Original article

Prevention of Hepatitis B Recurrence in Liver Transplant Patients Using Oral Antiviral Therapy with Long-Term Low and High Dose Hepatitis B Immunoglobulin

(Karaciğer nakli yapılan hastalarda Hepatit B nüksünü engellemek amacıyla kullanılan oral antiviral tedaviye eklenen Hepatit B immunoglobulin tedavisinin düşük doz uzun dönem ile yüksek dozunun karşılaştırılması)

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ÖZET

Hepatit B virus (HBV) ilişkili orthotropik karaciğer transplant (OLT) alıcıları, post-operatif HBV enfeksiyonu için yüksek riske sahiptir. Hepatit B immunglobulin (HBIG) ve nucleos(t)ide kombinasyon profilaksi tedavisi, OLT sonrası HBV enfeksiyonuna karşı güncel olarak önerilmektedir. Buna karşın optimal protokol konusu tartışmalıdır. Bu çalışmada amaç; organ nakli merkezinde OLT sonrası uzun dönem nucleos(t)ide analoğu ve düşük ve yüksek doz HBIG tedavi profilaksi alan hastalarda HBV enfeksiyonu sonuçlarının araştırılmasıdır.

Materyal ve Metot: Akdeniz Üniversitesi Organ Nakli Merkezinde 2010-2012 yılları arasında OLT olan 42 HBV hastası incelenmiştir. Anhepatik fazda 24 hasta düşük doz (2 000 IU IV) HBIG ve 18 hastada yüksek doz (10 000 IU IV) HBIG almıştır. Uzun dönemde hastalar 2 gruba bölünmüştür. Birinci gruba Hepatit B yüzey antikor titresi 100 IU/dl den fazla olan, ikinci gruba 100 IU/dl'den düşük olan hastalar alındı.

Bulgular: 24 hasta düşük doz HBIG ve 18 hasta yüksek doz HBIG proflaksisiyle uzun dönem tedavi edilmiştir. 4 hasta ise HBIG proflaksisine devam edememiştir. 4 hastanın üçünde HBV enfeksiyonu ortaya çıkmıştır. Hastalar ortalama 33 ay (2-110 ay) takip edilmiş, 4 hastada HBV enfeksiyonu tekrar etmiştir. Yüksek doz HBIG ve oral antiviral ajan alan hastaların OTL sonrası HBV tekrarlama frekansı daha düşüktür.

Sonuçlar: Nükleosi(t)de analog tedavisi post-LT HBV enfeksiyon tekrarlarının önlenmesinde etkili ve güvenlidir. Bununla birlikte HBV proflaksisinde yüksek doz HBIG ve nüklesi(t)de anti-viral ajanların kombinasyon tedavisi OLT sonrası HBV enfeksiyon tekrarlama riskini belirgin düşürmektedir.

Anahtar Kelimeler: Hepatit B; Karaciğer transplantasyonu; Hepatit B immunglobulin

ABSTRACT

Background: Hepatitis B virus (HBV) related orthotropic liver transplant (OLT) recipients have a high risk of HBV reinfection in the absence of continuous post-operative HBV prophylaxis. The combination of hepatitis B immune globulin (HBIG) and nucleos(t)ide agents is currently recommended as prophylaxis against the recurrence of HBV after OLT. However optimal protocol is a matter of controversy. The aim of this study was to investigate the efficacy of nucleos(t)ide analogue with long-term low and high dose HBIG therapy after OLT at a single organ transplant center.

Material and Methods: Forty-two HBV patients undergoing OLT at a transplant center of Akdeniz University between 2000 and 2012 were evaluated. 24 patients received low-dose (2 000 IU) IV HBIG, 18 Patients received high dose (10 000 IU) IV HBIG in anhepatic phase. In long-term period patients were divided into two groups. First group of patients had hepatitis B surface antibody titers more than 100 IU/dl HBIG and second group of patients had less than 100 IU/dl HBIG titers.

