Role of nucleoside/nucleotide analogues and low-dose hepatitis B immune globulin in prophylaxis of hepatitis B recurrence among cadaveric liver transplant recipients

Tokunbo Ajayi[1,2], Harry Luu[2], Behnam Saberi[2], James P. Hamilton[2], Bugra Tolga Konduk[2], Burak Özşeker[2], Kawtar Al Khalloufi[2], Aliaksei Pustavoitau[3], Benjamin Philosophe[4], Andrew M. Cameron[4], Ahmet Gürakar[2]

[1]Department of Internal Medicine, Johns Hopkins Howard County General Hospital, Columbia, MD
[2]Division of Gastroenterology and Hepatology, Transplant Hepatology, Johns Hopkins University School of Medicine, Baltimore, MD
[3]Department of Anesthesiology and Critical Care, Johns Hopkins University School of Medicine, Baltimore, MD
[4]Transplant Surgery, Johns Hopkins University School of Medicine, Baltimore, MD

Cite this article as: *Ajayi T, Luu H, Saberi B, et al. Role of nucleoside/nucleotide analogues and low-dose hepatitis B immune globulin in prophylaxis of hepatitis B recurrence among cadaveric liver transplant recipients. Turk J Gastroenterol 2018; 29: 61-6.*

ABSTRACT

Background/Aims: *Hepatitis B core antibody (HBcAb) positivity of the donor or the recipient may pose a risk of hepatitis B virus (HBV) reactivation following liver transplantation (LT). We retrospectively investigated patient survival and reactivation among recipients who were given low-dose Hepatitis B Immune Globulin (HBIG) plus antiviral agent (AV) versus AV only.*

Materials and Methods: *Records of cadaveric LT recipients, between 2013 and 2016, with positive Hepatitis B surface Antigen (HBsAg) and/or HBcAb and recipients who had received LT from HBcAb-positive donors were reviewed. Patient characteristics and clinical data were extracted. Donor variables were retrieved from the United Network of Organ Sharing (UNOS) database. HBIG (1560 IU/mL) Intravenous (IV) was intraoperatively administered with three daily doses. Entecavir 1 mg daily was also given. STATA was used for statistical analysis.*

Results: *There were 53 recipients; 39 (73.6%) were male with a median age of 59 y. HCV was the major indication in 30 (55.6%) patients. There were 28 recipients (52.8%) who received HBIG plus AV and 25 (47.2%) received AV only. The Model of End Stage Liver Disease (MELD) score between the groups were similar. Survival rates at 6, 12, and 24 months were 100% (n=53), 93.2% (n=44), and 100.0% (n=26), respectively. There was no reactivation; two recipients in the AV group and one in the HBIG plus AV group died within 12 months.*

Conclusion: *This study supports the use of low-dose HBIG and AV for post-LT prophylaxis to be as effective as conventionally used high-dose HBIG (9600 IU) plus AV. Future prospective larger studies are warranted to examine the potential benefits of using AV alone without HBIG.*

Keywords: *Hepatitis B, liver transplant, recurrence, prophylaxis*

INTRODUCTION

Hepatitis B is a universal health problem. In the United States, approximately 800,000-1.4 million people are chronically infected with Hepatitis B virus (HBV) and 3000 per year die from HBV-related diseases (1). The transmission risk is 25%-60% in healthy patients and those who are infected through exposure to people who are positive for Hepatitis B surface antigen (HBsAg) and Hepatitis B e antigen (HBeAg) (2). Five-year survival rates in HBV patients with compensated and decompensated cirrhosis are 84% and 14%, respectively (3). The HBsAg and Hepatitis B core antibody (HBcAb) status of an organ donor or recipient determine the risk of infection and transmission of HBV following transplantation. The rate of HBV liver transplantation (LT) failure was high in the 1980s when there was no pre- and post-LT HBV treatment (3-5). The high rates of post-LT mortality from HBV in the 1980s underlined the importance of treatment and reactivation prevention of HBV. Seropositive HbcAb IgG is evidence of past exposure to HBV. HBcAb-positive donors and recipients are at a risk of reactivation and reinfection, especially during the early post-LT phase. The risk of reinfection is related to immunosuppression in the post-LT phase, leading to enhanced viral replication of the HBV genome and expansion of extrahepatic reservoirs of HBV (6,7).

