ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2018; 23: 789-801
DOI: 10.12659/AOT.910176

Received: 2018.03.24
Accepted: 2018.07.17
Published: 2018.11.13

Recurrence of Hepatitis B Infection in Liver Transplant Patients Receiving Long-Term Hepatitis B Immunoglobulin Prophylaxis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Susanne Beckebaum
BE 2 Kerstin Herzer
ADE 3 Artur Bauhofer
BE 4 William Gelson
BE 5 Paolo De Simone
BE 6 Robert de Man
BE 7 Cornelius Engelmann
BE 8 Beat Müllhaupt
BE 9 Julien Vionnet
BE 10 Mauro Salizzoni
BE 11 Riccardo Volpes
BE 12 Giorgio Ercolani
BE 13 Luciano De Carlis
BE 14 Paolo Angeli
BE 14 Patrizia Burra
BE 15 Jean-François Dufour
BE 16 Massimo Rossi
BE 17 Umberto Cillo
BE 18 Ulf Neumann
BE 19 Lutz Fischer
DE 3 Gabriele Niemann
BE 20 Luca Toti
BE 20 Giuseppe Tisone

1 Department of Gastroenterology and Hepatology, University Hospital Münster, Münster, Germany
2 Department of Gastroenterology and Hepatology, University Hospital Essen, Essen, Germany
3 Corporate Medical Affairs and Corporate Clinical Research and Development, Biotest AG, Dreieich, Germany
4 Cambridge Liver Unit, Addenbrooke's Hospital, Cambridge, U.K.
5 Hepatobiliary Surgery and Liver Transplantation, Chirurgia Epatica e del Trapianto Fegato Pisa, Pisa, Italy
6 Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands
7 Department of Gastroenterology and Rheumatology, University of Leipzig, Leipzig, Germany
8 Swiss HPB Center and Gastroenterology and Hepatology, University Hospital Zürich, Zürich, Switzerland
9 Transplantation Centre and Service of Gastroenterology and Hepatology, Lausanne, Switzerland
10 Chirurgia Generale 2U, Centro Trapianto Fegato, AO Città della Salute e della Scienza di Torino, Turin, Italy
11 Hepatology and Gastroenterology Unit, ISMETT-IRCCS, Palermo, Italy
12 Department of General Surgery, Morgagni-Pierantoni General Hospital, University of Bologna, Bologna, Italy
13 Surgery and Abdominal Transplantation Division, Niguarda Ca' Granda Hospital, Milan, Italy
14 Multivisceral Transplant Unit, Padua University Hospital, Padua, Italy
15 University Clinic for Visceral Surgery and Medicine, Inselspital, Bern, Switzerland
16 Department of General Surgery and Organ Transplantation, Umberto I Policlinic, Sapienza University, Rome, Italy
17 Multivisceral Transplant Unit, Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University Hospital of Padua, Padova, Italy
18 Department of Visceral and Transplantation Surgery, University Hospital RWTH Aachen, Aachen, Germany
19 Department of Hepatobiliary and Transplant Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
20 Transplant Centre, Faculty of Medicine, Azienda Ospedaliera Policlinico Tor Vergata, Rome, Italy

This work was presented in part as an oral presentation at the 18th Congress of the European Society for Organ Transplantation (ESOT), Barcelona, Spain, 24–27 September 2017

Corresponding Author: Susanne Beckebaum, e-mail: susanne.beckebaum@googlemail.com

Source of support: The study was funded by Biotest AG, Dreieich, Germany. Editorial support by a freelance medical writer (C. Dunstall) was funded by Biotest AG

Background: Long-term real-world data are relatively sparse regarding recurrence of chronic hepatitis B virus (HBV) infection after liver transplantation using hepatitis B immunoglobulin (HBIg) and nucleos(t)ide analogue (NUC) prophylaxis.

Material/Methods: Data from 371 adults transplanted for HBV-related disease at 20 European centers and given HBIg for ≥12 months ± NUC therapy were analyzed retrospectively.

Results: HBIg comprised Hepatect® (iv HBIgB; n=299), subcutaneous Zutectra® (sc HBIg, n=236), and other HBIg preparations (n=130); 93.5% received NUC therapy. Mean follow-up was 6.8±3.5 years. The primary efficacy variable, freedom from HBV recurrence, occurred in 95.7% of patients (95% CI [93.1%, 97.5%]). The observed incidence of recurrence was 16/371 (4.3%) (annual rate 0.65%); 5/16 patients with recurrence had discontinued HBIg and 7/16 had anti-HBs <100 IU/l. Excluding these 7 patients, the HBV recurrence rate was 2.4%. The recurrence rate while on HBIg therapy was 1 per 2069 months. In patients who discontinued HBIg, risk of HBV recurrence versus sc HBIg users was increased by 5.2-fold (1 per 1 603 versus 1 per 8379 treatment months). The annual rate of HBV-related hepatocellular carcinoma (HCC) recurrence was 1.7%.

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Conclusions: These results support the long-term use of HBIg with NUC therapy as an effective management strategy to minimize risk of HBV recurrence and virus-related complications after liver transplantation.

MeSH Keywords: **Hepatitis B virus • Liver Transplantation • Recurrence**

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/910176

Background

Chronic hepatitis B virus (HBV) infection is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) and is a major cause of mortality worldwide [1]. Although antiviral therapy with nucleos(t)ide analogues (NUCs) can prevent the need for transplantation in as many as 35% of patients with decompensated HBV-related cirrhosis, HBV infection remains a major indication for liver transplantation [2]. Due to the favorable impact of antiviral treatment on decompensated disease, the proportion of wait-listed HBV-positive patients who have HBV-related HCC (HBV-HCC) has increased, while decompensated HBV-disease has become less frequent [3]. Following transplantation, combined prophylactic treatment with hepatitis B immunoglobulin (HBIg) and NUC therapy has profoundly reduced the risk of HBV recurrence [4], substantially improving graft and patient survival rates [2], and is considered the standard of care in this setting [5]. HBIg therapy is usually started intravenously for at least 1 week post-transplant, after which it can be switched to subcutaneous or intramuscular preparations.

Although highly effective, even combined prophylactic therapy cannot entirely prevent recurrence of HBV infection after liver transplantation. A systematic review of 46 studies by Cholongitas and colleagues, involving over 2000 HBV-positive patients treated with HBIg and NUC therapy (lamivudine and/or adefovir), showed recurrence in 6.6% of cases [6]. Patients with HBV-HCC appear to be at higher risk for HCC recurrence than those with non-HBV-HCC [7], and a recurrence rate of 14.8% has been reported even under HBIg and NUC therapy [8]. The available evidence relating to HBV or HBV-HCC recurrence, however, is typically based on single-center cohorts of fewer than 100 patients [6]. Follow-up times are often short (mean 21 months in the 46 studies included in the analysis by Cholongitas et al) [6], but the average time to recurrence has been reported to be up to 44 months for HBV infection [9] and ~26 months for HBV-HCC [8]. Moreover, most estimates are derived from populations in which ongoing prophylaxis with both HBIg and NUC therapy was mandatory for inclusion. This does not necessarily reflect routine practice, in which HBIg is withdrawn in low-risk patients by some centers.

An international, multicenter retrospective analysis was undertaken to evaluate the recurrence of HBV infection and to assess other clinical and serological efficacy endpoints during long-term follow-up in a large cohort of patients who had undergone liver transplantation for HBV-related disease.