Results: Twenty-four patients were treated with low dose HBIG, on the other hand 18 patients were treated with high dose HBIG prophylaxis in the follow-up period. Four patients could not continue the HBIG prophylaxis. In three of four patients, HBV appeared. At a median time of 33 months (range 2-110 months) post-LT, 4 of the 38 patients had recurrent HBV infection. Patients receiving high dose HBIG and an oral antiviral agent have a lower frequency of HBV recurrence after OLT.

Conclusions: Nucleosi(t)de analogue therapy was effective and safe to prevent post-LT HBV recurrence. However, combination of long-term high dosage of HBIG and nucleos(t)ide antiviral agents for HBV prophylaxis significantly reduces the risk of HBV recurrence after OLT.

Key Words: Hepatitis B; Liver transplantation; Hepatitis B immune globulin

INTRODUCTION

Despite dramatic improvements in the treatment of patients with hepatitis B virus (HBV) infection it still accounts as a leading cause of recurrence for liver transplants in many countries. HBV transplant patients have a high risk of recurrence leading to graft failure, increased patient mortality, and the need for re-transplantation.

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Arrival date : 17.10.2012
Acceptance date : 07.02.2013

Prevention of HBV recurrence in patients undergoing liver transplantation will remain important challenge worldwide. In the last 15-20 years, very effective prophylactic and therapeutic methods have been developed in regards of prevention of HBV re-infection of transplant organ[1]. When used as single agents, HBIG and lamivudine (LAM) both reduced recurrence rate in approximately 50% of patients[2,3]. However, when used in a combination therapy, they have a synergistic effect of reducing the recurrence rates to less than 5% at 5 years[4]. A combination of HBIG and a nucleos(t)ide antiviral has become the standard of care to prevent disease recurrence after liver transplantation and improving patient survival, but optimal protocol is a matter of controversy[5-10]. Duration, dose and ideal serum HBsAb level of this combination treatment is still controversial.

Many studies have shown that HBIG in combination with antiviral therapy has been effective in decreasing hepatitis B recurrence[11].

Since 1993 the use of high-doses of intravenous HBIG in long term, has become a routine procedure after LT due to HBV related liver diseases. The mechanism whereby HBIG protects the transplanted liver against HBV re-infection is not well understood. Initial HBIG protocols consisted of high dose regimens utilizing 10,000 IU of IV HBIG in the anhepatic phase of transplantation and daily for a week. HBIG may protect naive hepatocytes by neutralizing HBV by forming immune complexes with circulating viruses, and by blocking HBV receptors on hepatocytes[2,12]. Strategies developed to reduce cost of the treatment have included reducing the amount of HBIG administration[13].

In this study, long-term results of low and high dose intramuscular HBIG and antiviral combination treatment for recurrence prophylaxis in patients with liver transplants with HBV, in an organ transplant center are evaluated.

MATERIAL AND METHODS

We reviewed the medical records of all patients with HBV who underwent liver transplantation between 2000 and 2012 at Akdeniz University. Forty-two HBsAg positive liver transplant patients were divided into two groups. First group of patients had hepatitis B surface antibody titers more than 100 IU/dl HBIG and second group of patients had less than titers 100 IU/dl HBIG. In two groups, patients were treated with oral antiviral agents after transplantation. Each patient was treated with HBIG in anhepatic phase, at first week and upon long time follow-up was calculated. High dose HBIG (10 000 IU) and low dose (2 000 IU) were used in anhepatic phase. 6 000 IU dose during first week of post-LT and in continuation with keeping HBsAb level above the 100 IU/dl and below the 100 IU/dl in intramuscular form, and at an average 1000 IU/ month dose for almost 12 years. Serum HBV DNA levels and loss of HBsAg were checked quarterly. HBV recurrence is described as hepatitis occurring with viral HBV at DNA level of 10^4 copies/ml and HBs Ag positive. In our center, each patient had a monthly follow-up to keep serum HBsAb level at 100 IU/dl in first year. Post-transplant patients were followed up weekly and if they have no problems they were followed monthly in the first year and quarterly after that. In this study, besides the evaluation of recurrence in treatment groups who received low and high HBIG, effectiveness of new potent antivirals is assessed in HBV recurrent patients. Hematological, biochemical and serologic markers for viral hepatitis were done regularly. Patients who died perioperatively from non-HBV related causes were excluded from the analysis. Patients used calcineurine inhibitors (tacrolimus or cyclosporin) and sirolimus as a standard immune suppressive therapy and their serum levels were controlled regularly. Steroid therapy was initiated for six months of the post-transplant period. Mutations of HBV were not done routinely. At the clinical follow-up stage, liver biopsies were performed in order to evaluate rejection if there are high levels of liver function tests.

