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Long-Term Effectiveness, Safety, and Patient-Reported Outcomes of Self-Administered Subcutaneous Hepatitis B Immunoglobulin in Liver Post-Transplant Hepatitis B Prophylaxis: A Prospective Non-Interventional Study

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: Self-administered subcutaneous hepatitis B immunoglobulin (s.c. HBIg) in combination with nucleos(t)ide analogs (NUCs) has proved to be effective and safe in preventing hepatitis B virus (HBV) reinfection after liver transplantation.

Material/Methods: This non-interventional, prospective, single-arm, multicenter, international study collected data on long-term effectiveness, safety, patient satisfaction (Treatment Satisfaction Questionnaire for Medication, TSQM-11), and quality of life (EQ-5D questionnaire) in routine practice over a 2-year treatment period. Data analysis was based on 195 adults (82.1% male) transplanted for HBV-related liver diseases and treated with s.c. HBIg with/without NUC(s).

Results: HBV recurrence (seropositivity of HBV surface antigen and/or HBV DNA) was observed in 7/195 (3.6%) patients (annual rate: 2.01%). Hepatocellular carcinoma (HCC) recurred in 4/83 (4.8%) patients transplanted for HBV-HCC (annual rate: 2.88%). Twenty-nine adverse drug reactions occurred in 16/195 (8.2%) patients. Convenience and overall satisfaction scores of the TSQM-11 were significantly ($P<0.05$) improved under treatment at the 3-month, 2-year, and last follow-up visits. Quality of life remained constant over the entire observation period (EQ-5D index [$P\geq0.075$]). S.c. HBIg was mainly self-administered (6458/9021 administrations, 71.6%) at home (8514/9021 administrations, 94.4%).

Conclusions: The results indicate long-term effectiveness and safety of s.c. HBIg in combination with NUC therapy in preventing post-transplant HBV reinfection under real-life conditions. The convenience of the therapy contributed to the high overall treatment satisfaction and acceptance by the patients.

Keywords: Carcinoma, Hepatocellular • Hepatitis B Antibodies • Hepatitis B virus • Liver Transplantation • Recurrence

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Background

Recurrent graft infection with hepatitis B virus (HBV) has been one of the major complications of liver transplantation (LT) in patients with HBV-related liver diseases. The underlying reasons for HBV recurrence are complex and not yet fully explored. Molecular mechanisms playing a role in post-transplant HBV reactivation include intra- and extrahepatic HBV replication, HBV genotype, and certain variations in the recipient's genetic make-up [1].

Survival rates of liver transplant recipients have significantly improved in recent decades mainly due to advances in surgical techniques and management of post-transplant complications, including prophylaxis of HBV reinfection [2,3]. The introduction of human plasma-derived hepatitis B immunoglobulin (HBIg), which acts through passive immunization by binding to the HBV surface antigen (HBsAg), was a milestone in the development of effective strategies for preventing HBV reinfection [4-7]. Currently, the universally accepted post-transplant prophylactic therapy is based on HBIg combined with potent antiviral agents, particularly second-generation nucleos(t)ide analogs (NUCs) [8]. While lifelong NUC therapy is recommended after transplantation regardless of pre-transplant HBV envelope antigen (HBeAg) or HBV DNA levels [9], there is no consensus on optimal dosing regimen and treatment duration of HBIg. Therapy success is dependent on multiple factors, including the patients' acceptance of and compliance to treatment. In recent years, intramuscular (i.m.) and subcutaneous (s.c.) HBIg preparations have been investigated as more convenient and cost-effective options replacing conventional intravenous (i.v.) HBIg. Both routes allow at-home treatment, whereas advantages of the s.c. route are the possibility of self-administration and less discomfort or pain [10].

Currently, only 1 HBIg preparation is approved for s.c. administration after LT (Zutectra®, Biotest AG, Dreieich Germany). Efficacy, safety, and feasibility of self-administration of the product were demonstrated in several clinical studies [11,12]. In addition, 2 multicenter observational studies, ie, a single-arm, 18-week prospective study [13] and a retrospective data analysis [14], supported the effectiveness of s.c. HBIg in the management of post-transplant HBV prophylaxis in routine practice.

This prospective, non-interventional study (NIS) aimed at gathering further 'real-life' data on the effectiveness and safety of s.c. HBIg by including a larger international patient set and by prolonging the observation period to 2 years. Furthermore, treatment satisfaction and quality of life were evaluated for the first time during long-term prophylactic therapy with s.c. HBIg.

