

# Hepatitis B immune globulin and HBV-related liver transplantation

## Hepatitis B immunoglobulin ve HBV nedeni ile karaciğer transplantasyonu

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### ABSTRACT

The risk of recurrence of liver cirrhosis and hepatocellular carcinoma due to hepatitis B virus (HBV) infection was 90% following liver transplantation before 1990's but now we rarely see recurrence due to the highly effective prophylactic treatments. In this review, we discussed the achievements of the prophylactic treatments in patients transplanted for HBV diseases. Options for hyperimmune globulin usage and high genetic barrier anti-viral drugs can be used to prevent the recurrence.

**Keywords:** Liver transplant, Hepatitis B hyperimmune globulin, Recurrence

### ÖZ

Hepatitis B nedeni ile oluşan karaciğer sirozu veya hepatosellüler karsinoma hastalarında karaciğer transplantasyonu sonrası nöks 1990'lı yıllarda ciddi bir sorun olarak gündemde bulunmaktaydı. Ancak hiperimmün globulin tedavileri ve yüksek direnç bariyerli ilaçlar ile günümüzde nöks sorunu hemen hemen ortadan kalkmıştır. Bu derlemede bu hastalarda kullanılan profilaktik tedavi seçenekleri tartışılmıştır.

**Anahtar kelimeler:** Karaciğer transplantasyonu, Hepatitis B hiperimmün globulin, Nüks

### Introduction

More than 350 million chronic carriers of hepatitis B virus (HBV) are present worldwide, and one million deaths occur each year due to cirrhosis and hepatocellular carcinoma [1]. HBV-related end-stage liver disease or hepatocellular carcinoma (HCC), currently represent 5–10% of cases of liver transplantation (LT) in the West, and is the most common indication for LT in Asia [2]. The risk of hepatitis B viral recurrence, without prophylaxis, following transplantation was reported to be approximately 90%, until 1990's [3]. Presence of delta coinfection and fulminant hepatitis were the factors decreasing the risk of recurrence. After the introduction of passive immunoprophylaxis using parenteral hepatitis B immune globulin (HBIG), post-transplant recurrence of HBV steeply decreased [4]. However, cessation of HBIG therapy resulted in recurrence and graft failure. Within a short period of time, long term prophylaxis with intravenous HBIG became the standard medication for liver transplant recipients infected with HBV [5].

The introduction of nucleoside/nucleotide analogues such as lamivudine brought in another option for post-transplant HBV prophylaxis and for treatment of recurrent disease, but these drugs alone have been inadequate yet to replace HBIG. By using combination prophylaxis with indefinite HBIG and oral antiviral therapy, recurrence rate of hepatitis B can be reduced to 0-10% [6]. In recent years, new nucleos(t)ide analogues have been approved for the treatment of hepatitis B. Higher efficacy and lower rates of resistance have transformed these new oral medicines such as entecavir and tenofovir into first-line treatments for chronic hepatitis B patients [7]. Post-transplant hepatitis B prophylaxis with HBIG chronologically follows high dose HBIG, low dose HBIG, limited-duration HBIG, to no HBIG using combination of NAs or monotherapy with NA with

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high barrier to resistance, with the latter showing excellent clinical outcome.

### **HBIG alone**

Hepatitis B immune globulin (HBIG) was first introduced in 1974 for passive immunization against infection with hepatitis B virus. HBIG is prepared from plasma donated by individuals with high titers of anti-HBs. Long-term prophylaxis with HBIG is expensive, inconvenient and has been associated with the development of surface antigen mutations [8].

It is accepted that the first dose of HBIG (usually 10 000 IU, ranging 2 000 – 20 000 IU) should be administered at the anhepatic phase during OLT, at a time when major bleeding and oozing has been controlled. In order to prevent reinfection from the extrahepatic reservoirs of virus this protocol is regarded as a must. This initial flooding with anti-HBs, during and immediately after OLT, is followed by daily administration of 400-10,000 units (changes upon protocol) in the first 5 to 10 postoperative days irrespective of actual anti-HBs levels and in some protocols guided by HBs Ag levels (9). Outcome of this regimen is a variable anti-HBs titers among patients, as well as within patient. The high-dose regimens used in US centers have been reported to decrease the rate of recurrent hepatitis B to less than 20% [10].