Material and Methods

Study design

A retrospective analysis was performed at 20 liver transplant centers in Italy, Germany, Switzerland, the Netherlands, and the United Kingdom. The inclusion period was from January 2000 to May 2016. From a list of eligible patients, 50% of patients with HBV-HCC and 50% without HCC were to be selected randomly for documentation, stratified by year of transplant. Random selection was performed centrally. It was planned to recruit approximately 400 patients, with an average of 20–25 patients per center (approximately 200 from Italy and approximately 200 in total from Germany, Switzerland, the Netherlands and the United Kingdom).

For patients not alive at time of documentation, no demographic characteristics were collected except for the year of birth. Approval from the Institutional Review Board was obtained for all sites and all living patients signed informed consent before data were collected.

Eligibility criteria

Patients were eligible for inclusion if they were aged ≥18 years and had undergone primary transplantation for fulminant hepatitis B, hepatitis B cirrhosis, or HBV-HCC inside the Milan criteria, or liver re-transplantation except due to HBV recurrence, from 2000–2014. All patients were required to have received treatment with HBIg for at least 1 year during the post-transplant period, including a minimum of 6 months' treatment with intravenous Hepatect® CP (iv HBIgB, Biotest AG, Dreieich, Germany) or subcutaneous Zutectra® (sc HBIg, Biotest AG, Dreieich, Germany), with or without concomitant NUC therapy, and to have a minimum of 1 year's data available. Patients could receive more than 1 HBIg therapy.

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Data collection

Data were captured from clinical documentation and patients' hospital records at time of transplant, and after transplantation until the end of the documentation period. Documentation was obtained for a minimum of 1 year and a maximum of 10 years post-transplant. Demographic and clinical data at the point of transplantation were recorded (unless unavailable for deceased patients). Any HBV recurrence during the documentation period was captured, defined as detection of hepatitis B surface antigen (HBsAg), and/or HBV DNA in the serum based on licensed diagnostic test systems for HBV. Additionally, all pre- or post-transplant measurements of antibodies against hepatitis B surface antigen (anti-HBs) or core antigen (anti-HBc), HBsAg, and HBV DNA were recorded. All clinical signs of HBV recurrence (e.g., jaundice) were documented, as well as recurrence of HBV-HCC or development of *de novo* malignancies other than HCC. Liver and kidney function test results were recorded pre-transplant and, if applicable, at the time of HBV recurrence. Individual adverse drug reaction reporting was not performed other than routine spontaneous adverse drug documentation by the treating physician via standard pharmacovigilance procedures.

Study endpoints

The primary efficacy variable was the proportion of patients free from HBV recurrence, as assessed by non-detectability of HBsAg and/or HBV DNA in serum during the documentation period. Secondary efficacy variables were the proportion of patients with HBV recurrence, the time to HBV recurrence, the proportion of patients with HBV-HCC recurrence, and serum levels of anti-HBs, HBsAg, and HBV DNA. Other efficacy variables included viral status, exposure time to different HBIg therapies, use of different antiviral treatments, immunosuppressive treatments, graft rejection (acute and chronic), and occurrence of *de novo* malignancies other than HCC. There were no safety variables.

Statistical analysis

No formal sample size calculation was performed. For the primary endpoint a 2-sided 95% confidence interval (CI) was calculated based on the Clopper-Pearson method. Two-sided 95% CIs were also calculated for the percentages of patients with HBV recurrence, HBV-HCC recurrence, or occurrence of any new non-HCC malignancy during the period of documentation. Times to first HBV recurrence, HBV-HCC recurrence, or onset of any *de novo* malignancy (non-HCC) were estimated by the Kaplan-Meier method. All analyses were performed using SAS® version 9.3.

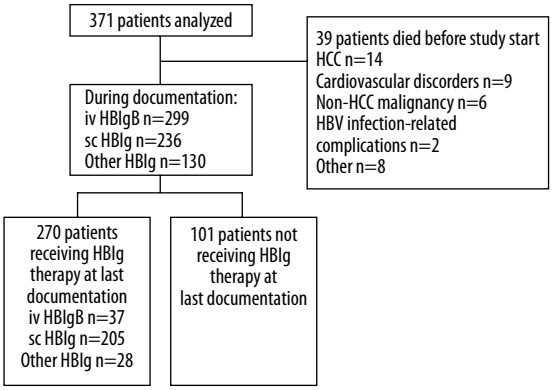

Figure 1. Flow diagram of the 371 patients transplanted for hepatitis B virus (HBV)-related disease who were included in the analysis, of whom 332 (89.5%) were alive at the time of study entry. More than 1 type of hepatitis B immunoglobulin (HBIg) could be given (iv HBIgB, sc HBIg, or other licensed HBIg preparations). By the final documentation, 270/332 patients (81.3%) were receiving HBIg therapy. HCC, hepatocellular carcinoma.

Results

Study population

In total, 371 patients met all eligibility criteria and were included in the analysis (Figure 1). Of the 332 who were alive at the time of study initiation, 257 were male (77.4%) and the mean (±SD) age was 58.5 (±10.7) years (data were not available for deceased patients). Characteristics of the study population overall, and for the subgroup for whom the primary indication for liver transplantation was HBV-HCC (n=147), are shown in Table 1. Five patients with HBV-HCC as the primary indication for transplantation who underwent downstaging pre-transplant were formally outside the Milan criteria according to the documented radiological results. Since the histology results indicated successful downstaging and the participating physicians considered all patients to be inside the Milan criteria at the time of liver transplantation, the patients were not excluded from the analysis.

Among patients in whom serological data were available before liver transplantation, 183/227 (80.6%) were anti-HBc positive, 279/300 (93.0%) were HBsAg-positive, and 101/239 (42.3%) had detectable levels of HBV DNA. For donors in whom data were available, 36/131 (27.5%) were anti-HBs-positive, 53/264 (20.1%) were anti-HBc-positive, and 4/279 (1.4%) were HBsAg-positive.

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 1. Patient characteristics in the total HBV study population and in the subpopulation in whom HCC was the primary indication for transplantation.

