Inonu University Liver Transplant Institute

Liver Transplantation and Hepatitis B Symposium

1 March 2024

From the Symposium President

Dear Participants,

Before the use of antiviral prophylaxis and hepatitis B immune globulin, posttransplantation recurrence of hepatitis B virus infection was almost universal and was commonly associated with accelerated hepatitis B virus-related graft injury leading to graft failure and death.

Many studies showed that the application of hepatitis B immune globulin and antiviral drugs is effective to prevent hepatitis B reinfection after liver transplantation. However, there are still many controversial issues regarding hepatitis B immune globulin prophylaxis, including dosage and time. In the meeting, an attempt was made to find answers to the controversial issues in hepatitis B immune globuline treatment.

The president of the Symposium

Prof. Burak ISIK, MD, FACS

Director of Inonu University

Liver Transplant Institute

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Kemal Baris SARICI
Ersoy KEKILLI

Symposium program

1 March 2024

Session I

Chairperson: Prof. Burak Isik; MD and Prof. Cemalettin Koc; MD

Yilmaz Bilgic

14.00-14.20 Liver transplantation management from Anti HBc positive donors to HBV negative recipients in Liver Transplantation

Deniz Yavuz Baskiran

14.30- 14.50 Inonu University Experience in Hepatitis B Recurrence After Liver Transplantation

Ahmet Sami Akbulut

15.00- 15.20 Protocols with and without Hepatitis B immunoglobulin following Liver Transplantation

15.30 - 15.40 Tea/Coffee Break

Session II

Chairperson: Prof. Dincer Ozgor; MD and Prof. Fatih Ozdemir; MD

Murat Harputluoglu

15.40 - 16.00 Approach to patients whose Hepatitis B surface antigen does not become negative and have early hepatitis B virus recurrence after liver transplantation

Murat Yavuz

16.10 - 16.30 Effectiveness, Patient Contentment, and Safety Profile of Subcutaneous Hepatitis B Immunoglobulin Therapy Following Liver Transplantation

Kemal Baris Sarici

16.40 - 17.00 HBV Prophylaxis After Liver Transplantation in HCC

17.40 CLOSING REMARKS

Liver transplantation management from Anti HBc positive donors to HBV negative recipients in Liver Transplantation

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Abstract

Anti HBc + people are in the marginal donor group. It is considered as a donor source, especially in places where Hepatitis B is endemic. In endemic areas, 21.4% of donors are HBcAb positive. In regions where HBV is not endemic, it is 4.75%-7%. De novo hepatitis may develop in liver transplants from anti-HBc+ donors. The most important factors for de novo hepatitis are the presence or absence of anti-HBc and anti-HBs positivity. If both antibodies are positive, the risk of denovo hepatitis is least and if both antibodies are negative, it is highest. High genetic barrier antivirals alone are recommended for the treatment and prophylaxis of developing de novo hepatitis. Hepatitis B immune globulin has no place in de novo treatment and prevention.

Introduction

Anti-HBc positivity can be explained by more than one scenario. Anti-HBc is a 'non-neutralizing' antibody that does not provide immune protection. In other words, it is a 'serological scar' (i.e. evidence of previous exposure to HBV). Anti-HBc+ status can be seen both after acute infection and chronic infection.[1]

This large cohort study described the long-term results of HBIG monotherapy preventing de novo HBV infection after LT using HBcAb positive liver grafts in an area where HBV is endemic. There is no advantage over monotherapy. HBcAb-negative recipients were more likely to develop new HBV infection than HBcAb-positive recipients. A high MELD score was significantly associated with de novo HBV infection.[2]

Between 2000 and 2010, 71 anti-HBs negative adult patients who received anti-HBc+ grafts were vaccinated against hepatitis B virus to ensure that Anti-HBs was >1000 IU/L before transplantation and >100 IU/L after transplantation. The cohort was divided into 3 groups: patients who did not need post-transplantation prophylaxis, patients with pre-transplant anti-HBs titer >1000 IU/L (group 1, n=24), patients with pre-transplant anti-HBs titer <1000 IU/L and anti-HBs administered. Patients who received post-transplant lamivudine prophylaxis and responded appropriately to post-transplant vaccination by maintaining anti-HBs titers >100 IU/L (group 2, n=30) and low titer non-responders (anti-HBs titer <100 IU/L despite vaccination) to lamivudine patient continued indefinitely (group 3, n=17). All DNHB occurred in group 3 patients with posttransplant anti-HBs levels <100 IU/L; The incidence rate was 17.6% compared to 0% in patients with post-transplant anti-HBs levels >100 IU/L (p=0.001). A pretransplantation anti-HBs level >1000 IU/L was significantly associated with early access and a persistent posttransplantation anti-HBs level of >100 IU/L (p<0.001). Active immunization is effective in preventing DNHB in adult LDLT if the post-transplant anti-HBs level is kept above 100 IU/L by vaccination.[3]