ORCID IDs of the authors: *T.A. 0000-0001-6098-6017; H.L 0000-0001-6130-9915; B.S. 0000-0002-7157-5827; B.T.K. 0000-0002-9138-9984; B.Ö. 0000-0001-5429-513X; K.A.K. 0000-0003-1609-6222; A.M.C. 0000-0002-5810-2398; A.P. 0000-0003-2104-3598; A.G. 0000-0002-2221-9148*

Address for Correspondence: ***Ahmet Gürakar*** *E-mail:* ***aguraka1@jhmi.edu***
Received: ***September 11, 2017*** *Accepted:* ***November 11, 2017***

DOI: ***10.5152/tjg.2018.17595***

The prognosis for HBV patients during the pre-Hepatitis B immunoglobulin (HBIG) era was not promising. The introduction of HBIG, followed by antivirals (AV), gave hope to these patients. The prophylactic use of HBIG alone resulted in 1- and 5-year post-LT survival rates as high as 85% and 75%, respectively; less than 5% graft reinfections was also observed (8,9). HBIG use as prophylaxis was based on the hypothesis that antibodies to HBsAg would bind and neutralize the circulating virions and reduce HBsAg secretion, thereby preventing graft infection (10). The combined use of HBIG and AV now has become the standard of care. However, HBIG typically costs patients about $30,000-$50,000 per year when given intravenously for the first week and monthly thereafter (11). In addition to cost, side effects from these regimens include headache, flushing, muscle ache, and lactic acidosis (12). Because of limitations in access, high cost, and side effects of HBIG therapy, various groups have developed alternative regimens that are effective and are associated with lower cost.

The duration, dosage, and route of HBIG administration may vary according to local clinical practice (13). It has been postulated that HGIB can be discontinued both 1 month or 1 year post-transplant (14-17). Fung et al. (15) followed 80 patients with chronic HBV who received entecavir therapy without HBIG, and after 2 years post-transplant, most of the recipients have their lost HBsAg. Teperman et al. (18) also showed that dual therapy with two different AVs can be as effective as combination therapy of HBIG with one or two AVs after a limited period of HBIG. These findings demonstrated the possibility of limiting or even eliminating HBIG from the current standard of practice of immunoprophylaxis against HBV in LT recipients. Nath et al. (19) revealed similar results in 14 patients, who received two AVs and 7-day use of HBIG post-LT.

Previous studies on different strengths of HBIG and AV have shown mixed results on survival and recurrence rates. In this study, we retrospectively compared patient survival and HBV reactivation rates among HBcAb-positive LT recipients who were given low-dose HBIG plus AV and AV only.

MATERIALS AND METHODS

After Institutional Review Board (IRB) approval was obtained (IRB 00098506), we retrospectively reviewed electronic medical records of all adults (age ≥18 y) undergoing cadaveric LT at Johns Hopkins Hospital (Baltimore, MD, USA) between January 2013 and December 2016. We excluded those who received living donor LT, had more than one transplants, had acute liver failure, or expired within 30 days of the operation. We identified 53 patients who were either HBcAb-positive or had donors with HBcAb-positive status. Recipient demographics, including age, race, gender, and transplant indication, were obtained from electronic medical records. Donor demographics were retrieved from the United Network for Organ Sharing (UNOS) database. Histopathology results and medical records were used to confirm indication for LT.

Patients receiving prophylaxis after transplant were categorized into two treatment arms: combination therapy (HBIG plus AV agent) and AV agent only. HBIG was administered Intravenous Route (IV), intraoperatively at a dose of 1560 IU/mL during the anhepatic phase followed by three daily doses post-LT. Entecavir 1 mg (Bristol-Myers Squibb Company, Princeton, NJ, USA) daily was the oral AV agent administered starting on the first post-transplant day. The choice of prophylaxis treatment was based on both donors' and recipients' Hepatitis B status. Recipients who were actively infected [HBsAg (+)] were given the combination therapy of HBIG and AV regardless of the donors' status. Recipients who were once infected [HBcAb (+)] and received grafts from donors with the same status [HBcAb (+)] were also given the combination therapy. Recipients who had HBcAb (+) status but received grafts from donors with HBcAb (-) status were given AV therapy only. The recipient HBsAb titer was not taken into consideration because the titers of the antibody were not available. We measured post-transplant survival and recurrence of HBV as the primary outcomes.