	All HBV patients (n=371)		HBV-HCC (n=147)	
At Time of Transplant				
Primary indication for liver transplant, n (%)				
HBV-related liver cirrhosis	195	(52.6)	0	
HBV-HCC	147	(39.6)	147	(100.0)[a]
HBV-related fulminant hepatitis	29	(7.8)	0	
HBsAg-positive, n/N (%)	279/300 (93.0)		114/125 (91.2)	
HBV DNA-positive, n/N (%)	101/239 (42.3)		48/104 (46.1)	
Serum trough level, copies/mL, median (range)	2.7×10^3 ($0.2, 2.35\ 10^{11}$)		1.93×10^3 ($10.0, 2.35\ 10^{11}$)	
Previous liver transplantation, n (%)	7	(1.9)	3	(2.0)
Decompensated liver disease, n (%)	191	(51.5%)	38	(25.9)
Type of transplant, n (%)				
Whole liver	342	(92.2)	135	(91.8)
Split liver, living donor	13	(3.5	2	(1.4)
Split liver, deceased donor	12	(3.2)	4	(2.7)
Combined liver and kidney	4	(1.1)	6	(4.1)
MELD score at time of transplant, mean (±SD)	18.0	(±9.2)	14.7	(±7.2)
Viral co-infection, n (%)				
Hepatitis D	114	(30.7)	37	(25.2)
Hepatitis C	37	(10.0)	15	(10.2)
Concomitant liver disease, n (%)				
Alcoholic liver disease	41	(11.1)	16	(10.9)
Non-alcoholic steatohepatitis	3	(0.8)	1	(0.7)
Autoimmune hepatitis	3	(0.8)	2	(1.4)
Primary biliary cholangitis	1	(0.3)	0	
Concomitant non-hepatic disease, n (%)				
Diabetes mellitus	49	(13.2)	24	(16.3)
Arterial hypertension	34	(9.2)	25	(17.0)
Kidney disease	27	(7.3)	12	(8.2)
Allergy	15	(4.0)	7	(4.8)
Non-HCC malignancies[b]	7	(1.9)	2	(1.4)
Nucleos(t)ide analogue, n (%)[c]	217	(58.5)	108	(73.5)
After Transplantation				
Induction therapy				
Anti-IL-2 receptor antibody	36	(9.7)	20	(13.6)
Rabbit antithymocyte globulin	9	(2.4)	4	(2.7)
Initial maintenance immunosuppression post-transplant, n (%)				
Calcineurin inhibitors	348	(93.8)	142	(96.6)
Corticosteroids	253	(68.2)	108	(73.5)
Mycophenolate mofetil	140	(37.7)	68	(46.3)
Azathioprine	35	(9.4)	11	(7.5)
mTOR inhibitors	25	(6.7)	16	(10.9)
Sotrastaurin	3	(0.8)	2	(1.4)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 1 continued. Patient characteristics in the total HBV study population and in the subpopulation in whom HCC was the primary indication for transplantation.

	All HBV patients (n=371)		HBV-HCC (n=147)	
Nucleos(t)ide analogue, n (%)	347	(93.5)	145	(98.6)
Lamivudine	225	(60.6)	82	(55.8)
Entecavir	87	(23.5)	45	(30.6)
Tenofovir	87	(23.5)	33	(22.4)
Adefovir	54	(14.6)	27	(18.4)
Telbivudine	3	(0.8)	1	(0.7)

[a] HBV-HCC histopathology on explant in 118/135 patients in whom data was available. [b] Previous B-cell lymphoma/seminoma, neuroendocrine tumor of the pancreas (patient transplanted for HCC), Waldenström's macroglobulinemia, previous urothelial carcinoma, adenocarcinoma of the right colon (patient transplanted for HCC), ependymoma, yolk sac tumor. [c] Lamivudine, entecavir, tenofovir, adefovir or telbivudine. HBsAg – hepatitis B surface antigen; HBV – hepatitis B virus; HCC – hepatocellular carcinoma; mTOR – mammalian target of rapamycin; MELD – model for end-stage liver disease; n/N – number of patients with characteristic/number of patients with data available.

Table 2. Hepatitis B immunoglobulin (HBIg) formulations and antiviral treatment after liver transplantation.

	iv HBIgB (n=299)	sc HBIg (n=236)	Other HBIgs (n=130)
Duration of exposure, months			
Mean ±SD	31±37	36±19	42±33
Median (range)	14 (0–176)	35 (4–117)	37 (0–159)
Total duration of treatment, months	8993	8379	5392
Time to first treatment, days post-LT			
Mean ±SD	22±139	1349±1331	548±913
Median (range)	1 (1–1691)	847 (1–5347)	208 (1–5029)
Daily dose during treatment, IU[a]			
Mean ±SD	1658±2902	71±28	181±669
Median (range)	238 (12–10 000)	71 (16–143)	71 (16–5000)

[a] Including all treatment periods during documentation. LT – liver transplantation.

The most frequent immunosuppressive agents in the initial post-transplant maintenance regimen were calcineurin inhibitors (93.8%), mycophenolate mofetil (37.7%), and corticosteroids (68.2%) (Table 1) and these percentages were 82.7%, 31.3%, and 28.6%, respectively, at the last documentation.

The mean (±SD) follow-up time was 6.8 (±3.5) years (median 7.0 years, range 1.0–15.1 years). The total observation period across all patients was 30 781 months, including time with or without HBIg treatment. The mean (±SD) survival time was 6.8 (±3.5) years.

HBIg therapy

All patients received intravenous HBIg immediately after transplantation, except for 2 patients who were given sc HBIg. In total, iv HBIgB was given to 299/371 patients (80.6%). At least 1 change in HBIg therapy occurred in 250 patients (67.4%), with 179, 47, 17, 4, and 3 patients changing 1, 2, 3, 4, or 5 times, respectively. After initial intravenous therapy, a total of 236 patients (63.6%) were switched to sc HBIg (Table 2). One hundred and thirty patients (35.0%) received another HBIg product, including intramuscular Igantibe® (Instituto Grifols S.A., Barcelona, Spain) and intravenous Niuliva® (Instituto Grifols S.A., Barcelona, Spain). At the end of documentation, 270/371 patients (73.8%) were still receiving HBIg therapy (iv HBIgB n=37, sc HBIg n=205, other HBIgs n=28).

The mean duration of exposure was 30.8, 36.4, and 42.1 months for iv HBIgB, sc HBIg, and other HBIgs, respectively, with total treatment durations of 8993, 8379, and 5392 months. For a total of 8017 months, no HBIg treatment was given. The median time to starting therapy was 1 day for iv HBIgB compared to 847 days for sc HBIg and 208 days for other therapies. The median daily dose of iv HBIgB (238 IU, range 12–10 000) was higher than for sc HBIg (71 IU, range 16–143) or other HBIgs (71 IU, range 16–5000), reflecting use of higher dosing in the early post-transplant period (Figure 2A). From month 3

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

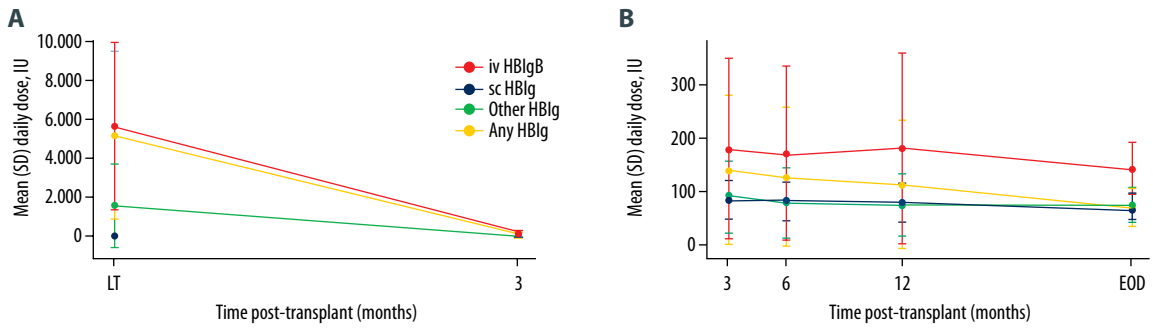

Figure 2. Mean [SD] daily dose of hepatitis B immunoglobulin (HBIg) therapies (**A**) from time of liver transplantation (LT) to month 3 post-transplant, (**B**) from month 3 post-transplant therapies to end of documentation (EOD) in patients transplanted for hepatitis B virus (HBV)-related disease. Data are shown for any HBIg therapy and for iv HBIgB, sc HBIg, and other HBIg products. LT was defined as day of LT and up to 7 days after LT.

post-transplant onwards, the mean dose was stable for each category of HBIg therapy, but remained higher for iv HBIgB than for sc HBIg or other HBIg products (Figure 2B). Almost all patients received sc HBIg at home (96.6%), compared to no patients given iv HBIgB and 56.9% of patients given other HBIg therapies.