The study data were analyzed in SPSS 18.0 software. Numeric variables were expressed as mean±standart deviation and median (minimum-maximum), categorical data as rates. Two group comparisons for categorical data were performed by Fischer Exact test. All the hypotheses were constructed as two tailed and an alpha critical value of 0.05 was considered as significant.

RESULTS

Twenty-four males and 8 females underwent liver transplantation. The etiology of 32 cases was cirrhosis and 10 cases was hepatocellular carcinoma. Demographic characteristics of patients are shown in Table 1.

HBsAg was positive pre-LT in all patients. As it is shown, 95 % of patients were HBeAg negative prior to LT. Patients were followed for a median of 33 months (range 2-110 months). There were 4 deaths unrelated to HBV recurrence which 2 cases were due to HCC recurrence, 1 case was due to lymphoma and 1 case was due to pneumonia.

Summary of the therapy groups are shown in Table 2. The patients received 10.000 IU IV HBIG therapy in anhepatic phase. HBV recurrence for both groups was evaluated. Mean application of HBIG and serum HBsAb levels and the results obtained after starting on antiviral therapy were evaluated. The average HBIG dose was 6.000 IU during first week of the post-transplant phase in all patients. Treatment groups had been followed-up for 35 months (range 2-110). Before LT, 14 patients received lamivudine, 2 patients adefovir, 4 patients entecavir and only a patient tenofovir.

Patients were categorized according to two different treatment groups in anhepatic phase and post-transplant period. First group consisted of 19 patients who received high HBIG dosage (≥10.000 IU) in anhepatic phase and second group consisted of 23 patients who received low HBIG dosage (2.000 IU) IV in anhepatic phase. In long-term period there were two different treatment groups; first group (18 patients) had mean HBsAb titers equal or more than 100 IU/dl and second group (24 patients) had mean HBsAb titers less than 100 IU/dl. The groups consisted of patients who received long term HBIG and oral antiviral agents. After LT, 36 patients received a combination of LAM and HBIG therapy, 1 received adefovir therapy, 4 received entecavir therapy and only 1 received tenofovir therapy. Patients had a monthly follow-up program to keep serum HBsAb levels at 100 IU/dl in the first year. Most of the patients who received HBIG had mean HBsAb value less than 100 IU/dl.

Table 1. Demographic Features of Patients

	Mean±SD
Age	51.3±10.4
Gender (M/F)	34/8 (81/19)
Total HBIG dosage in first post-operative week	6000±0
Follow-up duration (months)	35±26
HBV AB level (IU/dl)	120.8±112
The time of HBV recurrence (month)	16.9±12
Child	**n (%)**
A	6 (14.3)
B	22 (52.4)
C	14 (33.3)
Liver transplantation	
Cadaveric donor	35 (83.3)
Living donor	7 (16.7)
Post-LT HBIG prophylaxis	38 (90.5)
HBV recurrence	8 (19)
Deaths	4 (9.5)
Causes of death	
HCC recurrence	2 (4.7)
Lymphoma	1 (2.3)
Pneumonia	1 (2.3)

Abbreviations: M/F: male and female,
Ig: immunglobuline; HBV AB: Hepatitis B virus antibody;
LT: liver transplantation, HCC: hepatocellular carcinoma