Data were stored on Microsoft Excel (Microsoft Corp., Richmond, WA, USA). Statistical analyses were performed using STATA 12.0 (StataCorp LP, College Station, TX, USA). We defined survival as time from transplant to study termination. Comparisons between the two treatment groups were done using the Fisher's exact test. Because of insufficient number of patients and the non-parametric distribution of the data, the Mann-Whitney U test was used to compare continuous variables. P value ≤0.05 was considered statistically significant.

RESULTS

Among the 53 eligible patients, 39 (73.6%) were males. The median age at the time of LT was 59 years. More than half

of the patients were Caucasians (56.6%), followed by African American (30.2%). Forty-one (77.4%) recipients were HBcAb-positive. The most common indication for LT was Hepatitis C infection (56.6%), followed by primary Hepatitis B infection (15.1%) (Table 1). Eighteen (34%) patients received HBcAb-positive donor grafts, 28 (52.8%) received HBIG and AV combination therapy, and 25 (47.2%) received AV agent only (Table 2). At the end of the study period, all patients had passed the 6-month follow-up mark, whereas 44 had passed the 12-month follow-up mark and 26 had passed the 24-month mark. Survival rates at 6, 12, and 24 months were 100% (n=53), 93.2% (n=44), and 100% (n=26), respectively (Tables 1 and 2).

In the group that received AV treatment, only two patients died at 12 months. In the combination therapy of HBIG and AV agent, one patient died at 12 months. No death was related to HBV (Figure 1). Comparison of the 12-month survival rates between the two treatment groups showed no statistically significant difference.

Table 1. Patient characteristics (n=53)

Sex	
Male	39 (73.6%)
Female	14 (26.4%)
Race	
Asian	2 (3.8%)
African American	16 (30.2%)
White	30 (56.6%)
Hispanic	2 (3.8%)
Other	3 (5.6%)
Recipient	
HBcAb (+)	41 (77.4%)
HBsAg (+)	10 (18.9%)
HBsAg (-)	43 (81.1%)
Donor	
HBcAb (+)	18 (34.0%)
HBcAb (-)	35 (66.0%)
Prophylaxis post Liver Transplant	
HBIG + Antiviral	28 (52.8%)
Antiviral alone	25 (47.2%)
Transplant Indication	
Hep B	8 (15.1%)
Hep C	30 (56.6%)
Hep B & C	4 (7.5%)
Alcoholic Hepatitis	3 (5.6%)
Alcoholic Hepatitis + Hep C	2 (3.8%)
Alcoholic Hepatitis + Hep B + Hep C	1 (1.9%)
Primary Biliary Cholangitis	2 (3.8%)
Other	3 (5.6%)
Survival	
6 months (n=53)	53 (100%)
12 months (n=44)	41 (93.2%)
24 months (n=26)	26 (100%)

HbcAb: Hepatitis B core Antibody; HBsAg: Hepatitis B surface; Antigen HBIG: Hepatitis B Immune Globulin

DISCUSSION

We report survival rates in two groups of patients who had similar survival rate in both treatment arms of the study: patients who received low-dose HBIG and AV versus AV only. This study was an offshoot of a similar study that was conducted by Malik et al. (20), which investigated the survival in three subgroups of LT patients: those receiving HBV prophylaxis with AV alone, HBIG alone, or in combination. However, the HBIG dose was higher. There was no difference in survival among all groups, showing similar results to the current observation. In addition, a pivotal study involving 80 patients using entecavir monotherapy as prophylaxis showed 23% HBsAg positivity at the end of a 26-month study period with 90% HBV DNA negativity (15). Another study involving 362 patients who received combination AV therapy had an HBV reinfection rate of 5% after 1 y, 13% after 5 y, and 16% at 8 y. Subanalysis on each AV showed lamivudine was the least effective, whereas entecavir was the most effective (21). Our study revealed similar survival rate in both monotherapy and combination groups, and such similarity is possibly due to the prolongation of HBIG half-life by AV and the ability of AV to reduce circulating virions in the blood of recipients (22).