There were no reports of HBIg-associated adverse events.

Antiviral therapy

Prior to transplantation, 217 patients (58.5%) received a NUC, most frequently lamivudine (n=127). After transplantation, 347 patients (93.5%) were given at least 1 antiviral medication, including a NUC in each case. Lamivudine was again the most frequently prescribed NUC (225/272, 60.6%) (Table 1), with lamivudine/adefovir the most common combination of NUCs (12.1% of patients). Twenty patients (5.4%) received antivirals for reasons other than HBV prophylaxis.

Anti-HBs

At the end of the documentation period, anti-HBs test results were available for 317 patients, of whom 275 (86.8%) had a positive result. Of the 273 patients with quantitative data, 231 (84.6%) had a serum level ≥100 IU/l.

In the subgroup who were receiving HBIg therapy at the end of documentation and for whom data were available, 239/243 (98.4%) were anti-HBs-positive and 204/239 (85.4%) had a serum level ≥100 IU/l (Table 3).

HBV recurrence

The proportion of patients free of HBV recurrence was 95.7% (95% CI [93.1%, 97.5%]). HBV recurred in 16 patients (4.3%; 95% CI [2.5%; 6.9%]) during the documentation period, at a mean (±SD) of 36.3 (±35.6) months post-transplant (median 22.3 months, range 0.2–103.3 months) (Figure 3). Characteristics of the 16 patients with recurrence are shown in Table 4. The immunosuppression regimen immediately after liver transplantation in this subgroup included calcineurin inhibition in 15/16 cases (93.8%), mycophenolate mofetil in 4/16 cases (25.0%), azathioprine in 4/16 cases (25.0%), and corticosteroids in 10/16 cases (62.5%), with anti-IL-2 receptor antibody induction given to 3/16 patients (18.8%).

The rate of HBV recurrence per year was 0.65% across the total observation period.

Table 3. Anti-HBs test results at the end of the documentation period in patients receiving hepatitis B immunoglobulin (HBIg) treatment at final documentation.

	N=270
Status	
No. patients with data	243
Anti-HBs-positive, n/N (%)	239/243 (98.4)
Anti-HBs-negative, n/N (%)	4/243 (1.6)
Missing, n/N (%)	27/270 (10.0)
Serum level	
No. patients with data	239
≥100 IU/l, n/N (%)	204/239 (85.4)
<100 IU/l, n/N (%)	35/239 (14.6)
Mean ±SD, IU/l	204±137
Median (range), IU/l	188 (10–1024)
Missing, n/N (%)	31/270 (11.5)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

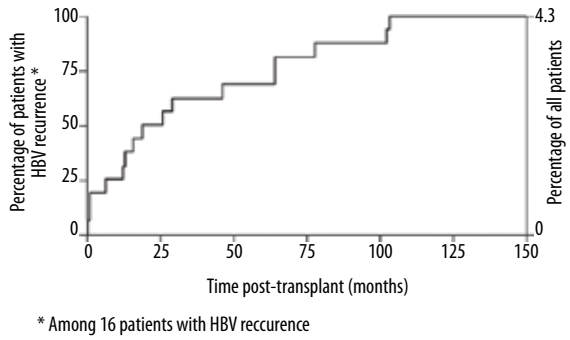

Figure 3. Time to first hepatitis B virus (HBV) recurrence in the 16 patients who developed HBV recurrence out of 371 patients (4.3%) transplanted for HBV-related disease.

Among patients with HBV recurrence for whom pre-transplant HBV test results were available, 12/12 were HBsAg-positive and 8/12 were HBV DNA-positive. Hepatitis D virus (HDV) co-infection was present in 4/16 patients who experienced HBV recurrence (Table 4). Thus, HBV recurrence occurred in 4/114 (3.5%) of HDV-co-infected patients over the whole documentation period and in 0.5% patients per year.

The duration of exposure to sc HBIg or other HBIg therapies, but not iv HBIgB, was shorter in patients with HBV recurrence versus those without recurrence (Table 5). Eleven of the 16 patients with HBV recurrence were receiving HBIg therapy at time of recurrence (6 iv HBIgB, 1 sc HBIg, 4 other HBIg) (11/371, 3.0%) (Figure 4). The remaining 5 patients were not receiving HBIg (2 had stopped treatment <3 months previously). When HBV recurrence was analyzed according to the time during which patients were on HBIg treatment (22 764 months) or not on treatment (8017 months), there was 1 on-treatment recurrence per 2069 months of treatment (11/22 764) and 1 recurrence while not on HBIg therapy per 1603 months without treatment (5/8017). In patients who stopped HBIg treatment compared to those given sc HBIg, the risk of developing HBV recurrence was increased by a factor of 5.2 (1 per 1603 versus 1 per 8379 treatment months).

Table 4. Characteristics of patients with HBV recurrence (n=16).

Patient	Time to recurrence (months)	Treatment at time of recurrence			Determination of first HBV recurrence		Risk factors at time of LT		
		HBIg	Anti-HBs level (IU/l)	Antiviral therapy	HBV DNA (copies/ml)	HBs Ag	HBV DNA/HBsAg (copies/ml IU/ml)	HCC	HDV co-infection
#1	6.2	iv HBIgB	NA	LAM	NA	+	ND/+	–	–
#2	46.2	iv HBIgB	NA	LAM	5.6×10^3	NA	NA/NA	–	–
#3	0.7	iv HBIgB	>100 (1000)	TDF	1.85×10^2	NA	8.5×10^4/+	–	–
#4	0.2	iv HBIgB	NA	TDF	2.1×10^2	ND	6.5×10^5/+	–	–
#5	64.4	iv HBIgB	>100 (178)	TDF, ETV	9.82×10^5	+	3.66×10^7/+	–	+
#6	13.0	iv HBIgB	<100 (61)	LAM	+	+	NA/+	+	–
#7	77.4	sc HBIg	<100 (18)	LAM, ADV	ND	+	NA/+	+	+
#8[a]	18.9	Other HBIg	<100 (3)	LAM, ADV	ND	+	ND/250	+	–
#9[a]	12.3	Other HBIg	<100 (18)	LAM, ADV	2.95×10^3	+	ND/250	+	–
#10	102.3	Other HBIg	NA	–	2.75×10^2	NA	NA/NA	–	+
#11	64.4	Other HBIg	NA	–	50	ND	8.1×10^2/NA	+	+
#12	103.3	No HBIg	NA	TDF	ND	+	5.93×10^3/+	–	–
#13	15.6	No HBIg	<100 (ND)	LAM	6.65×10^4	+	4.14×10^4/+	+	–
#14	25.6	No HBIg	<100 (ND)	–	6.64×10^7	+	ND/236	–	–
#15	0.8	No HBIg	NA	LAM	60	NA	7.5×10^4/NA	+	–
#16	29.0	No HBIg	<100 (ND)	LAM, ADV	+	+	+/+	–	–

[a] Concomitant HBV-HCC recurrence also occurred. ADV – adefovir; ETV – entecavir; HBIg – hepatitis B immunoglobulin; HCC – hepatocellular carcinoma; HDV – hepatitis D virus; LAM – lamivudine; LT – liver transplantation; NA – not available; ND – not detectable; TDF – tenofovir disoproxil fumarate.