In another article investigating the risk of De novo hepatitis B virus infection developing after liver transplantation using a hepatitis B core antibody positive graft, the incidence of de novu hepatitis B was evaluated according to the anti-HBc and anti-HBs positivity or negativity of the recipient. De novo hepatitis developed in one of them. While the most risky group was the group in which both antibodies were negative, the risk was found to be lowest in the group in which both antibodies were positive. When the risk groups of patients who developed de novo hepatitis were examined, age, anti-HBc positivity and anti-Hbs positivity were found to be significant. Antivirals were started in patients who developed de novo hepatitis B. It was observed that HBsAg turned negative in all patients who developed de novo hepatitis after treatment.[4]

Treatment of de novo hepatitis;[5]

- HBIG+LAM combination compared to LAM monotherapy in HBV DNA(-) patients receiving HBcAb(+) liver grafts;
- LAM monotherapy has the same efficacy as HBIG+LAM combination therapy
- Entecavir and tenofovir monotherapy is safer.
- Therefore, we recommend that clinicians administer nucleoside(t)ide analogs with lower resistance profiles to recipients of HBcAb(+) liver allografts without additional HBIG therapy.
- AASLD and EASL recommend monotherapy.

The role of immunosuppressants used in the development of de novo hepatitis

The immunosuppressive regimen using mTOR inhibitors after liver transplantation has been shown to generally reactivate HBV infection, as well as viral infections such as HCV, cytomegalovirus (CMV), HIV-1, human papillomavirus (HPV), and Epstein Barr.[6]

Survival in de novo hepatitis

The 5-year survival rate for recipients of HBcAb-positive grafts was 97.5% and 89.7% for recipients of HBcAb-negative grafts. It shows that the survival rate does not differ significantly depending on the HBcAb status of the donor.[3]

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Inonu University Experience in Hepatitis B Recurrence After Liver Transplantation

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Abstract

We will introduce the HBV virus closely and share the health problems of HBV in the world and in our country in the literature data. We will evaluate patients who underwent liver transplantation due to HBV at İnönü University Liver Transplant Institute in terms of HBV recurrence, our results and recommendations.

Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence.

In our clinic , HBIG treatment is given for life. In the unhepatic phase, HBIG is given for 7 days postoperatively and every month, depending on the AntiHbs level. Anti-HBS level is tried to be kept above 100 IU/L. The HBV recurrence rate seen in our clinic shows that patients are not fully compliant with medical treatment and that patients must receive postoperative education. In particular, antiviral treatment and access to HBIG should be provided, and a prospective study should be started in our liver transplantation institute to investigate HBV recurrence.

Introduction

Hepatitis B virus (HBV), one of the biggest health problems of the world and our country, still constitutes the largest cause of liver failure and liver transplantation in the world. Here, we will introduce the HBV virus closely and share the health problems of HBV in the world and in our country in the literature data. We will evaluate patients who underwent liver transplantation due to HBV at İnönü University Liver Transplant Institute in terms of HBV recurrence, our results and recommendations.

HBV Epidemiology

In the 1980s, cirrhosis due to HBV was considered a relative contraindication for liver transplantation.[1] Because without antiviral prophylaxis, the recurrence rate of HBV after liver transplantation was close to 100% and the mortality rate in the first year after transplantation was approximately 50%. With the discovery of hepatitis B immunoglobulin (HBIG), a polyclonal antibody developed against HBV surface antigen, in the early 1990s, HBV recurrence after liver transplantation decreased significantly and survival increased.[2] HBIG has a polycolonal immunoglobulin G (IgG) structure and is in the IgG subclass. Its distribution is very close to the rates in human plasma.

High Risk Groups for HBV Recurrence;[8,9]

- Pre-Transplant Hbv DNA +
- Pre-Transplant Hbe-ag
- Presence of HCC
- Low compliance with antiviral treatment
- Resistance to antiviral treatment
- Concomitant HIV or HDV infection

Low Risk Group for HBV Recurrence[8,9]

- Pre-Transplant HBV DNA negativity
- Pre-Transplant Hbe-ag negativity
- No HCC
- High compliance with antiviral treatment
- Lack of resistance to antiviral treatment
- No accompanying HIV or HDV infection

Material Method

İnönü University Liver Transplant Institute Patients who underwent liver transplantation due to any reason related to HBV were included in the study.

Patients who underwent liver transplantation due to liver diseases caused by HBV in our institute between 2009 and 2023 were included in the study, A total of 3679 patients underwent liver transplantation between 2002 and 2024. Of these patients, 1275 patients were operated on with the diagnosis of HBV. When 530 patients whose data were not available and 49 patients who were retransplanted were excluded from the study, a total of 695 patients were included in the study. Of these patients, no HBV recurrence was observed in 599 patients. HBV recurrence was observed in 96 of these patients (13.8%).

Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence.

Findings

Hepatitis B recurrence is observed in a total of 112 patients (16.1%) and when the Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence.