Hepatitis B immunoglobin was discovered in the 1990s and became the "savior" drug for HBV LT patients who were at increased risk of reinfection and graft failure (23). Howev-

Table 2. APCs (%), 2005-2010, male and female

	Donors	
Recipients	HBcAb (-)	HBcAb (+)
HBsAg (+)	10 (HBIG + Antiviral)	0
HBsAg (-)/HBcAb (+)	25 (Antiviral only)	6 (HBIG + Antiviral)
HBsAg (-)/HBcAb (-)	0	12 (HBIG + Antiviral)

HbcAb: Hepatitis B core Antibody; HBsAg: Hepatitis B surface; Antigen HBIG: Hepatitis B Immune Globulin; APC: argon plasma coogulation

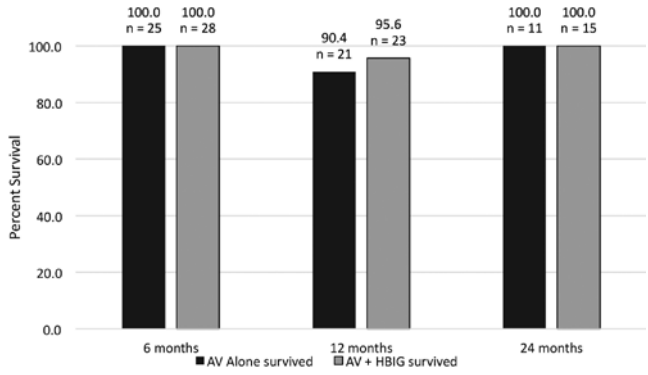

Figure 1. Post Transplant Survival

er, with the discovery of AV and widespread use of these drugs, the use of HBIG for prophylaxis is now evolving (23). Most centers seem to use HBIG when patients are HBV DNA-negative and their viral load is less than 100,000 copies/mL (<20,000 IU/mL) or HBeAg-negative pre-transplant (24). The standard of practice for HBV prophylaxis used to be the combination of HBIG and AV (13). However, recent studies seemed to show that AV monotherapy or shorter duration of HBIG could be sufficient, leading to practice changes among transplant centers (13,23).

There are variations in the use of AV and HBIG in HBV patients post-LT. Different agent strengths, routes of administration, and types of AV have shown little or no effect on patient survival (25,26). The study by Angus et al. (27) showed significant reduction in the rate of HBV recurrence in the first year post-LT in patients using lamivudine and HBIG. Also, a review of 46 studies showed that second-generation AV was more efficacious than first-generation AV when combined with HBIG (26). This result has prompted most liver centers, including our own institution, to use second-generation AV. Furthermore, studies have been conducted to investigate whether HBIG could be reduced in strength and duration or even eliminated from prophylaxis protocol, and a few studies have shown that entecavir alone as HBV prophylaxis post-LT was safe and effective (15,28).

Although newer AV appears effective in short-term HBV prophylaxis post-LT, the risk of recurrence is still a concern. Several studies have shown that with appropriate patient selection (high- vs. low-risk), recurrence could be minimized (26,29). The factors that impact recurrence include the presence of hepatocellular carcinoma (HCC) are LT, HCC recurrence, and types of HCC treatment (13). Elevated viral load at transplantation, HBeAg positivity, and history of AV drug resistance also carry increased risk of recurrence. Patients with low viral load, HBeAg-negative status, acute liver failure, and Hepatitis D virus coinfection are considered to have the lowest risk for recurrent HBV infection post-LT (13). HBV DNA levels pre-and post-transplant are extremely important as it determines whether the patient is in the low- or high-risk category. In addition, some studies have shown that there was little to no reinfection in patients with undetectable HBV DNA pre- and post-LT (30). This has led to the practice of monitoring HBV DNA level post-transplant for HBV recurrence surveillance in most liver centers.

Because there is variation in the use of HBIG and AV, which patient should be considered for HBIG-free regimen or low-dose HBIG regime? High-risk patients such as those with HCC at LT, significant risk or history of nonadherence to AV therapy, high HBV DNA titers pre-transplant, and limited AV options in case of HBV recurrence (HIV or HDV coinfection, pre-existing intolerance, or drug resistance) should not be started on HBIG-free regimen. If HBIG is given, it should be done with caution and on case-by-case basis (31). The standard of care based on the American Association for the Study of Liver (AASLD) and Asia Pacific Association for the Study of Liver guidelines on the prevention of recurrent HBV post-LT recommend that in low-risk patients, who have undetectable HBV DNA levels at the time of transplant, high-potency AVs alone can be used indefinitely. However, in high-risk patient population, 10,000 IU IV HBIG in the anhepatic phase should be given followed by 600-1000 IU IM or IV daily for 7 days, then weekly for 3 weeks, and then monthly to keep anti-HBs levels >100 mIU/mL for 1 y. After 1 y, HBIG may be discontinued. High-potency AVs should be continued simultaneously indefinitely in all patients (12,32,33).