Table 2. Treatment Characteristics

HBIG dosage in anhepatic phase	n (%)
High dose (10 000 IU IV)	19 (45)
Low dose (2000 IU IV)	23 (55)
re-LT antiviral therapy	21 (50)
LAM	14 (33.3)
Adefovir	2 (4.8)
Entecavir	4 (9.5)
Tenofovir	1 (2.4)
Post-LT antiviral therapy	
LAM	36 (85.7)
Adefovir	1 (2.4)
Entecavir	4 (9.5)
Tenofovir	1 (2.4)
Post-LT antiviral therapy of recurrent patients	
Tenofovir	5 (29)
Entecavir	2 (29)
Post-LT HBIG t, n.(%)	
HBIG first week of treatment, daily, mean	42 (100)
HBIG, outpatient, monthly, no continuous	38 (90)
prophylaxis doses, mean	4 (10)
Post-LT HBsAb (mean)	
≥100 IU/dl	18 (43)
<100 IU/dl	24 (57)
Immunosuppression n (%)	
TAC	34 (81)
CsA	4 (9.5)
Sirolimus	4 (9.5)

Abbreviations: Ig: Immunglobuline;
HBsAb: Hepatitis B surface antibody,
LAM: Lamivudinee, LT: liver transplantation,
TAC: Tacrolimus; CsA: Cyclosporine

Table 3. HBV Recurrence

Variable	**HBV recurrense**	**P Value**
Anhepatic Phase HBIG dosage		1
High	4 (17.4)	
Low	3 (21.1)	
Postoperative Antiviral Treatment		*
LAM	7 (19)	
Adefovir	0 (0)	
Entecavir	1 (25)	
Tenofovir	0 (0)	
Post-LT HBIG prophylaxis, n (%)	8 (13.2)	0.018
HBsAb (mean)		
≥100 IU/dl	0 (2)	0.014
<100 IU/dl	7 ( )	

Abbreviations: Ig: Immunglobuline;
LAM: Lamivudine; HBsAb: Hepatitis B surface antibody
*Inappropriate data for statistical analysis

During the follow-up stage, HBV recurrence, HBsAg positivity, two folds increase of transaminase, and an average increase of 10^4 copies/ml of serum HBV DNA level (Table 3) were realized. Patients who had mean HBsAb titers equal or more than 100 IU/dl had a lower frequency of HBV recurrence (p= 0.014). There was no significant difference regarding with high and low HBIG dosage in anhepatic phase (p=1). In both

treatment groups LAM was the most commonly used antiviral agent. Seven of 37 patients receiving LAM treatment had 19% HBV recurrence. No fatal events occurred due to HBV in both groups. All experienced recurrences, 7 patients were started a potent antiviral agent; 5 tenofovir and 2 patients entecavir. Seven patients receiving LAM therapy were observed to experience HBV recurrence for an average of 16.9±12 months. No HBV recurrence was observed among the patients who received potent antiviral therapy.

The patients were monitored for 35±26 months and they received combination therapy, continued with the HBIG treatment. No side effects either with HBIG therapy nor with antiviral therapy were observed.

DISCUSSION

Although the exact mechanism for prevention of HBV recurrence after HBIG liver transplant is not completely completly, consensus about the use of combination with oral antiviral agents has been achieved. In the literature, studies that showed 75-85% prevention rate of HBV recurrence were performed with small number of patients.

The main goal is the suppression of HBV replication in patients with HBV-related liver disease. An important step has been the introduce of nucleos(t)ide analogues in the treatment of HBV infections. Especially, starting oral antiviral therapy prior to transplantation has a significant value to prevent recurrence in patients with HBV DNA positivity. It was mentioned that there is a consensus regarding HBIG and lamivudine combination to reduce HBV recurrence and less than 10% recurrence occurred after 3 years of combination[14,15].

HBIG prevents recurrence by reducing the development of mutation and providing fast clearance of HBV in circulation after liver transplantation. However there are lots of factors limiting the use of HBIG such as; marked cost, uncertainty about standard dose and duration, patients' noncompliance to the therapy, parenteral usage, permanent recurrence risk and development of escape mutations[4,16-18]. Headache, myalgia, flushing, pain and mercury toxicity has been issued as the side effects. Due to these limitations, there are lots of studies which showed the necessity of limitation of duration for HBIG therapy and intramuscular application of HBIG and regulating HBIG dosage according to serum HBs AB level[16-18].