For patients with high pre-LT serum titres, neither lamivudine nor HBIG as single agents could prevent graft re-infection. The published experience with lamivudine as single agent prophylaxis is not large. The pitfalls were soon exposed, and the majority of units probably shifted quite quickly from either HBIG or lamivudine as single agents to prophylaxis that combined the two products.

### **HBIG plus lamivudine**

Since the mechanisms of action and resistance profiles of HBIG and lamivudine are different, combination prophylaxis could potentially reduce the development of resistant mutations and decrease the rate of treatment failures. In addition, combination prophylaxis also creates the possibility of lowering the doses of HBIG, which would result in significant cost reduction.

Angus et al. reported that thirty-one of 32 patients were HBsAg negative, and all 32 patients were HBV DNA negative by PCR followed-up for a mean of 18 months (range, 5 to 45 months)[11]. In this study, HBIG

was administered as intramuscular (IM) injections in doses of 400 or 800 IU daily for the first week and monthly thereafter. In this regimen amount of HBIG used was less than one tenth in comparison with most US centers. Long-term administration of low doses of HBIG by the IM route rendered immune prophylaxis more widely available and cost-effective.

Gane et al. confirmed the efficacy of very low-dose HBIG plus lamivudine treatment, in which 85% of the patients were HBV DNA positive prior to lamivudine treatment. In the post-transplant period, patients received initially 400-800 IU daily im HBIG for one week then monthly thereafter. The risk of post-transplant HBV recurrence was found to be 1% at one year and 4% at four years [12].

In our country, Turkey, HBV infection is a real public health problem. Almost one-third of the population have antiHBc and almost 4% of the people are HbsAg carriers [13]. Not surprisingly, HBV cirrhosis is the leading cause of liver transplantation. In adult population, almost half of the liver transplant patients have HBV infection. Considering the economical condition of our country, and because of the high cost and difficulties in availability of HBIG, high dose HBIG regimens would not be convenient for us.

Combination of lamivudine with low dose HBIG was very effective in posttransplant HBV prophylaxis, in our earlier study we reported that

the recurrence occurred in about 6 % of patients in a follow-up period of approximately 24 months, in more than 300 adult patients [14]. We obtained similar results with the same protocol in living donor liver transplant recipients, too [15]. Anna Lok has reviewed results of 12 studies of prophylactic combination therapy with HBIG and lamivudine, and reported that post-transplant HBV recurrence was observed in only 7/168 (4%) patients during a mean follow-up of 13-22 months [16].

The combination of HBIG together with lamivudine has formed the cornerstone of antiviral therapy after surgery in many liver transplant centers worldwide for the best part of the past 15 years. Recent evidence have shown the efficacy of newer and more potent antiviral agents such as entecavir and tenofovir to be effective in the prevention of recurrent HBV-related graft hepatitis in CHB patients after liver transplantation [17].

### **HBIG plus entecavir**

So far, a regimen completely without HBIG is not

recommended, but with newer NAs, withdrawal of continuous lifelong administration of HBIG might be feasible. Kim et al retrospectively assessed the clinical outcomes in 154 patients who received entecavir and HBIG after liver transplantation with a median follow-up of 22 months. A total of 5 patients (3.2%) were diagnosed with HBV reinfection without entecavir resistance. In 4 of those 5 patients, recurrence of HCC was detected prior to the recurrence of HBV. Recurrent HCC was found to be an independent risk factor for the recurrence of HBV ( $P = 0.06$ ) [18].

Na et al reported that 4 of 262 recipients who received entecavir combined with HBIG experienced a recurrence of HBV infection after liver transplantation during the median 49-mo follow-up period. They also showed that the incidence of pre-transplant HCC was significantly associated with the recurrence of hepatitis B [19].