Limitation and generalizability

Our study has several limitations that include the lack of capability to infer causality among our outcomes and variables, a common limitation seen with most retrospective studies. Moreover, our study did not try to determine the factors or mediations that affect graft survival. Generalizability of this study will be cautioned because of limited sample size and our inability to further analyze the different intervention groups with different HBV exposure. Nevertheless, our study can add to the body of literature concerning HBV prophylaxis and give reason to the possible role of AV alone in clinical practice sooner rather than later.

In conclusion, our results support the recent practice of using four low doses of HBIG (1560 IU) and AV for post-LT prophylaxis in high-risk recipients. It is as effective as previous regimen of seven high doses of HBIG (9600 IU) and AV. No serum HBsAb levels were followed in this group of patients. Future prospective studies with larger sample size and randomized controlled trials are warranted to examine the potential benefits of using AV alone without HBIG in high-risk patients.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - A.G., J.P.H., B.S.; Design - T.A., H.L.; Supervision - A.G., J.P.H., B.S.; Resource - T.A., A.G.; Materials - T.A., A.G.; Data Collection and/or Processing - T.A., A.G.; Analysis and/or Interpretation - T.A., A.G., B.S.; Literature Search - B.T.K., B.Ö., K.A.K.; Writing - T.A., B.S., A.G.; Critical Reviews - B.P., A.M.C. , J.P.H. , B.S., A.P.

Conflict of Interest: Dr.Gürakar reports personal fees from Gilead, grants and personal fees from BMS, during the conduct of the study.

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

REFERENCES

1. Commentary | U.S. 2015 Surveillance Data for Viral Hepatitis | Statistics & Surveillance | Division of Viral Hepatitis | CDC. (cited 2017 Jun 1). Available from: URL: https://www.cdc.gov/hepatitis/statistics/2015surveillance/commentary.htm.

2. Schillie S, Murphy TV, Sawyer M, et al. CDC Guidance for Evaluating Health-Care Personnel for Hepatitis B Virus Protection and for Administering Postexposure Management. (cited 2017 Sep 11). Available from: URL: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6210a1.htm.

3. de Jongh FE, Janssen HL, de Man RA, Hop WC, Schalm SW, van Blankenstein M. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. Gastroenterology 1992; 103: 1630-5. [CrossRef]

4. O'Grady JG, Smith HM, Davies SE, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. J Hepatol; 14: 104-11. [CrossRef]

5. Starzl TE, Demetris AJ, Van Thiel D. Liver Transplantation. N Engl J Med 1989; 321: 1014-22. [CrossRef]

6. McMillan JS, Shaw T, Angus PW, Locarnini SA. Effect of immunosuppressive and antiviral agents on hepatitis B virus replication in vitro. Hepatology 1995; 22: 36-43. [CrossRef]

7. Omata M. Significance of extrahepatic replication of hepatitis B virus. Hepatology 1990; 12: 364-6. [CrossRef]

8. Kim WR, Terrault NA, Pedersen RA, et al. Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. Gastroenterology 2009; 137: 1680-6. [CrossRef]

9. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med 1993; 329(25): 1842-7. [CrossRef]

10. Schilling R, Ijaz S, Davidoff M, et al. Endocytosis of hepatitis B immune globulin into hepatocytes inhibits the secretion of hepatitis B virus surface antigen and virions. J Virol 2003; 77: 8882-92. [CrossRef]

11. Terrault NA, Zhou S, Combs C, et al. Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. Hepatology 24: 1327-33. [CrossRef]

12. Terrault NA, Bzowej NH, Chang KM; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016; 63: 261-83. [CrossRef]

13. Maiwall R, Kumar M. Prevention and treatment of recurrent hepatitis B after liver transplantation. J Clin Transl Hepatol 2016; 4: 54-65. [CrossRef]

14. Degertekin B, Han S-HB, Keeffe EB, et al. Impact of virologic breakthrough and HBIG regimen on hepatitis B recurrence after liver transplantation. Am J Transplant 2010; 10: 1823-33. [CrossRef]

15. Fung J, Cheung C, Chan SC, et al. Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. Gastroenterology 2011; 141: 1212-9. [CrossRef]

16. Yi NJ, Lee KW, Kong SY, et al. Outcome of various treatments for posttransplant hepatitis B virus recurrence. World J Surg 2013; 37: 812-9. [CrossRef]