Variables		n	(%)
DIAGNOSIS	HBV	454	65.3
	HBV+HCC	151	21.7
	HBV+HDV	61	8.8
	HBV+HDV+HCC	24	3.5
	HBV+HCV	3	0.4
	HBV+HDV+HCV+HCC	1	0.1
	HBV+HCV+HCC	1	0.1
HBSAG 1st month after liver transplantation	Negative	583	83.9
	Positive	112	16.1
Last check HBSAG	Negative	599	86.2
	Positive	96	13.8

Discussion

In a study, subcutaneous HBIG was given to patients who had completed 1 year after liver transplantation, with an anti-HBS titer of >150 Iu/L. After 48 weeks, the average anti-HBs titer was found to be 232 Iu/L, and no HBV recurrence was observed in any of the patients.[3]

In our clinic, HBIG treatment is given for life. In the unhepatic phase, HBIG is given for 7 days postoperatively and every month, depending on the AntiHbs level. Anti-HBS level is tried to be kept above 100 IU/L. The HBV recurrence rate seen in our clinic shows that patients are not fully compliant with medical treatment and that patients must receive postoperative education.

In another study involving 176 patients, the combination of HBIG and potent antivirals was targeted to have an anti-HBS titer of 100-250 Iu/l in the post-transplant period. It was reported that only 2 patients developed relapse during an average follow-up of 43 months and one of these patients did not use the treatment.[11th]

Treatment is given in combination with antiviral and HBIG. It is available in centers where powerful antivirals are used alone. Although the approaches of the centers vary, patients who have had a liver transplant due to HBV definitely need postoperative medical treatment to prevent HBV recurrence.

Anti-HBS level differences may be required in the follow-up of high-risk and low-risk groups. However, monitoring this requires detailed information about the patient discharged from the hospital.

When the effect of high-risk patient group on postoperative HBV recurrence was examined, it was seen that noncompliance with medical treatment was effective.

Despite all these findings, it has been reported that the use of HBIG has additional contributions such as reducing rejection and HCC recurrence rates after liver transplantation.[4]

Conclusion and Recommendations

Patients who have undergone liver transplantation due to HBV must have their Hbs-ag level checked when they are discharged from the hospital. Informing the patient about HBV recurrence and medical treatment provides a more meticulous medical treatment. In particular, antiviral treatment and access to HBIG should be provided, and a prospective study should be started in our liver transplantation institute to investigate HBV recurrence. The shortcomings of the study are that it is a retrospective study, not all patient data can be accessed in the study (Hospital automation system change), and the HBIG doses taken by the patient cannot be determined.

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Protocols with and without Hepatitis B immunoglobulin following Liver Transplantation

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Abstract

Hepatitis B Virus (HBV) is the most frequent etiology of liver failure requiring liver transplantation. The crucial point of liver transplantation for HBV-related liver disease is the prevention of HBV relapse in the postoperative period. Current evidence suggests combining Hepatitis B Immunoglobulin (HIBIG) and nucleotide/nucleoside analogs. The decision to start HIBIG therapy and its duration is controversial. However, studies suggest that it should be tailored according to individual patients. Generally, HIBIG monotherapy is not recommended. Short-term HIBIG in combination with antiviral agents followed by monotherapy with newer and potent antiviral agents is recommended in low—risk patient groups. On the other hand, long-term HIBIG with nucleotide/nucleoside analogs is effective in the prevention of post-transplant HBV relapses.

Key words: Hepatitis B virus; Liver Transplantation; Hepatitis B immunoglobulin

Introduction

Liver transplantation for Hepatitis B virus (HBV)-related to end-stage liver disease is a rapidly developing topic. Prevention of relapse of Hepatitis B virus following liver transplantation is critical. Before the development of effective antiviral treatment HBV recurrence rates were 100% and the 2-years survival rates were nearly 50%. Together with the current antiviral therapies combined with Hepatitis B Immunoglobulin (HIBIG), the survival rates rose above 75% and the relapse rates dropped below 10%. For these reasons, the combination of HIBIG with nucleoside (lamivudine, entecavir, and telbivudine) and nucleotide (tenofovir and adefovir) analogs is the standard treatment protocols for prevention of HBV relapse in the post-transplant period. These protocols can prevent the relapse of HBV in more than 90% of the recipients in the post-transplant period. Entecavir, Tenofovir disoproxil, and tenofovir alafenamide are antiviral agents with a high potency. These antiviral therapies should be continued indefinitely in the post-transplant period regardless of the Hepatitis B envelope antigen (HBeAg) and HBV DNA status of the patient.

HBV recurrence in the post-transplant period can be defined as relapse of HBsAg positivity and/or HBV-DNA positivity or the presence of specific histopathological changes. The risk factors for HBV recurrence are summarized in Table 1.

There are many protocols combining HIBIG and antiviral treatments. However, the data in the literature regarding the use of a combination of HIBIG and antivirals are still controversial. For example, many protocols include HIBIG in the treatment. Some of them use high or low-dose HIBIG, some use HIBIG for a limited period and some use HIBIG as monotherapy. However, with the development of high-potency antiviral agents, protocols combining HIBIG and antivirals are preferred.

The current Regulations for Health Care Applications state that the reimbursement of HIBIG therapy is indicated under the following conditions; i) during the unhepatic phase of the liver transplantation, 10.000

Table 1. Summary of the risk factors for HBV recurrence in the post-transplant period.

