to support the protective effect of HBV vaccination on HBVr. However, all published guidelines recommend vaccinating all patients who turned to be negative for HBV markers unless they have Anti-HBs above 10 IU/mL [39-42,67,74-76].

All patients who are negative for HBV markers should be vaccinated against HBV (III-1).

3.3. Monitoring During Follow Up

Despite lack of strong evidence for frequency of monitoring patients at risk of HBVr, we accepted the suggested recommendations found in the updated guidelines [67,77-81].

• All patients with high and moderate risk who are on HBV prophylaxis should be screened for hepatic profile and HBV-DNA every three to six months (III-1)

• Renal function need to be monitored for possible nephrotoxicity (III-2).

• Patients with negative HBsAg and positive anti-HBs who received B-cell depleting agents should be monitored for HBsAg reverse seroconversion (II-1).

• Low risk patients need not to be monitored (III-2).

3.4. Management of HBV Prophylaxis

Metanalysis has shown significant reduction in HBVr and related mortality by using lamivudine prophylaxis in patients receiving chemotherapy [10,57-59,61]. Because of the high rate of resistance to Lamivudine only NAs with high efficacy and high genetic barrier to resistance should be used [60,62,67,68,77,82-84,85].

• All high and moderate risk patients for HBVr should receive TDF, TAF, or ETV (I-1)

• Lamivudine may be used in short courses (less than 1 year) of prophylaxis in moderate risk patients (III-2)

• For dosing, major side effects, precautions and renal dose adjustment, refer to table-2 and table-3.

3.5. Timing of prophylaxis

Although the use of HBV prophylaxis had been proven to be effective in preventing HBVr, The time to start the prophylaxis is based on opinions adopted by the current guidelines [34,67,72,77,78].

• HBV prophylaxis should be started before or concurrently with chemotherapy or biological therapy in high and moderate risk patients if possible (III-2)

• The start of Chemotherapy or biological therapy should not be delayed for HBV prophylaxis (III-2)

3.6. Duration of prophylaxis

There are no controlled studies to decide on the duration of NAs prophylaxis, however data suggest that 6-12 months after last dose of (CT) is a reasonable duration based on risk stratification.10,34,67

• The (NAs) needs to be continued for a minimum of 6 months after the last dose of the (CT/BT) (III-2)

• Patient who received B-cell depleting agents should continue (NAs) prophylaxis for 12 months after the last dose of that medication. (II-1)

3.7. Management of Organ Transplantation and Hepatitis B

Hepatitis B used to be a contraindication to organ transplantation before the advent of HBIG and NAs, Since then there had been significant improvement in the prevention and treatment of HBVr in transplanted patients [39,67,76,86-95].

3.8. Screening and Vaccination for Solid Organ Transplant and HSCT

Very similar to the section on patients receiving (IS/CT/BA):

- All potential organ recipients should be tested for HBsAg, Anti HBc, Anti-HBs (I-1)

- Test for HBeAg and HBV-DNA in HBsAg and/or Anti-HBc pos-

itive patients (I-1)

- Potential recipients must be vaccinated if they are HBV naïve (II-1)

- Aim for anti-HBs titer >10 IU/mL (II-1)

- Consider high dose vaccination (40 ug) in patients who fail to achieve the protective anti-HBs level with the standard dosing (III-2)

3.9. Donor and Recipient HBV Status

The risk of de novo hepatitis from anti-HBc positive HBsAg negative donors is seen mainly in liver transplant recipients.44,47 The risk of de novo hepatitis without NAs prophylaxis depends on the recipient status. 58% in HBV naïve (negative for all markers for HBV), 18% in those who received vaccine, 14% in anti-HBc positive recipients and 4% in recipients with natural immunity [45-47]. Naturally immune patients going for organ transplantation needs no prophylaxis except for HSCT.