Twenty-six patients who received entecavir plus HBIG after liver transplantation were compared with 63 patients who received LAM and HBIG. No HBV recurrence was detected during the median follow-up period of 25.1 mo in the entecavir group, whereas the HBV recurrence rate was 4% at 3 years and 6% at 5 years in the LAM group [20].

### HBIG plus tenofovir

Post-transplant renal dysfunction is commonly seen in liver transplant recipients with long-term utilization of calcineurin inhibitors being a major contributing factor. There may be concern that the use of nucleotides such as adefovir or tenofovir could worsen renal dysfunction. Nephrotoxicity associated with adefovir and tenofovir (both acyclic nucleotide analogs) is related to mitochondrial toxicity in proximal renal tubular cells which manifests as defective proximal phosphate reabsorption and in some instances full-blown Fanconi syndrome.

It was shown that resistance to tenofovir did not emerge in patients in six years of follow-up time after transplant. Studies regarding the efficacy of tenofovir in the prevention of hepatitis B recurrence after liver transplantation are limited.

A small trial reported that four patients received tenofovir plus HBIG with or without entecavir for the prevention of hepatitis B recurrence. After 12 months, no hepatitis B recurrence was observed in these four patients [21].

In a study by Teperman et al, 19 patients were administered emtricitabine/ tenofovir combined with

HBIG post-liver transplantation. No patient experienced a recurrence of HBV infection at 96 wk, and no tenofovir related renal failure was observed in the study [22].

### HBIG for a certain period

Strategies aimed at HBIG discontinuation after a defined period of combination therapy of HBIG and nucleos(t)ide analogues reduce the costs and inconvenience associated with providing HBIG long-term. There is emerging experience examining the efficacy and safety of HBV prophylaxis using a single nucleos(t)ide for CHB patients undergoing OLT.

The use of emtricitabine/tenofovir after HBIG discontinuation was evaluated by Teperman et al. In this randomized trial, subjects at a median of 3.4 years after transplant with no evidence of recurrent HBV and creatinine clearance  $>40$  ml/min were treated with combination emtricitabine/tenofovir and HBIG for 24 weeks and then randomized to continue that regimen ( $N = 19$ ) or discontinue HBIG and continue emtricitabine/ tenofovir alone ( $N = 18$ ). Of all patients, 47% had detectable HBV DNA at the time of transplant. At 72 weeks post-randomization, only one patient in the emtricitabine/tenofovir group developed a transient increase in HBV DNA to 314 copies/ml in the setting of poor adherence, and ultimately returned to undetectable levels on follow-up testing. Although  $>80\%$  of participants had baseline mild to moderate renal insufficiency at the outset, no significant change in renal function occurred during tenofovir/ emtricitabine treatment [23].

Cholongitas et al. reported the efficacy of entecavir or tenofovir as monotherapy in preventing HBV recurrence in CHB patients who underwent OLT previously treated with HBIG. Eleven patients with entecavir and 17 patients with tenofovir received HBIG for 6 months. Subsequently, HBIG was discontinued and patients were followed for a median 21 months. Both HBsAg and HBV DNA remained negative in all patients [24].

By considering that HBV recurrence occurs mostly in the first 3 years (25); after a combination prophylaxis of a 3 years in our center, monoprohylaxis with entecavir or tenofovir is continued by quitting HBIG in patients determined to be HBV DNA negative by PCR in serum and liver tissue. Although there is a limited number of patients (about 30) and the follow-up period is short (approximately 1 year after cessation of HBIG), the recurrence has not developed yet in any of our patients through this approach (unpublished data).

### Regimes without HBIG

The use of two nucleos(t)ides initiated prior to OLT as prophylaxis without the utilizing HBIG at all was reported by Gane et al. to be effective in preventing recurrent HBV after OLT. The study included 18 CHB patients who had been treated with dual nucleos(t)ides prior to liver transplant that were continued after OLT. During a median 57 months of follow-up, none of the patients developed detectable HBsAg or HBV DNA [26].