The Risk Factors for HBV Recurrence
The presence of high concentrations of HBV DNA in the pretransplant period
HBeAg positivity
History of resistance to antiviral treatments
Presence of HCC at the time of liver transplantation
HCC recurrence
History of chemotherapy for HCC
Treatment non-compliance of the patient
Presence of coinfection with either HDV or HIV

HDV: Hepatitis D; HIV: Human immunodeficiency virus; HCC: Hepatocellular carcinoma; HBeAg: Hepatitis B envelope antigen; DNA: Deoxyribonucleic acid.

IU HIBIG in high-risk patients and 5000 IU HIBIG in low-risk patients are reimbursed, ii) following the liver transplantation, 2000 IU/day of HIBIG for postoperative first 7 days are reimbursed. At the end of the period, if the HBSag is negative or anti-HBS antibodies are >100 IU/l, maintenance therapy 2000 IU HIBIG /month is performed, iii) if HBSAg is still positive or anti-HBs antibody titers are < 100 IU/l, another week of daily 2000 IU HIBIG therapy is indicated and at the end of these 14 days, maintenance therapy of monthly 2000 IU HIBIG is performed, iv) Every prescription of HIBIG (ether therapy or maintenance)should include the up-to-date HBV DNA or HBsAg concentrations, v) if the results of the HBV DNA or HBsAg concentrations are positive, then the HIBIG therapy is discontinued, vi) The HIBIG therapy is continued up to 1 year following liver transplantation in low-risk patients and it is continued for 10 years following transplantation in high-risk patients who have HCC. HIBIG can be continued for 5 years following the transplant procedure in other high-risk patients, vii) patients who are coinfected with delta hepatitis virus (HDV) and human immunodeficiency virus (HIV) are entitled to lifelong HIBIG treatment.

Acute Liver Failure and Liver Transplantation Special Interest Group have prepared detailed recommendations for post-transplant HIBIG treatment and are summarized in Table 2.[1]

The Protocol for HIBIG Maintenance Treatment of Inonu University Liver Transplant Institute

We taper the dose according to the anti-HBs antibody titers. The monthly dose of the HIBIG can be waived if anti-HBs titers are > 100 IU/l. If the anti-HBs titers were between 50-100 IU/l, 500 IU HIBIG is recommended. If antibody titers are below 50 IU/l, 1000IU HIBIG is recommended.

Literature Review on this Issue

We have performed a literature review regarding the protocols of post-transplant HBV therapies to prevent HBV relapse. The data regarding the subject seems controversial in terms of the use and duration of the treatment of HIBIG. Buti et al.[2] reported that the short course of Lamivudine and HIBIG was as effective as a combination of HIBIG and Lamivudine for the first 18 months. Another study showed the beneficial effects of new nucleotide/nucleoside analogs as maintenance once HIBIG therapy was stopped.[3] It has been demonstrated that entecavir monotherapy has been very effective in HBsAg and HBV DNA clearance rate approaching 90-100% with a sustained effect between 8 to 9 years following liver transplantation for chronic HBV infections.[4]

Manini et al.[5] have reported that maintenance therapy with Entecavir and Tenofovir after HIBIG and nucleotide/ nucleoside analog combination therapy for 6 months was very effective in preventing HBV relapse after liver transplantation performed for chronic HBV-related liver disease.

The Spanish Association for the Study of the Liver has stated that HIBIG treatment can be stopped 4 months after liver transplantation in low-risk individuals. If the recipient had a positive HBV DNA before the liver transplant, they recommend continuing the HIBIG treatment for 1 year. In addition, they recommend HIBIG therapy indefinitely in high-risk individuals who have HCC or coinfection with HIV or HDV.[6]

The Turkish Acute Liver Failure and Liver Transplantation Special Interest Group emphasized the necessity for discontinuation of HIBIG therapy to prevent adverse effects and to reduce the costs of the treatment.[1] In low-risk patients, the preferred treatment protocol includes a brief period of low-dose HIBIG and nucleotide/nucleoside analogs followed by monotherapy with potent antiviral therapies. On the other hand, in high-risk patients, discontinuation of HIBIG requires close surveillance of the patients. A study by Sheng et al. has shown the efficacy and safety of nucleotide/nucleoside analog monotherapy in comparison to combination with HIBIG therapy.[7] Combination therapy seems to be a reasonable approach for the prevention of HBV relapse following liver transplantation for HBV. Indefinite use of HIBIG treatment in combined with potent antivirals is more effective in preventing HBV recurrence when compared to a shorter duration of HIBIG therapy. On the other hand, while tapering the HIBIG titers, slow reduction is more effective than rapid reduction of the HIBIG titers in prevention of the HBV relapse.[8,9]

A combination of HIBIG with older antivirals is more effective than monotherapies. Therefore, the presence of HIBIG in combination with antiviral medications has lower HBV recurrence rates.[10] On the other hand, studies evaluating the combination versus monotherapy of HIBIG with newer and more potent nucleotide/nucleoside analogs are needed. On the other hand, the combination of HIBIG with nucleotide and nucleoside analogs is more effective in high-risk groups. The efficacy of combining HIBIG with antiviral therapies has no superior effect on HBV recurrence in low-risk patients.[11]

The European Association for the Study of the Liver (EASL)[12] recommends a combination of HIBIG and potent antiviral agents for the prevention of post-transplant HBV recurrence ((Evidence level II- 1, grade of recommendation 1). On the other hand, they recommend discontinuation of HIBIG in low-risk patients followed by monotherapy with a potent nucleotide/nucleoside analog (Evidence level II-1, grade of recommendation 2).[12]

American Association for the Study of Liver Diseases (AASLD)[13] recommends that all patients with HBV undergoing liver transplantation should receive nucleotide/nucleoside analogs with or without HIBIG regardless of the HBeAg and HBV-DNA concentration of the

Table 2. The summary of the recommendations of the Acute Liver Failure and Liver Transplantation Special Interest Group.