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 5. Duration of hepatitis B immunoglobulin (HBIg) therapy in patient subgroups that received either of the indicated HBIgs at any time point during the observation period.

	iv HBIgB	sc HBIg	Other HBIgs
No HBV recurrence (n=355)	n=283	n=233	n=120
Mean, months ±SD	31±37	37±18	44±34
Median months (range)	13 (0–176)	35 (4–117)	39 (0–159)
HBV recurrence (n=16)	n=16	n=3	n=10
Mean months ±SD	29±31	14±7	23±22
Median months (range)	23 (1–102)	13 (9–22)	15 (0–63)
No HBV-HCC recurrence (n=357)	n=289	n=230	n=121
Mean months ±SD	32±38	37±18	44±34
Median months (range)	14 (0–176)	35 (4–117)	41 (0–159)
HBV-HCC recurrence (n=14)	n=10	n=6	n=9
Mean, months ±SD	9±8	23±20	16±9
Median, months (range)	7 (0.2–24)	18 (7–60)	15 (7–36)

HBV – hepatitis B virus; HBV-HCC – HBV-related hepatocellular carcinoma; SD – standard deviation

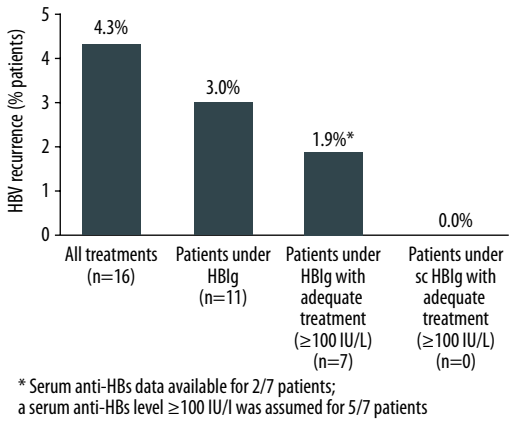

Figure 4. Rate of HBV recurrence according to type and adequacy of hepatitis B immunoglobulin (HBIg) treatment, based on the total population of 371 patients transplanted for HBV-related disease. HBIg included iv HBIgB, sc HBIg, or other licensed HBIg preparations. '*All treatment*' includes all patients who developed HBV recurrence regardless of the type or duration of HBIg treatment; '*Patients under HBIg*' includes all patients who developed HBV recurrence while receiving HBIg therapy; '*Patients under HBIg with adequate treatment*' includes all patients who developed HBV recurrence while receiving any HBIg therapy and who had a serum level of anti-HBs ≥100 IU/l; '*Patients under sc HBIg with adequate treatment*' includes all patients who developed HBV recurrence while receiving sc HBIg therapy and who had a serum level of anti-HBs ≥100 IU/l. If the serum anti-HBs level was not available, it was assumed conservatively to be ≥100 IU/l for the purposes of analysis.

The serum anti-HBs level at time of recurrence was available in 10/16 patients, 7 of whom had a level <100 IU/l (with 6 patients <50 IU/l) (Table 6). Among these 7 patients, the HBIg treatment was iv HBIgB in 1 case, sc HBIg in 1 case, other HBIgs in 2 cases, and no HBIg in 3 cases. Seven of the remaining 9 patients were receiving HBIg at the time of recurrence, 2 of whom were known to have serum anti-HBs ≥100 IU/l. Assuming conservatively that the other 5 patients also had serum anti-HBs ≥100 IU/l, the rate of recurrence in adequately-treated patients was 1.9% (7/371) (Figure 4). No patient switched to adequate treatment with sc HBIg had recurrent HBV.

At time of recurrence, 13/16 patients were under NUC treatment. Recurrences were observed in patients receiving NUC alone, HBIg with lamivudine, and HBIg with adefovir, but also when HBIg was given in combination with more potent NUCs (Table 4).

Graft rejection

Acute rejection occurred in 37/371 (10.0%) of patients and chronic rejection occurred in 7/371 (1.9%) of patients.

HBV-HCC recurrence

HBV-HCC recurred in 14/147 (9.5%; 95% CI [5.3%, 15.5%]) of patients transplanted due to HBV-HCC. The annual rate of recurrence was 1.7% and the mean (±SD) time to recurrence was 17.6 (±10.8) months (median 14.1 months, range 5.5–41.9 months) (Figure 5A).

Characteristics of the patients with HBV-HCC recurrence are shown in Table 6. Each of these 14 patients had HBV-HCC within Milan criteria confirmed by histopathology at the time

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

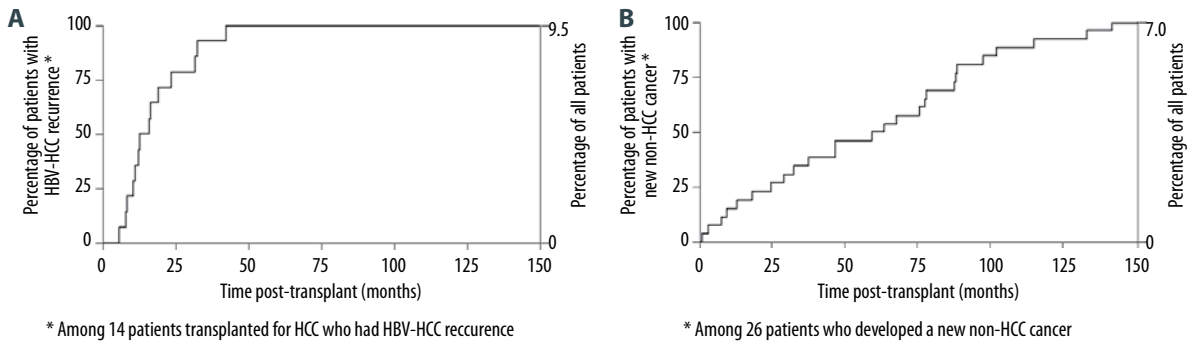

Figure 5. (**A**) Time to first recurrence of hepatitis B virus (HBV)-hepatocellular carcinoma (HBV-HCC) in the 14 patients (14/147, 9.5%) transplanted for HCC and who had HBV-HCC recurrence, (**B**) time to first occurrence of *de novo* non-HCC cancer in the 26 patients (26/371, 7.0%) transplanted for HBV-related disease who developed a *de novo* non-HCC cancer.

Table 6. Characteristics of patients with HBV-HCC recurrence (n=14).

Patient	Year of recurrence	Time to recurrence [months]	Treatment at time of HBV-HCC recurrence		Manifestation of HBV-HCC recurrence	Number of nodules/total size [cm]	Treatment before liver transplant	Down-staging
#1	2009	15.7	iv HBIgB	LAM, ADV	Extrahepatic	NA/NA	RFA	No
#2[a]	2005	7.8	iv HBIgB	LAM, ADV	Extrahepatic	1/2	TACE	Yes
#3	2005	23.2	iv HBIgB	LAM	Liver	1/7	TACE	No
#4	2014	12.4	sc HBIg	LAM	Extrahepatic	Multiple/NA	TACE	No
#5	2011	31.3	sc HBIg	LAM	Liver & extrahepatic	NA/NA	n.a.	No
#6	2015	10.2	sc HBIg	ETV	Liver & extrahepatic	NA/NA	RFA/SOR	No
#7	2012	16.2	sc HBIg	ETV	Extrahepatic	NA/NA	TACE/ resection	Yes
#8	2014	8.1	sc HBIg	TDF	Extrahepatic	NA/NA	RFA	Yes
#9[a,b]	2007	18.9	Other HBIg	LAM, ADV	Liver	1/3	TACE	Yes
#10[b]	2006	12.1	Other HBIg	LAM	Liver & extrahepatic	2/10	TACE	No
#11	2012	42.0	Other HBIg	LAM	Liver & extrahepatic	1/1.8	n.a.	n.a.
#12	2009	5.5	Other HBIg	LAM	Liver & extrahepatic	Multiple/8	TACE	Yes
#13	2013	11.0	Other HBIg	TDF	Liver	1/3.3	RFA/TA	Yes
#14	2015	32.3	No HBIg	ETV	Extrahepatic	1/0.5	TACE/RFA	Yes