17. Wong SN, Chu CJ, Wai CT, et al. Low risk of hepatitis B virus recurrence after withdrawal of long-term hepatitis B immunoglobulin in patients receiving maintenance nucleos(t)ide analogue therapy. Liver Transpl 2007; 13: 374-81. [CrossRef]

18. Teperman LW, Poordad F, Bzowej N, et al. Randomized trial of emtricitabine/tenofovir disoproxil fumarate after hepatitis B immunoglobulin withdrawal after liver transplantation. Liver Transpl 2013; 19: 594-601. [CrossRef]

19. Nath DS, Kalis A, Nelson S, Payne WD, Lake JR, Humar A. Hepatitis B prophylaxis post-liver transplant without maintenance hepatitis B immunoglobulin therapy. Clin Transplant 2006; 20: 206-10. [CrossRef]

20. Malik MU, Ucbilek E, Trilianos P, Cameron AM, Gurakar A. Prophylaxis among hepatitis B Core antibody-positive deceased-donor

liver transplant recipients: hepatitis B immunoglobulin plus oral antiviral agents versus antiviral agents alone: a single-center experience. Exp Clin Transplant 2017; 15: 183-8.
21. Fung J, Chan SC, Cheung C, et al. Oral nucleoside/nucleotide analogs without hepatitis B immune globulin after liver transplantation for hepatitis B. Am J Gastroenterol 2013; 108: 942-8. **[CrossRef]**
22. Dickson RC, Terrault NA, Ishitani M, Reddy KR, Sheiner P, Luketic V, et al. Protective antibody levels and dose requirements for IV 5% Nabi Hepatitis B immune globulin combined with lamivudine in liver transplantation for hepatitis B-induced end stage liver disease. Liver Transpl 2006; 12: 124-33. **[CrossRef]**
23. Jiménez Pérez M, González Grande R, Mostazo Torres J, González Arjona C, Rando Muñoz FJ. Management of hepatitis B virus infection after liver transplantation. World J Gastroenterol 2015; 21: 12083-90. **[CrossRef]**
24. Marzano A, Gaia S, Ghisetti V, Carenzi S, Premoli A, Debernardi-Venon W, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. Liver Transpl 2005; 11: 402-9. **[CrossRef]**
25. Di Costanzo GG, Lanza AG, Picciotto FP, et al. Safety and efficacy of subcutaneous hepatitis B immunoglobulin after liver transplantation: an open single-arm prospective study. Am J Transplant 2013; 13: 348-52. **[CrossRef]**
26. Cholongitas E, Goulis J, Akriviadis E, Papatheodoridis GV. Hepatitis B immunoglobulin and/or nucleos(t)ide analogues for prophylaxis against hepatitis b virus recurrence after liver transplantation: a systematic review. Liver Transpl 2011; 17: 1176-90. **[CrossRef]**
27. Angus PW, Patterson SJ, Strasser SI, McCaughan GW, Gane E. A randomized study of adefovir dipivoxil in place of HBIG in combination with lamivudine as post-liver transplantation hepatitis B prophylaxis. Hepatology 2008; 48: 1460-6. **[CrossRef]**
28. Gane EJ, Patterson S, Strasser SI, McCaughan GW, Angus PW. Combination of lamivudine and adefovir without hepatitis B immune globulin is safe and effective prophylaxis against hepatitis B virus recurrence in hepatitis B surface antigen-positive liver transplant candidates. Liver Transpl 2013; 19: 268-74. **[CrossRef]**
29. Cholongitas E, Vasiliadis T, Antoniadis N, Goulis I, Papanikolaou V, Akriviadis E. Hepatitis B prophylaxis post liver transplantation with newer nucleos(t)ide analogues after hepatitis B immunoglobulin discontinuation. Transpl Infect Dis 2012; 14: 479-87. **[CrossRef]**
30. John S, Andersson KL, Kotton CN, et al. Prophylaxis of hepatitis B infection in solid organ transplant recipients. Ther Adv Gastroenterol 2013; 6: 309-19. **[CrossRef]**
31. Roche B, Samuel D. Prevention of hepatitis B virus reinfection in liver transplant recipients. Intervirology 2014; 57: 196-201. **[CrossRef]**
32. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016; 10: 1-98. **[CrossRef]**
33. Practice Guidelines. (cited 2017 Jun 1). Available from: URL: https://www.aasld.org/publications/hepatitis-b-chronic.