The recommendations of the Acute Liver Failure and Liver Transplantation Special Interest Group
Anhepatic Phase
5000 IU HIBIG in low-risk patients
10000 IU HIBIG in high-risk patients
Post-transplant early period (first two weeks following the procedure)
Daily 2000IU HIBIG for 7 days followed by surveillance of HBsAg and/or HBV DNA
If HBsAg and/or HBV DNA negative, daily HIBIG administration is discontinued and a monthly maintenance dose of 2000 IU is initiated
If HBsAg and/or HBV DNA positive, another 7-day course of daily 2000IU HIBIG is continued which is followed by maintenance therapy regardless of the HBsAg and HBV DNA status
If there is a coinfection with HDV, another 14-day (a total of 28 days) course of 2000IU HIBIG can be given before the initiation of the maintenance therapy
Maintenance Therapy
A monthly dose of 2000 IU HIBIG is given for 1 year in low-risk groups
A monthly dose of 2000IU HIBIG is given for a long period (inconclusive statement) in high-risk patients for
The target anti-HBs antibody titers should be >50 IU/l and the monthly dose could be waived if the anti-HBs antibody titers are > 200 IU/l

HBV: Hepatitis B Virus; HBs Ag: Hepatitis B surface antigen; HBV DNA: HBV deoxyribonucleic acid; HIBIG: Hepatitis B Immunoglobulin; HDV: Delta hepatitis virus.

patients. HIBIG monotherapy is not recommended. Newer and more potent antiviral agents (such as Entecavir, Tenofovir disoproxil, and Tenofovir alafenamide) have a low rate of resistance and therefore they are recommended. In low-risk patients, HIBIG may be discontinued in 5 to 7 days following the transplant procedure or may not be initiated. A combination of HIBIG and antiviral agents is more effective in high-risk patients. Therefore, individualized therapy is recommended according to different patient groups.[13]

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Approach to Patients Whose Hepatitis B Surface Antigen Does Not Become Negative and Have Early Hepatitis B Virus Recurrence After Liver Transplantation

Murat Harputluoglu

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Abstract

There are very few publications on the effects of hepatitis B recurrence on transplanted liver and the management of these patients. The aim of this paper is to summarize the approach to patients whose Hepatitis B surface antigen (HBsAg) does not become negative and experience early hepatitis B virus (HBV) recurrence after liver transplantation (LT). Definition of hepatitis B recurrence is reappearance or persistence of circulating HBsAg with or without detectable HBV DNA. Although there are studies reporting that HBsAg positivity alone under antiviral treatment may not have a negative impact on patient and graft survival during antiviral treatment, some studies suggest the opposite. HBV recurrence after liver transplantation is an important risk factor for hepatocellular carcinoma (HCC) recurrence. Recurrent HBV patients should be evaluated in detail in terms of treatment compliance, and treatment should be changed if necessary. HBIG treatment should be discontinued and lifelong antiviral treatment should be given.

Key words: Liver Transplantation, hepatitis B, hepatitis B recurrence

Introduction

The course of hepatitis B after transplantation and its effects on patient and graft survival are still intensely debated in the transplant community. The aim of this article is to summarize the approach to patients whose Hepatitis B surface antigen (HBsAg) does not become negative and experience early hepatitis B virus (HBV) recurrence after liver transplantation (LT).

Definition of Hepatitis B recurrence

It is commonly based on the reappearance or persistence of circulating HBsAg with or without detectable HBV DNA.[1] It is not clear how long to wait for HBsAg to become negative after transplantation.

Outcomes of Hepatitis B recurrence

It has been reported that clinically significant HBV relapse (increase in aminotransferase levels and acute or chronic hepatitis) is observed only in patients with persistent HBV DNA positivity. Additionally, in cases of HBV DNA negativity in serum, persistence or reappearance of HBsAg positivity is not associated with graft hepatitis.[2] Fung et al. reported that elastography results were not significantly different between patients those with and without HBsAg seroclearance, and with HBsAg re-appearance. Moreover, this result was associated with an overall 85% 9-year survival, without any graft loss or death due to HBV recurrence.[3] Contrary to these studies, there are also studies reporting that post-transplantation HBV recurrence leads to important consequences. For example, Lerut et al reported that 3 of 16 recurrent HBV patients had developed fibrosing cholestatic hepatitis and all patients died within the first 1 year postoperatively.[4]

HBV Recurrence in Special Patient Groups

Hepatocellular Carcinoma

HBV recurrence after liver transplantation is an important risk factor for HCC recurrence. One study reported that the HCC recurrence rate in patients with HBV recurrence was significantly higher compared to patients without HBV recurrence (40% and 5.7%, respectively, $p<0.001$).[5]