Fung et al. studied 362 consecutive CHB patients that were transplanted without utilization of HBIG. Patients were treated either with lamivudine, entecavir, or a nucleoside/nucleotide combination. The median follow-up length was 53 months. The virological relapse rates (>1 log increase IU/ml) at 1, 3, 5, and 8 years was 5, 10, 13 and 16%, respectively. The rate of hepatitis B surface antigen seronegativity and hepatitis B virus (HBV) DNA suppression to undetectable levels at 8 years was 88 and 98%, respectively. The virological relapse rate at 3 years for LAM, ETV, and combination group was 17, 0, and 7%, respectively ( $P < 0.001$ ). Forty-two patients had virological relapse, of which 36 had YMDD mutation (31 in the LAM group and 5 in the combination group) [27].

Fung and colleagues have published data on 80 patients undergoing transplant for complications of chronic HBV infection who were maintained on an "HBIG free" regimen consisting of entecavir monotherapy. In this cohort, 33 (41%) were not on antiviral therapy prior to starting entecavir and only 21 (26%) had undetectable HBV DNA at the time of transplant. Using entecavir monotherapy after transplant, the cumulative rate of HBsAg clearance approached 90% at one year. Interestingly, a key determinate of HBsAg loss was the pre-transplant quantitative HBsAg level such that those with lower HBsAg titers (<3log IU/ml) had a significantly higher rate of HBsAg seroconversion at one year (90% vs. 74%,  $p = 0.025$ ). In those with persistent or recurrent HBsAg, the pretransplant median HBsAg titers were also shown to be significantly higher than in those without persistence/recurrence. Interestingly, low pre-transplant HBV DNA levels alone were not significantly associated with HBsAg loss, however, when a low HBV DNA (<5log copies/ml) was paired with a low HBsAg level (<3log IU/ml) the cumulative rate of HBsAg seroconversion at 18 months was 100% [7].

There are ten case series involving 237 patients utilizing dual antiviral therapy. The mean rate HBsAg reappearance was 5.1 % (range 0–14.1 %). Virological recurrence

characterized by detectable HBV DNA was rare, occurring in only one patient who was noncompliant with tenofovir and emtricitabine [28].

A conceivable risk with using a single oral antiviral for prophylaxis is the emergence of viral resistance. Use of drugs with a high genetic barrier to resistance such as entecavir and tenofovir are superior to drugs such as lamivudine and adefovir, as shown in non-transplant patients [29]. The combination of a nucleotide analogue with an nucleoside analogue has been associated with a very low rate of virologic resistance and the specific combination of lamivudine and adefovir has shown efficacy in the post-transplant setting [30]. The combination of a nucleoside and nucleotide analogue may represent the most effective long-term prophylactic strategy. However, in the aforementioned study by Fung and colleagues that examined the role of entecavir monotherapy after transplant, no resistance mutations were identified after a median follow-up of 26 months [7]. The disadvantages of combination antiviral therapy include higher pill burden (and possibly reduced adherence) and higher cost. The latter issue would depend upon the individual costs of the drugs and this varies considerably by country. Tenofovir-emtricitabine is also an alternative effective combination.

After transplantation, life-long prophylaxis to prevent recurrent hepatitis flares is required. Tendency from using high dose HBIG, low dose HBIG, limited-duration HBIG, to no HBIG using combination of NAs or monotherapy with NA with high barrier to resistance has been observed, with the latter showing excellent clinical outcomes. Cessation of HBIG followed by treatment with new nucleos(t)ide analogues, such as entecavir and tenofovir, is a promising alternative strategy for the prevention of hepatitis B recurrence. The timing for cessation of HBIG is still controversial; however, one year post-transplantation seems to be reasonable.

### Key Points

- Life-long prophylaxis to prevent recurrent hepatitis flares is required in patients with HBV related liver transplantation.
- Hyperimmune globulin combination with Nucleosid Analogs can be a good option.
- Monotherapy with NA with high barrier to resistance has been observed with excellent clinical outcomes.
- However, timing for cessation of HBIG is still a controversial point.

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