Material and Methods

Study Design

This prospective, single-arm, post-approval NIS was conducted at 19 liver transplant centers in France and Spain between July 2015 and March 2021. The NIS was performed in accordance with the principles of the Declaration of Helsinki and all applicable national regulatory requirements, including approval by local ethics committees. All patients provided written informed consent. Commercially available s.c. HBIg (Zutectra®, Biotest AG, Dreieich, Germany) was prescribed and used guided by the specifications given in the summary of product characteristics (SmPC) [15]. All therapy decisions were at the sole discretion of the participating physicians.

Patients

Adult patients (≥18 years) who had undergone LT for fulminant hepatitis B, hepatitis B cirrhosis, or HBV-induced hepatocellular carcinoma (HCC), or who had had a liver retransplantation, except due to HBV recurrence, were eligible for study participation. Patients had to be under treatment with s.c. HBIg without or with a concomitant NUC. Treatment with HBIg and/or NUC is provided lifelong to these patients. The time point for initiation of s.c. HBIg after LT was not predefined. In general, the SmPC requests previous treatment with i.v. HBIg to ensure sufficiently high serum levels of antibodies against HBV surface antigen (anti-HBs) before switching to s.c. HBIg maintenance therapy [15].

Data Documentation

Study-related data were collected, stored, and processed in pseudonymized form. Documentation was to begin immediately after start of s.c. HBIg treatment and was to be continued over a 2-year period. Data were recorded in a standardized (electronic) case report form during a baseline visit and all subsequent visits performed as per normal routine practice. Physicians were required to specify each documented follow-up (FU) as either regular 3-month FU, regular 2-year FU, intermediate FU, or early discontinuation visit. Demographic and medical history data, including data on previous immunosuppressive and/or antiviral treatments and pre-transplant laboratory test results, were taken from the patients' medical records. All other study-related data were documented prospectively. Adverse events (AEs) were assessed continuously at each routine FU visit.

Study Endpoints

The primary variables of effectiveness were the proportion of patients with HBV recurrence after LT, the incidence rate per year,

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and the time to recurrence. HBV recurrence was defined as reappearance of HBsAg and/or HBV DNA in serum at any time after start of s.c. HBIg treatment and after at least 1 previous respective negative test result. If only a single measurement during the follow-up was positive and not confirmed thereafter, HBV recurrence was not assumed unless the positive result was the last documented measurement and the patient was still under s.c. HBIg therapy. The primary variable of safety was the proportion of patients with AEs, including categories by AE term (verbatims were coded using the Medical Dictionary for Regulatory Activities version 23.1), seriousness, and causal relationship. AEs assessed as being possibly related to s.c. HBIg were identified as adverse drug reactions (ADRs). Secondary variables included serum trough levels of anti-HBs (as a measure of effectiveness and treatment compliance) and viral markers (HBsAg, HBeAg, HBV DNA), post-transplant recurrence of HCC, details on s.c. HBIg treatment, use of immunosuppressives, prior and concomitant antiviral medications, clinical laboratory tests for liver and kidney function, treatment satisfaction, and quality of life.

Questionnaires

Patients voluntarily completed pseudonymized questionnaires for measuring treatment satisfaction and quality of life at the baseline visit and regular FU visits. The Treatment Satisfaction Questionnaire for Medication (TSQM-11) consists of 11 items scored on either a 2-, 5-, or 7-point Likert scale measuring 4 dimensions of treatment satisfaction: effectiveness, adverse effects, convenience, and overall satisfaction [16]. Item scores were transformed into dimension scores ranging from 0 to 100, where higher scores represent better satisfaction. Adverse effect dimension scores were calculated only for patients with adverse effects. The EuroQol 5-dimension (EQ-5D) questionnaire was used to measure health-related quality of life [17]. Patients assessed each dimension on a 3-level scale (no problems, some problems, extreme problems). The combination of the dimension scores yielded a health state code from which the EQ-5D index was calculated [18]. Patients also rated their perceived health state on a visual analog scale (EQ-VAS), ranging from 1 (worst) to 100 (best imaginable health state) [19].

Statistical Analysis

No formal sample size calculation was performed. With an anticipated sample size of n=200 and an expected HBV recurrence rate of 5%, the 95% confidence interval for the primary variable was between 2.4% and 9.0%. Statistical analyses were based on the full analysis set defined as all patients included in the study in accordance with the eligibility criteria and treated with at least 1 dose of s.c. HBIg. Data were analyzed descriptively. Two-sided Clopper-Pearson 95% confidence intervals were calculated for the proportions of patients with HBV recurrence and HCC recurrence. Changes from baseline in TSQM-11 and EQ-5D scores were tested nonparametrically using the Wilcoxon signed rank test at the 5% level of significance. Statistical analyses were performed with SAS® 9.4 (SAS Institute, Inc., Cary, USA).