Hepatitis D

Patients with hepatitis D are considered to be at low risk of HBV recurrence after liver transplantation.[1] Data on HDV recurrence after liver transplantation and its long-term consequences are very limited.[6] There is currently no treatment available for Hepatitis D recurrence after liver transplantation. A review published in 2022 reported that patients who underwent liver transplantation in Europe due to HBV/HDV cirrhosis had a good prognosis and long-term results despite recurrent infection.[7]

Survival in Patients with HBV Recurrence

In one study, the 5-year overall survival rate and recurrence-free survival rate after liver transplantation in recipients with HBV reactivation were significantly lower than those without (32.0% vs 62.3%; $p<0.01$, and 16.4% vs 63.1%; $p<0.01$, respectively).[8]

Treatment of HBV Recurrence

The British Transplantation Society Guidelines, published in 2018, recommend careful questioning of antiviral drug compliance and lifelong antiviral treatment in all recurrent HBV patients.[9] EASL and The British Transplantation Society Guidelines recommend that treatment with entecavir and tenofovir should be started immediately.[10] When choosing a medication, it is recommended to take into consideration the history of antiviral use in the past and to prefer tenofovir in patients using lamivudine. In patients who use their medication properly, switching to another antiviral or combination therapy and additional resistance testing are recommended.[11] It is recommended that hepatitis B immunglobuline (HBIG) treatment be discontinued in recurrent HBV patients and management be carried out in cooperation with a hepatologist.[12]

In conclusion, HBV recurrence is very important, especially in HCC patients. Recurrent HBV patients should be evaluated in detail in terms of treatment compliance, and treatment should be changed if necessary. HBIG treatment should be discontinued and lifelong antiviral treatment should be given.

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Effectiveness, Patient Contentment, and Safety Profile of Subcutaneous Hepatitis B Immunoglobulin Therapy Following Liver Transplantation

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Abstract

Recurrent hepatitis B virus (HBV) infection after liver transplantation carries substantial complications, such as graft malfunction and rejection. HBV recurrence can be prevented by combining antiviral treatment with Hepatitis B immunoglobulin (HBIG) therapy. Subcutaneous HBIG (SC HBIG) has become a successful substitute for intravenous administration, providing ease and high levels of patient contentment. This study focuses on the effectiveness, safety, and level of satisfaction experienced by patients who underwent (SC HBIG) treatment after liver transplantation.

Keywords: HBV recurrence, liver transplantation, hepatitis B, immunoglobulin therapy

Introduction

The occurrence of hepatitis B virus (HBV) infection again after liver transplantation is a major risk to the health of patients and the survival of the transplanted organ. Although there have been improvements in transplantation medicine, the recurrence of HBV continues to be a difficult problem, sometimes resulting in negative consequences such as malfunction of the transplanted organ, rejection, and death.[1] Therefore, it is crucial to implement efficient preventive measures in order to avoid HBV reinfection after transplantation.[2]

Recent research has yielded persuasive findings concerning the effectiveness of subcutaneous HBIG (SC HBIG) in mitigating the recurrence of HBV following liver transplantation.[3-5] The efficacy of SC HBIG in combination with nucleoside analogues (NA) in preserving protective anti-HBs levels and decreasing the likelihood of HBV reinfection in comparison to HBIG therapy cessation has been established by these studies.[5-7] By combining SC HBIG and NA therapy, HBV recurrence can be effectively prevented prophylactically, leading to improved patient outcomes and graft survival.[7-10]

An essential advantage of SC HBIG is its ease of administration, which contributes to improved patient satisfaction.[11] Unlike intravenous HBIG (IV HBIG), which often requires hospital-based administration, SC HBIG can be self-administered by patients in an outpatient setting.[12] This convenience factor significantly enhances patient compliance and adherence to the prophylactic regimen. Patients report high levels of satisfaction with SC HBIG, citing its user-friendly nature and the ability to incorporate it seamlessly into their post-transplant routine.[13] Moreover, the option for self-administration empowers patients, giving them a sense of control over their treatment regimen.[14]

Beyond its clinical efficacy, SC HBIG may offer cost advantages over IV HBIG, making it an economically viable option for HBV prophylaxis post-transplantation. The transition from IV to SC HBIG has been associated with cost savings, primarily due to reduced dosage requirements and lower administration costs.[15] Additionally, the ability for patients to self-administer SC HBIG reduces the need for healthcare facility resources, further contributing to cost savings over time. As healthcare systems continue to prioritize cost-effective interventions, SC HBIG emerges as a financially prudent choice for HBV prophylaxis in the post-transplant setting.[16]

SC HBIG has an overall favorable safety profile, as the majority of adverse events are modest and controllable. Injection site reactions, including erythema and pain, are frequent adverse effects that are generally temporary in nature and resolve on their own.[17] Although hypersensitivity reactions and other rare adverse events have been documented, the overall incidence is minimal. Therefore, for the overwhelming majority of patients, the benefits of SC HBIG outweigh the associated risks. Adverse event management and vigilant observation guarantee the health and safety of patients undergoing SC HBIG therapy.[18]

Conclusion

To summarize, the subcutaneous injection of HBIG is an effective approach to prevent the return of HBV after liver transplantation. The shown effectiveness, together with benefits such as simplicity of use, cost efficiency, and a positive safety record, make SC HBIG the recommended option for doctors who are responsible for monitoring post-transplant HBV prophylaxis. By integrating SC HBIG into transplant procedures, healthcare practitioners can maximize patient outcomes and improve the long-term effectiveness of liver transplantation.