[a] Outside the Milan criteria at time of transplant as determined by the radiological report, but this was not confirmed by later histopathology. [b] Concomitant HBV recurrence. ADV – adefovir; ETV – entecavir; HBIg – hepatitis B immunoglobulin; HBV – hepatitis B virus; HCC – hepatocellular carcinoma; LAM – lamivudine; NA – not available; n.a. – not applicable; RFA – radiofrequency ablation; SOR – sorafenib; TACE – transarterial chemoembolization; TDF – tenofovir disoproxil fumarate.

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

of transplantation. Two of the patients also experienced HBV recurrence. Two patients had concomitant alcoholic liver disease and 3 patients had HDV co-infection. HCC recurrence occurred in 3/37 (8.1%) patients co-infected with HDV. The diagnosis of recurrence was based on clinical/radiological findings in 8 cases, with histopathological evidence in 7 cases (confirmation was by both methods in 1 case).

For all 3 categories of HBIg, the mean duration of HBIg therapy was shorter among patients with HBV-HCC recurrence (9, 23, and 16 months for iv HBIgB, sc HBIg, and other HBIgs, respectively) versus patients without HBV-HCC recurrence (32, 37, and 44 months, respectively) (Table 5). Documentation in patients with HBV or HCC recurrence was stopped at the time of determination, which led to a shorter documentation time in these patients. At the time of recurrence, 8 patients were receiving either iv HBIgB or sc HBIg, 5 were being treated with another HBIg, and 1 was not receiving HBIg therapy. All 14 patients were being treated with antivirals, most frequently lamivudine (9/14) (Table 6).

***De novo* malignancies other than HCC**

In total, 26/371 patients (7.0%; 95% CI [4.6%, 10.1%]) were diagnosed with *de novo* malignancies during the documentation period, representing an incidence of 1.05% per year. The most frequent of these were skin cancers (squamous cell carcinoma n=3, basal cell carcinoma n=2, cutaneous carcinoma n=2). Kaposi's sarcoma and lung cancer occurred in 2 patients each; no other cancer occurred in more than 1 patient. The mean (±SD) time to onset was 59.4 (±40.7) months (median 61.4; range 0.8–141.7 months) (Figure 5B). At the time of diagnosis, 16 patients were receiving HBIg therapy and 10 patients had stopped HBIg treatment. The incidence of *de novo* malignancies in the cohort of patients with HCC recurrence was 12.5% (2/16 patients).

Discussion

This retrospective analysis represents one of the largest data sets available to determine HBV recurrence rates in HBV-infected patients after liver transplantation and explore HCC recurrence in this population. In this European multicenter study, combination prophylaxis with HBIg and NUC therapy was associated with low rates of HBV recurrence (4.3%) over a mean follow-up of almost 7 years. The HBV-HCC recurrence rate was 9.5%.

A recent systematic review which pooled data from 17 randomized or observational studies found the HBV recurrence rate to be 7.1% for patients treated with HBIg and lamivudine, or 1.3% with HBIg and either entecavir or tenofovir (there was no restriction of HBIg duration in either group) [10]. The latter rate is strikingly lower, but comparison with the recurrence rate in the present study (4.3%) is difficult because the follow-up periods differ markedly, with a mean of ~3 years in the pooled analysis compared to 6.8 years in the present study. HBV recurrence has been reported to occur most frequently at approximately 2–4 years post-transplant [8,11], consistent with our observation (mean 36±36 months).

NUC therapy alone, however, has also been explored. Recently, an observational study of 265 Asian liver transplant patients with chronic HBV infection was published, in which patients received entecavir without HBIg therapy [12]. During a maximum follow-up of 8 years, 14/265 (5.3%) patients remained persistently positive for HBsAg. Among 242 patients who experienced HBsAg seroclearance after transplantation, 36 developed HBsAg and none had HBV DNA reappearance. This corresponds to a recurrence rate of 14.8% (36/242), considerably higher than in our study. However, in the Asian population, no HDV-co-infected patient was included, in contrast to our European cohort in which the proportion with HDV infection was relatively high. In our study, the HBV recurrence rate was 3.5% for HDV-co-infected patients, a subgroup in whom life-long combination therapy with HBIg and NUC is recommended [5].

In the present series, 5 of the 16 patients with HBV reinfection had stopped HBIg therapy by the time of recurrence. Notably, 7 patients had documented inadequate HBIg therapy (6 of those had serum anti-HBs <50 IU/l and 1 had <100 IU/l). The threshold of ≥100 IU/l is defined by the European Medicines Agency Committee for Medicinal Products for Human Use as the minimum threshold for effective protection against HBV reinfection using HBIg therapy [13]. Excluding the 7 patients in whom an inadequate serum anti-HBs level (<100 IU/l) was confirmed, the reinfection rate was only 2.4% of all 371 patients at risk. Higher HBIg dosage is associated with a lower frequency of HBV recurrence even in patients receiving combination prophylaxis [7]. When dosed correctly, HBIg is highly effective in maintaining adequate titers [14,15]. In the present cohort, 14.6% of patients had a serum anti-HBs level <100 IU/l, suggesting failure to maintain protective titers in this subpopulation. Withdrawal of HBIg in low-risk patients after a defined course of combined therapy, or use of low-dose or on-demand HBIg therapy, are valid strategies to reduce treatment costs [16,17]. Typically, transplant centers administer higher HBIg doses during the anhepatic phase and the very early phase post-transplant. Various HBIg minimization strategies are then pursued [18]. However, patients must be evaluated carefully before HBIg reduction, based on risk factors such as high pre-transplant HBV DNA, co-infections, and transplantation for concomitant HBV-HCC [16,17]. According to EASL 2017 guidelines, discontinuation should be restricted to patients who were HBV DNA-negative pre-transplant [5].

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Here, the shorter duration of exposure to HBIg in patients with HBV recurrence compared to recurrence-free patients is of interest. The observational study design, however, does not permit firm conclusions from this finding; for example, HBIg therapy may have been discontinued after diagnosis of HBV recurrence. Another interesting finding is that, despite some missing values, patients with HBV recurrence had higher HBV DNA levels prior to liver transplantation (median HBV DNA levels were 2 log copies/mL, and only 1 of the patients with recurrence had DNA levels below 2 log copies/mL). This is a risk factor influencing recurrence in some patients.