Four predefined visits were included in the analysis of prospective data: baseline (BL), 3-month FU, 2-year FU, and a patient's last FU visit (FU last). BL was the last measurement/treatment before start of s.c. HBIg treatment, the 3-month FU was 91 days after treatment start (window: 71-181 days), the 2-year FU was 730 days after treatment start (window: ≥640 days), and FU last was the respective last available follow-up value of a patient. Visits that had taken place >62 days after last s.c. HBIg intake were not considered for analysis. Questionnaire results were presented by visit according to the physicians' visit specifications provided on the case report forms.

Results

Study Population and Medical History

The total study population comprised 202 patients (**Figure 1**). Analysis was based on 195 patients who met all inclusion criteria and received s.c. HBIg. The study was completed after 2 years by 147/195 (75.4%) patients. The mean (±SD) interval between baseline and last follow-up visit was 21.4 (±7.3) months. Demographics and medical history data of the analyzed patient set are shown in **Table 1**. Most patients were male (82.1%) and the mean (±SD) age at study entry was 58.4 (±10.5) years. Cirrhosis (51.3%) and HCC (42.6%) were the most frequent HBV-related main indications for LT. Pre-transplant downstaging of HCC to within Milan criteria had been performed in 18 patients (9.2%), including 3 patients with liver cirrhosis reported as main reason for LT. Before LT, 112/195 (57.4%) patients were HBsAg-positive (test results were not available for 34.4%), 13/195 (6.7%) were HBeAg-positive (results unavailable: 54.4%), and 42/195 (21.5%) had detectable serum HBV DNA (results unavailable: 41.0%); 43/195 (22%) patients had hepatitis D virus (HDV) co-infection.

S.c. HBIg and Concomitant Therapy

Treatment with i.v. or i.m. HBIg prior to starting s.c. HBIg was reported in 164/195 patients (84.1%). The interval between LT and start of s.c. HBIg therapy was highly variable between patients (mean [±SD]: 91.7 [±94.1] months); the mean (±SD) duration of treatment was 20.7 (±7.4) months (**Table 2**). S.c. HBIg was mainly self-administered (6458/9021 administrations, 71.6%) at home (8514/9021 administrations, 94.4%).

Frequencies of s.c. HBIg dosing regimens are summarized in **Table 2**. The most frequently prescribed regimen was 500 IU

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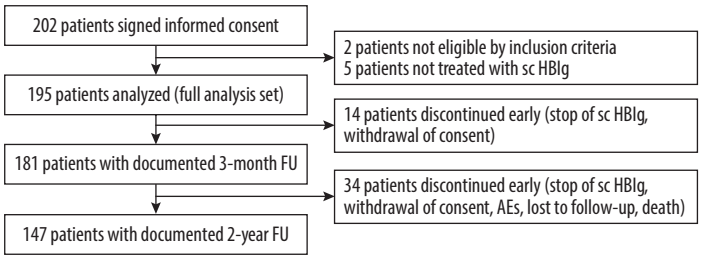

Figure 1. Patient flow chart (Prepared with Microsoft Office 2016).

Table 1. Demographic characteristics and relevant medical history data.

	Full analysis set (N=195)	
Age [years], median (range)	59.0	(19, 81)
Weight [kg]*, median (range)	74.0	(43, 129)
Sex, n (%)		
Male	160	(82.1)
Female	35	(17.9)
MELD score at the time of last LT, mean (±SD)	16.6	(±9.0)
Patients with previous LT, n (%)	14	(7.2)
HBV-related main reason for the last LT, n (%)		
HBV-induced liver cirrhosis	100	(51.3)
HCC	83	(42.6)
HBV-induced fulminant hepatitis	12	(6.2)
Type of transplant, n (%)		
Whole liver	179	(91.8)
Split liver, deceased donor liver transplant	8	(4.1)
Living donor liver transplant	5	(2.6)
Liver and kidney co-transplant	3	(1.5)

	Full analysis set (N=195)	
Histopathological determination of HCC in the explant, n (%)	91	(46.7)
Decompensated liver disease, n (%)	106	(54.5)
Concomitant non-HBV-related liver diseases, n (%)		
Alcoholic liver disease	39	(20.0)
Non-alcoholic steatohepatitis	7	(3.6)
Autoimmune hepatitis	2	(1.0)
Primary sclerosing cholangitis	2	(1.0)
Other	6	(3.1)
Concomitant non-hepatic diseases, n (%)		
Arterial hypertension	38	(19.5)
Diabetes mellitus	34	(17.4)
Kidney disease	26	(13.3)
Allergy	10	(5.1)
Cancer**	3	(1.5)
Viral co-infection, n (%)		
Hepatitis D virus	43	(22.1)
Hepatitis C virus	19	(9.7)
Human immunodeficiency virus	7	(3.6)