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HBV Prophylaxis After Liver Transplantation in HCC

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Abstract

Hepatitis B Virus (HBV) infection remains a major cause of chronic liver disease. Hepatitis B virus infection has a wide spectrum of clinical manifestations including: acute HBV infection, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). After the advent of HBIG monotherapy, the risk of HBV recurrence after LT was reduced and survival rates improved. After LT, Entekavir and tenofovir disoproxil fumarate (TDF) have been shown to be effective in preventing HBV relapse with HBIG combined with potent NA (nucleotide analogs). Recurrence after LT is defined as HBsAg positivity and/or detectable HBV DNA levels. HBIG and potent antivirals (ETV, TDF and TAF) are recommended to prevent HBV recurrence after liver transplantation. Serum HBV DNA, HBeAg positivity, presence of HCC, HDV and HIV co-infections before liver transplantation increase the risk of HBV recurrence after transplantation. To prevent HBV recurrence in patients with HCC, HDV and HIV co-infections, the combination of HBIG and antiviral therapy should be given for a long time, perhaps lifelong.

Introduction

Hepatitis B Virus (HBV) infection remains a major cause of chronic liver disease. Despite the successful HBV vaccination program in Turkey and efforts to reduce HBV transmission and prevention in the adult population, the infection remains a major public health problem. According to an epidemiologic study, hepatitis B surface antigen (HBsAg) positivity in the adult population in Turkey is around 4% and hepatitis B core antibody (anti-HBc) positivity is 31%.[1]

Clinical Course

Hepatitis B virus infection has a wide spectrum of clinical manifestations including: acute HBV infection, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). HBV infection is present in 50% of patients with HCC and most of them are also cirrhotic. HBV is also the cause of 40-50% of end-stage liver diseases leading to liver transplantation, with or without HCC.[2]

HBV Prophylaxis

Before the introduction of hepatitis B immunoglobulin (HBIG), patients with HBV-associated cirrhosis were not suitable candidates for LT due to high post-transplant HBV recurrence rates, resulting in low patient and graft survival rates.[3] After the advent of HBIG monotherapy, the risk of HBV recurrence after LT was reduced and survival rates improved. After LT, Entekavir and tenofovir disoproxil fumarate (TDF) have been shown to be effective in preventing HBV relapse with HBIG combined with potent NA (nucleotide analogs).[4]

Mechanism of Action of HBIG

The mechanism of action of HBIG is not known clearly, probably Hepatitis B immunoglobulin neutralizes HBV. HBIG has been shown to neutralize circulating virions, facilitate lysis of infected hepatocytes through antibody-dependent cellular cytotoxicity and block HBV receptors on hepatocytes. The half-life of HBIG is approximately 22 days.[5]

The disadvantages of HBIG are the need for lifelong treatment and the possibility of mutation in the "a" determinant region of the HBV surface gene,futhermore causing resistance disadvantage to treatment its high cost and parenteral administration are also.[6]

Recurrence After LT

Recurrence after LT is defined as HBsAg positivity and/or detectable HBV DNA levels. It has been reported that the presence of HCC before liver transplantation is associated with HBV recurrence after transplantation. In a study conducted in our country, it was reported that after 46 months of follow-up of 296 patients who underwent liver transplantation due to HBV, 8 of the patients developed HBV recurrence and 7 of these patients had HCC before transplantation. The investigators reported that the presence of HCC before liver transplantation increased post-transplant HBV recurrence risk by 12 folds.[7]

Of the 1005 HBV-related LT patients in our clinic, 163 patients underwent LT due to HBV+HCC and 31 patients underwent LT due to HBV+HDV+HCC. While 16 of these patients developed HCC recurrence with HBV, 13 developed HCC recurrence without HBV. Here, in the HDV-positive group, HCC recurrence was observed in all 7 HBV-positive patients who were excluded from the Milan criteria. Here we see how important HDV is in HCC recurrence. Considering that HBV

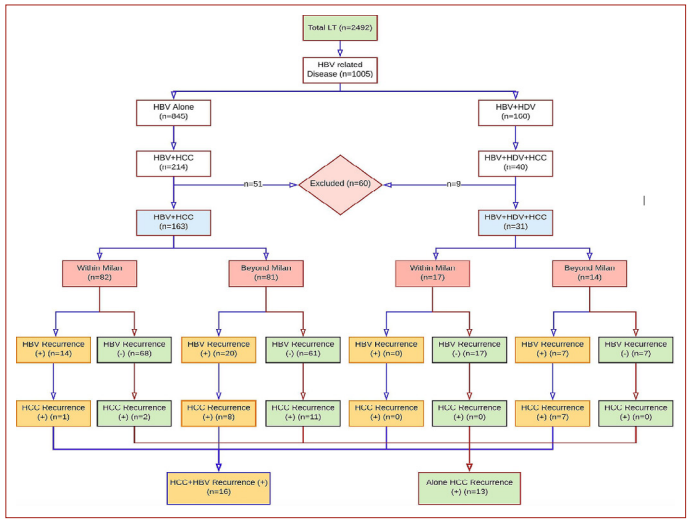

Figure 1. The processes of LT patients with HBV alone and HBV-HDV coinfection until HCC recurrence.