A prospective study showed that early switch to subcutaneous treatment with sc HBIg (days 8–18 post-transplant), dosed according to serum anti-HBs level in patients who were HBV-DNA-negative at time of transplant, maintained serum anti-HBs levels ≥100 IU/l and no patient developed reinfection [19]. It is striking in the present series that there was only 1 patient with HBV recurrence over a total of 8379 months of sc HBIg treatment. Sub-optimal dosing with sc HBIg may be responsible for this single occurrence, as the anti-HBs level of 18 IU/l was below the minimum threshold for effective protection. In terms of dosing, the median daily dose of sc HBIg over the entire study duration was lower than with iv HBIgB (71 versus 238 IU). This partly reflects the delayed starting time for sc HBIg compared to iv HBIgB, but a dosing difference was sustained even after the early post-transplant period (Figure 2B). sc HBIg was not licensed until 2009, when initiation of therapy was approved at month 6 after transplantation. It was not until late 2015 that a change in the labeling allowed initiation of therapy as early as 1 week post-transplantation. By this time, the last patient included in this study had already been transplanted.

The annual incidence of HCC recurrence in the present study was very low, at 1.7%. This compares favorably with rates of 3.2–6.7% reported elsewhere [8,12,20,21]. It is possible that factors such as tumor history (which was not captured by the present study), tumor stage at transplantation, differences in malignancy surveillance, and the period of transplantation may account for this difference. HBIg treatment may positively influence the risk of HBV-HCC recurrence after liver transplant, in particular for HCC patients within the Milan criteria [11]. Observational studies have shown an association between HBV recurrence and HBV-HCC recurrence after transplantation [20,22,23]. In addition, high HBV viral load is an independent risk factor for HBV-HCC recurrence [24]. These factors may explain why 2 patients with HBV recurrence also experienced HCC recurrence in our study; however, this remains speculative. High-dose HBIg may reduce the risk for HBV-HCC recurrence in patients who meet the Milan criteria [12]. In HDV-co-infected patients, the HCC recurrence rate was 8.1%, suggesting that HCC recurrence does not occur at any higher frequency in this high-risk group using HBIg and NUC combination prophylaxis.

The incidence of skin cancer and lymphoma in liver transplant patients is substantially increased compared to in healthy individuals [25,26]. Published reports of the incidence of *de novo* malignancy after liver transplantation vary widely, from 2.6% to 15.7% [27], influenced by risk factors such as older age [28], smoking [28,29], transplantation for alcoholic cirrhosis [27], and more intensive immunosuppression [30,31]. Against this background, the low rate of *de novo* malignancies observed here over this long-term follow-up, at an annual incidence of 1.05%, is encouraging but might be an underestimation due to the study design. Although numbers were small, results in our population did not appear to indicate any marked increase in risk among patients with HCC recurrence compared to the overall population.

In this series, there was a 10% incidence of acute rejection, which is relatively low for a mean follow-up period of almost 7 years. Long-term follow-up data from randomized trials have reported 5-year rejection rates of 11–18% [32,33]. Patients transplanted for chronic HBV-related disease have been reported to be at lower risk for acute rejection versus non-HBV indications [34–36]. There are limited *in vitro* data suggesting that HBIg may inhibit alloantigen specific T cell responses, dendritic cell maturation, and cytokine production [35]. A recent study [37], albeit with lower HBIg concentrations as in prior *in vitro* studies [38,39], found no enhancing role on regulatory T cell generation. However, more *in vivo* and *in vitro* data are needed to determine the possible immunosuppressive effect of HBIg.

Administration of HBIg in combination with NUC was well tolerated and no HBIg-related adverse events were reported. These findings are consistent with prospective and retrospective studies of combined post-transplant prophylaxis with HBIg and NUC therapy [40].

Some characteristics of the present study should be considered. The analysis was restricted to patients with a minimum of 1 year's HBIg therapy (and at least 6 months under either iv HBIgB or sc HBIg), but this applied to nearly all cases transplanted at the study centers over the period of documentation. The findings cannot be extrapolated to shorter periods of HBIg treatment. As a retrospective analysis, serological tests, notably anti-HBs levels, were missing or incomplete in some patients and differences in treatment protocols made comparisons between specific therapies impractical. It would have been relevant to document levels of anti-HBs routinely, but regular monitoring was not standard practice in this non-interventional study; levels would be expected to be low at the point of hepatitis B recurrence diagnosis. Patient monitoring, such as for skin cancers, may have been less systematic than in a controlled trial. Inevitably, in a long-term observational study of this type, the dataset is not complete, thus introducing a potential risk of bias. However, the analysis benefitted from

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

a large 'real-world' population transplanted since 2000, and a consistent definition for HBV recurrence was applied across all patients. Importantly, it offers a long-term follow-up period of up to 15 years.

Conclusions

Results from this multicenter European retrospective analysis in a large series of patients undergoing liver transplantation for HBV-related disease indicate that routine clinical use of HBIg prophylaxis for a minimum of 1 year, combined with NUC therapy, is associated with a low rate of HBV recurrence and HBV-HCC recurrence over the long-term. Low recurrence rates were also seen in patients with HDV co-infection. These data support the current EASL guidelines [5] that combination therapy with HBIg and NUC is an effective prophylactic strategy for the management of HBV infection in liver transplant recipients.

Acknowledgments

The authors thank Dr. Thomas Achtstätter for critical discussion of the design of the study and scientific input.

Disclosures

Susanne Beckebaum has received speakers' fees, travel reimbursement, and research funding from Biotest and was a member of the Biotest AG medical advisory board. Artur Bauhofer and Gabriele Niemann are employees of Biotest AG. Paolo De Simone has received speakers' fees and served as advisory board member for Biotest AG. Robert de Man has received research funding from Biotest AG. Beat Müllhaupt has received travel reimbursement from Biotest AG. Kerstin Herzer and Julien Vionnet have received travel grants and research funding from Biotest AG. Patrizia Burra has taken part in advisory boards and meetings sponsored by Biotest AG. Lutz Fischer has received travel reimbursement from Biotest AG. William Gelson, Cornelius Engelmann, Mauro Salizzoni, Riccardo Volpes, Giorgio Ercolani, Luciano De Carlis, Paolo Angeli, Jean-François Dufour, Massimo Rossi, Umberto Cillo, Ulf Neumann, Luca Toti, and Giuseppe Tisone have no conflicts of interest to declare.

References:

1. Lozano R, Naghavi M, Foreman K et al: Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet, 2012; 380(9859): 2095–128
2. Adam R, Karam V, Delvart V et al: Evolution of indications and results of liver transplantation in Europe: A report from the European Liver Transplant Registry (ELTR). J Hepatol, 2012; 57(3): 675–88
3. Young K, Liu B, Bhuket T et al: Long-term trends in chronic hepatitis B virus infection associated liver transplantation outcomes in the United States. J Viral Hepat, 2017; 24(9): 789–96
4. Papatheodoridis GV, Cholongitas E, Archimandritis AJ, Burroughs AK: Current management of hepatitis B virus infection before and after liver transplantation. Liver Int, 2009; 29(9): 1294–305
5. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol, 2017; 67(2): 370–98
6. 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(10): 1176–90
7. Dugum M, Hanouneh I, Lopez R et al: Hepatocellular carcinoma in the setting of chronic hepatitis B virus infection: Tumor recurrence and survival rates after liver transplantation. Transplant Proc, 2015; 47(6): 1939–44
8. Saab S, Yeganeh M, Nguyen K et al: Recurrence of hepatocellular carcinoma and hepatitis B reinfection in hepatitis B surface antigen-positive patients after liver transplantation. Liver Transpl, 2009; 15(11): 1525–34
9. Sun LY, Zhu ZJ, Qu W et al: Prognosis in liver transplantation recipients after hepatitis B virus recurrence. Hepatogastroenterology, 2014; 61(135): 2047–51
10. Cholongitas E, Papatheodoridis GV: High genetic barrier nucleos(t)ide analogue(s) for prophylaxis from hepatitis B virus recurrence after liver transplantation: A systematic review. Am J Transplant, 2013; 13(2): 353–62
11. Lee EC, Kim SH, Lee SD et al: High-dose hepatitis B immunoglobulin therapy in hepatocellular carcinoma with hepatitis B virus-DNA/hepatitis B e antigen-positive patients after living donor liver transplantation. World J Gastroenterol, 2016; 22(14): 3803–12
12. Fung J, Wong T, Chok K et al: Long-term outcomes of entecavir monotherapy for chronic hepatitis B after liver transplantation: Results up to 8 years. Hepatology, 2017; 66(4): 1036–44
13. Committee for Medicinal Products for Human Use. Guideline on the core SPC for human plasma derived hepatitis-B immunoglobulin for intravenous use (CPMP/BPWG/4027/02) *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003325.pdf Accessed 6 September 2017*
14. Klein CG, Cicinnati V, Schmidt H et al: Compliance and tolerability of subcutaneous hepatitis B immunoglobulin self-administration in liver transplant patients: A prospective, observational, multicenter study. Ann Transplant, 2013; 18: 677–84
15. Mas A, Castells L, Abradelo M et al: Evaluation of Anti-HBs serum levels and pharmacokinetic profile after intravenous administration of Niuliva, a new hepatitis B immunoglobulin, following liver transplantation. Transplant Proc, 2009; 41(10): 4253–58
16. Fox AN, Terrault NA: The option of HBIG-free prophylaxis against recurrent HBV. J Hepatol, 2012; 56(5): 1189–97
17. Roche B, Roque-Afonso AM, Nevens F, Samuel D: Rational basis for optimizing short and long-term hepatitis B virus prophylaxis post liver transplantation: Role of hepatitis B immune globulin. Transplantation, 2015; 99(7): 1321–34
18. Terrault N, Roche B, Samuel D: Management of the hepatitis B virus in the liver transplantation setting: A European and an American perspective. Liver Transpl, 2005; 11(7): 716–32
19. De Simone P, Romagnoli R, Tandoi F et al: Early introduction of subcutaneous hepatitis B immunoglobulin following liver transplantation for hepatitis B virus infection: A prospective, multicenter study. Transplantation, 2016; 100(7): 1507–12
20. Campsen J, Zimmerman M, Trotter J et al: Liver transplantation for hepatitis B liver disease and concomitant hepatocellular carcinoma in the United States with hepatitis B immunoglobulin and nucleoside/nucleotide analogues. Liver Transpl, 2013; 19(9): 1020–29
21. Wu TJ, Chan KM, Chous HS et al: Liver transplantation in patients with hepatitis B virus-related hepatocellular carcinoma: The influence of viral characteristics on clinical outcomes. Ann Surg Oncol, 2013; 20(11): 3582–90

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

22. Chun J, Kim W, Kim BG et al: High viremia, prolonged Lamivudine therapy and recurrent hepatocellular carcinoma predict posttransplant hepatitis B recurrence. Am J Transplant, 2010; 10(7): 1649–59
23. Faria LC, Gigou M, Roque-Afonso AM et al: Hepatocellular carcinoma is associated with an increased risk of hepatitis B virus recurrence after liver transplantation. Gastroenterology, 2008; 134(7): 1890–99
24. Hung IF, Poon RT, Lai CL et al: Recurrence of hepatitis B-related hepatocellular carcinoma is associated with high viral load at the time of resection. Am J Gastroenterol, 2008; 103(7): 1663–73
25. Zhou J, Hu Z, Zhang Q et al: Spectrum of *de novo* cancers and predictors in liver transplantation: Analysis of the Scientific Registry of Transplant Recipients database. PLoS One, 2016; 11(5): e0155179
26. Finkenstedt A, Graziadei IW, Oberaigner W et al: Extensive surveillance promotes early diagnosis and improved survival of *de novo* malignancies in liver transplant recipients. Am J Transplant, 2009; 9(10): 2355–61
27. Jiménez-Romero C, Justo-Alonso I, Cambra-Molero F et al: Incidence, risk factors and outcome of *de novo* tumors in liver transplant recipients focusing on alcoholic cirrhosis. World J Hepatol, 2015; 7(7): 942–53
28. Herrero JI, Pardo F, D'Avola D et al: Risk factors of lung, head and neck, esophageal, and kidney and urinary tract carcinomas after liver transplantation: The effect of smoking withdrawal. Liver Transpl, 2011; 17(4): 402–8
29. Mangus RS, Fridell JA, Kubal CA et al: Worse long-term patient survival and higher cancer rates in liver transplant recipients with a history of smoking. Transplantation 2015; 99(9): 1862–68
30. Tjon AS, Sint Nicolaas J, Kwekkeboom J et al: Increased incidence of early *de novo* cancer in liver graft recipients treated with cyclosporine: An association with C2 monitoring and recipient age. Liver Transpl, 2010; 16(7): 837–46
31. Aguiar D, Martínez-Urbistondo D, D'Avola D et al: Conversion from calcineurin inhibitor-based immunosuppression to mycophenolate mofetil in monotherapy reduces risk of *de novo* malignancies after liver transplantation. Ann Transplant, 2017; 22: 141–47
32. Boillot O, Seket B, Dumortier J et al: Thymoglobulin induction in liver transplant recipients with a tacrolimus, mycophenolate mofetil, and steroid immunosuppressive regimen: a five-year randomized prospective study. Liver Transpl, 2009; 15(11): 1426–34
33. Weiler N, Thrun I, Hoppe-Lotichius M et al: Early steroid-free immunosuppression with FK506 after liver transplantation: Long-term results of a prospectively randomized double-blinded trial. Transplantation, 2010; 90(12): 1562–66
34. Au KP, Chan SC, Chok KS et al: Clinical factors affecting rejection rates in liver transplantation. Hepatobiliary Pancreat Dis Int, 2015; 14(4): 367–73
35. Kwekkeboom J, Tha-In T, Tra WM et al: Hepatitis B immunoglobulins inhibit dendritic cells and T cells and protect against acute rejection after liver transplantation. Am J Transplant, 2005; 5(10): 2393–402
36. van Gent R, Metselaar HJ, Kwekkeboom J: Immunomodulation by hyperimmunoglobulins after solid organ transplantation: Beyond prevention of viral infection. Transplant Rev (Orlando), 2017; 31(2): 78–86
37. Veerappan A, Van Wagner LB, Mathew JM et al: Low incidence of acute rejection in hepatitis B virus positive liver transplant recipients and the impact of hepatitis B immunoglobulin. Hum Immunol, 2016; 77(4): 367–74
38. Amran D, Renz H, Lack G et al: Suppression of cytokine-dependent human T-cell proliferation by intravenous immunoglobulin. Clin Immunol Immunopathol, 1994; 73(2): 180–86
39. Toungouz M, Denys C, Dupont E: Blockade of proliferation and tumor necrosis factor-alpha production occurring during mixed lymphocyte reaction by interferon-gamma-specific natural antibodies contained in intravenous immunoglobulins. Transplantation, 1996; 62(9): 1292–96
40. Loomba R, Rowley AK, Wesley R et al: Hepatitis B immunoglobulin and lamivudine improve hepatitis B-related outcomes after liver transplantation: Meta-analysis. Clin Gastro Hepatol, 2008; 6(6): 696–700

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]