3.10. Organs from HBcAb Positive to HBV Non-Immune Recipients (Anti-HBs Negative)

• Vaccinate recipients and repeat vaccination with higher dose if required prior to transplantation if possible (II-1)

• Anti-HBc positive HBsAg negative organs should be considered for all adult transplant candidates (II-2) Lifelong prophylaxis in liver recipients (II-I)

• Recipients of kidneys from HBcAb positive donors should receive HBV prophylaxis (III-1)

• Consider discontinuing prophylaxis after 1 year (kidney recipients), if HBV DNA negative and Anti-HBs >10 iu/L (III-2)

• No prophylaxis required for other solid organs. However, they should be monitored 3 monthly for HBsAg, HBV DNA and Anti-HBs in the 1st year (III-2)

3.11. Organs from HBcAb positive offered to HBV Immune Recipients (HBs Ab positive >10 IU/ml)

• Give lifelong prophylaxis in liver recipients (II-1)

• Kidney recipients may receive HBV prophylaxis post-transplant. (II-2)

• HBsAg, HBV DNA and Anti HBs should be monitored 3 monthly in the 1st year

• Consider discontinuing prophylaxis after 1 year (non-liver recipients), if HBV DNA is negative and Anti HBsAb >10 iu/L (III-2)

3.12. Organs from HBcAb positive offered to HBcAb Positive Recipients

• Test for HBsAg, HBV DNA pre-transplant and monitor them 3-6 monthly (II-1)

• Vaccinate with single large dose (III-2)\

• Lifelong prophylaxis in liver recipients and those who failed to response to HBV vaccine (II-1)

• If non liver recipients mount Anti-HBs >10 iu no need for prophylaxis (III-2)

• Assess recipient for presence of liver disease before proceeding to transplantation (III-1)

3.13. HSCT Patient are at High Risk of HBVr

Patients going for HSCT are considered high risk for HBVr and should be screened like other transplant candidates. Patients may require high doses for graft versus host disease (GVHD).

- All potential HSCT recipients should be tested for HBsAg, Anti HBc, Anti-HBs (I-1)

- Test for HBeAg and HBV-DNA in HBsAg and/or Anti-HBc positive patients (I-1)

- If the patient has evidence of HBV infection or previous exposure to HBV he should be started on HBV prophylaxis before HSCT (1-1)

- Continue prophylaxis for at least one year after HSCT (III-2)

- Treatment of GVHD patient should be covered with NAs prophylaxis (III-1)

- If HBsAg positive donor is used, give NAs to donor to reduce viral load and give HBV prophylaxis to the recipient (II-1)

3.14. Organ Transplantation in Patients with Chronic HBV

Liver Recipients

- All patients listed for liver transplantation for hepatitis B related liver disease should be treated with NAs (I-1).

- Post liver transplantation NAs should be given in combination with HBIG (II-1)

O 10,000 IU during anhepatic phase and daily for the first week to keep the anti-HBs level above 500 IU/mL in first 3 months, 250 IU/L until 6 months and >100 IU/mL thereafter.

o Maintenance HBIG may be given im or sc. (III-2)

- After 1 year with no evidence of HBV recurrence, give HBV vaccine 40 ug im at 0, 1, 2, 6 and 12 months (III-2).

- Discontinue HBIG if there is confirmed HBV re-infection (high HBV DNA ± positive HBsAg or biopsy) (II-1)

3.15. Recipients of Organs Other Than Liver

- Test all patients for HBV DNA, HBsAg and HBsAg titer (I-1)

- Proper assessment for cirrhosis, if present consider double transplant if indicated (e.g. liver and kidney) (III-1)

- Start (NAs) before transplantation to reduce viral replication and continued prophylaxis for life after transplantation (II-1)

- Post transplantation minimize the dose and duration of steroids (II-1)

- monitor HBV DNA and HBsAg titer every 3 months (II-1)

- Screen with ultrasound liver for HCC every 6 moths (II-1)

3.16. Ethics

The King Faisal Specialist Hospital and Research Center's Institutional Review Board gave its approval for this work to be completed

and sent for publication. The IRB's approval number is 2235234. This article reviewed the research papers that are currently available and made recommendations on this topic. It was not necessary to obtain consent because there was no direct involvement of human subjects.

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