is needed for HDV to become positive, it will be understood how important HBV prophylaxis is in HCC recurrence (Fig. 1).[8]

In order to prevent HBV reccurence following LT, in 5000 IU HBIG should be administered intravenously to low-risk patients and 10 000 IU to high-risk patients. In anhepatic phase during the first 7 days after LT, HBIG administration continue continued at a maximum daily dose of 2000 IU until HBsAg seroconversion. Is achieved if seroconversion is not achieved in postoperative 7 days, 2000 IU per day HBIG is continued for an additional 7 days (Table1).[9]

Our prophylaxis protocol for the prevention of postoperative HBV recurrence after LT is as follows:

Cirrhotic patients with HBsAg (+) and HBVDNA (-) received 5000 IU HBIG and 2000 IU/day HBIG immediately after graft implantation. It was administered for 7 days postoperatively. The goal is to maintain anti-HBs titers above 50 IU/dL.

HBsAg (+) and HBVDNA (+) cirrhotic patients received 10,000 IU HBIG immediately after graft implantation and 2000 IU/day IV HBIG for 7 days postoperatively. The goal to maintain anti-HBs titers above 100 IU/dL.

Cirrhotic patients with HbsAg (+) and HBV-DNA (+) with HDV-free HCC receive 10,000 IU HBIG immediately after liver graft implantation and 10,000 IU/day IV HBIG for postoperative 7 days. The goal of target therapy is to maintain anti-HBs titers above 500 IU/dl.

Some centers suggest that anti-HBs titer should be > 500 IU/L first 3 months after transplantation, > 250 IU/L between 6 to 12 months, and > 100 IU/L thereafter.[10]

Table 1. High and low risk groups for HBV recurrence

High risk groups for HBV recurrence	Low risk groups for HBV recurrence
HBV DNA positivity before transplantation	HBV DNA negativity before transplantation*
HBeAg positivity before transplantation	HBeAg negativity before transplantation*
Presence of HCC before transplantation	No HSK before transplantation
Low adherence to antiviral therapy	High compliance with antiviral treatment
Antiviral drug resistance	No antiviral drug resistance
Concomitant HDV or HIV infection	No accompanying HDV or HIV infection

Maintenance HBIG should be administered at a monthly dose of 2000 IU and anti-HBs titers should be kept above 50 IU/L. If the anti-HBs titer is above 200 IU/dl, the HBIG dose should be skipped. HBIG is administered in 3 ways; IV, IM and SK.Different modes of administration has no difference in terms of efficiency.[11]

In the consensus report prepared by the Spanish Association for Liver Research, it was recommended that HBIG administration could be terminated at four weeks in patients who do not have risk factors for HBV recurrence, HBIG administration is recommended for up to 1 year in patients with positive HBV DNA levels before transplantation, and HBIG administration should be used continuously in the presence of HCC, HDV and HIV.[12]

Lifelong HBIG administration is recommended in high-risk patients or patients who do not comply to postoperative follow up. In low-risk patients, it is recommended to continue potent NA monotherapy following short-term HBIG administration after transplantation. Some centers recommend administration of from Turkey, HBV vaccines for anti-HBs formation after discontinuation of HBIG.[13]

In a retrospective study 128 patients with delta hepatitis received HBIG and antiviral therapy after transplantation, and no HDV recurrence was observed in any of the patients in a mean follow-up of 30 months.[14]

In another study, 104 patients with delta hepatitis received prophylaxis with HBIG and antiviral combination therapy in the post-transplant period, and HDV recurrence was observed in 13% of the patients at a mean follow-up of 82 months.[15]

Lifelong HBIG administration with antiviral therapy is recommended to prevent HBV recurrence in patients who underwent liver transplantation for delta hepatitis.

Conclusion

HBIG and potent antivirals (ETV, TDF and TAF) are recommended to prevent HBV recurrence after liver transplantation. HBIG treatment can be administered by IV, SC, IM route. The method of administration should be decided on a patient basis. Serum HBV DNA, HBeAg positivity, presence of HCC, HDV and HIV co-infections before liver transplantation increase the risk of HBV recurrence after transplantation. To prevent HBV recurrence in patients with HCC, HDV and HIV co-infections, the combination of HBIG and antiviral therapy should be given for a long time, perhaps lifelong. To prevent HBV recurrence in low-risk patients, short-term HBIG administration and continuous potent antiviral therapy is recommended. In the anhepatic phase, 10 000 IU of HBIG is recommended IV for high-risk patients and 5 000 IU for low-risk patients. In maintenance therapy, HBIG treatment should be individualized according to anti-HBs titer and anti-HBs titer should be kept above 50 IU/L.

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