The protocol used in the current study is the application of low and high HBIG dosage intravenously in the anhepatic phase and post-transplant first week, then following with continuous intramuscular treatment to keep HBs AB level equal or more than 100 IU/ml in first treatment group. The second group of patients had a mean HBs AB level less than 100 IU/ dl. Patients were monitored for a long time. Most of the patients were receiving LAM and HBIG combination. 19% HBV recurrence was observed in a group of patients who had mean HBsAb titers less than 100 IU/dl. But HBV recurrence was not observed in patients who had a mean HBsAb titer equal or more than 100 IU/dl. High dose of HBIG and lamivudine combination decreases HBV recurrence in post-LT patients after LT. However, patients receiving long-term low dose HBIG and LAM combination had high recurrence rates of HBV infection. Particularly it has been stated that high dose HBIG was the factor affecting recurrence, in the first week of post-transplantation period.

Potent antiviral agents were prescribed to patients with recurrence. No difference was observed between the groups receiving high and low dose HBIG treatment regarding recurrence in anhepatic phase. For the cost standpoint, nucleos(t)ide analogs, especially lamivudine became an alternative to HBIG treatment[10,19,20].

But the mono-therapy results of the antiviral agents are indicated to be observed with the long term use of lamivudine and high recurrence ratios related to YMDD mutations in literature, as high as 10 to 45%[21,22]. Patients receiving lamivudine treatment that had low mean HBsAb titers presented with a high frequency of HBV recurrence rate of 19%. Low dose of HBIG with lamivudine combination treatment had high rate of recurrence rate.

It was published that there was no recurrence in patients who received high dose HBIG and lamivudine treatment on 13,2 months[4]. There are very limited number of cases which were issued in literature that HBIG therapy was discontinued[16,23-26]. Improper relations with HBV recurrence have been stated.

Since potent antiviral agents are available, mono-therapy might come to agenda. But there is no issued protocol for ideal duration and dosage in literature yet. There are only some studies with few cases related to mono-therapy or in combination with HBIG therapy and no described optimal protocol exists. We think that there is a need for extensive studies with longer follow-up periods. Generally, results regarding combination of LAM and HBIG therapies are gathered in meta-analysis. Superiority of high dose HBIG and LAM combination therapy over mono-therapy is indicated. HBV recurrent patients received tenofovir

or entecavir and HBIG combination. Particularly it has been stated that high dose HBIG was the factor affecting recurrence, in the first week of post-transplantation.

Especially, there is not enough data related to tenofovir without resistance. In our study, 5 HBV recurrent patients received low dose of HBIG and tenofovir which was efficacious. There was very little information regarding new antiviral agents and low dose HBIG combination therapy results in the literature. The most important finding is the absence of recurrence with combination of low dose HBIG with tenofovir or entecavir[27]. In our opinion, results carry a significant importance due to the fact that patients had a lengthy follow up. Not observing any recurrence with combination of low dose HBIG with entecavir or tenofovir in our study indicates the usability of potent antiviral treatment in HBV prophylaxis after liver transplantation. Particularly, there is a need for further studies related with tenofovir mono-therapy which does not show any resistance yet. No recurrence was observed with entecavir and HBIG combination therapy in literature. Tenofovir is an acyclic adenine nucleotide and is much more potent than lamivudine. Furthermore, no resistance to tenofovir was observed. For these reasons, usage of tenofovir alone and/or in combination with short term use of low dose HBIG in liver transplant patients might be more efficient and cost effective which needs more extensive studies. Since HBV infections are the most common etiology of liver transplantation in our country, treatment and prevention of its recurrence has a great significance. Besides the fact that the use of long-term, low-dose HBIG and antiviral agents is the accepted treatment for prevention of recurrence of HBV infections, it should be considered that mono-therapy with strong potent antiviral agents or limited-term, low-dose HBIG combination can be an efficient and cost-effective treatment option for HBV prophylaxis.

Conflict of interest statement : None declared.

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