* Based on data of 188 patients; ** papillary thyroid carcinoma, prostatic adenocarcinoma, kidney carcinoma. HBV – hepatitis B virus; HCC – hepatocellular carcinoma; LT – liver transplantation; SD – standard deviation.

biweekly (134/195, 68.7%), followed by 500 IU weekly (107/195, 54.9%). Dosage or dosing interval was changed at least once in more than half of the patients (111/195, 56.9%). Most patients (158/195, 81.0%) received a mean daily dose <71.4 IU (averaged over the entire documentation period).

Most Patients received NUCs (159/195, 81.5%; **Table 2**), mainly tenofovir disoproxil (63/159, 38.9%), entecavir (59/159, 37.1%), and/or lamivudine (39/159, 24.5%). In all but 2 patients, immunosuppressive therapy over the entire observation period was documented, most commonly calcineurin inhibitors (BL: 165/195, 85.1%; 3-month FU: 154/181, 85.1%; 2-year FU: 116/147, 79.5%) and mycophenolate mofetil (BL: 131/195, 67.5%; 3-month FU: 123/181, 68.0%, 2-year FU: 93/147, 63.7%).

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Table 2. Post-transplant treatment with sc HBIg, concomitant antiviral medications, and anti-HBs serum levels.

	Full analysis set (N=195)	
sc HBIg:		
Time to first treatment after last LT [months], mean (±SD)	91.7	(±94.1)
Duration of exposure [months], mean (±SD)	20.7	(±7.4)
Average monthly dose [IU]*, mean (±SD)	1171	(±546)
Mean daily dose [IU]*, n (%)		
<71.4	158	(81.0)
71.4 (eq. to 500 IU/week)	33	(16.9)
>71.4	2	(1.0)
Missing information	2	(1.0)
Frequency of dosing regimens**, n (%)		
500 IU weekly	107	(54.9)
500 IU biweekly	134	(68.7)
500 IU every 3 weeks	66	(33.8)
500 IU every 4 weeks/monthly	68	(34.9)
1000 IU weekly	6	(3.1)
1000 IU biweekly	1	(0.5)
1000 IU monthly	10	(5.1)
Other	12	(6.2)
Missing information	1	(0.5)
Number of changes in dosing regimen, n (%)		
None	84	(43.1)
At least 1 change (max. 6 changes)	111	(56.9)
Concomitant antiviral therapy		
Nucleos(t)ide analog (NUC), n (%)	159	(81.5)
iv/im HBIg, n (%)	18	(9.2)
Protease inhibitors, n (%)	2	(1.0)
Integrase inhibitors, n (%)	2	(1.0)

Anti-HBs serum level	3-month FU	2-year FU	FU last
Patients with data available, n	170	112	194
Median (min, max) [IU/L]	199.1 (36, 1000)	144.0 (11, 558)	140.1 (11, 1000)

* Averaged over the entire treatment period of a patient; ** regimens/treatments documented over entire observation period; due to treatment changes, patients may have been counted in more than one category. FU – follow up; HBIg – hepatitis B immunoglobulin; im – intramuscular; IU – international unit; iv – intravenous; LT – liver transplantation; SD – standard deviation.

HBV Recurrence

As shown in **Table 3**, HBV recurrence was observed in 7/195 (3.6%) patients based on seropositivity of HBsAg and/or HBV DNA (corresponding to an annual incidence rate of 2.01%) and in 1/195 (0.5%) patients based on detectable HBV DNA alone. Time to HBV recurrence ranged between 13.1 and 34.6 months. Characteristics of patients with HBV recurrence are presented in **Table 4**. Clinical signs of recurrence were not observed in 2 patients and respective data were missing in the remaining patients. All 7 patients had at least 1 risk factor for HBV recurrence: HCC as main indication for LT (n=7) or positive HBV DNA test at the time of LT (n=1). At the time of recurrence, anti-HBs values were ≥100 IU/L in 3 patients, below this protective threshold in 2 patients, and not available in the remaining 2 patients (but last available values before recurrence were ≥100 IU/L in these patients). All 7 patients received concomitant therapy with a second-generation NUC.

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Table 3. Post-transplant HBV recurrence and HCC recurrence.

	HBV recurrence		HCC recurrence
	Based on HBsAg and/or HBV DNA	Based on HBV DNA only	
Patients, n (%)*/95% CI	7 (3.6)/1.5-7.3%	1 (0.5)/0-2.8%	4 (4.8)/1.3-11.9%
Annual rate	2.01%	0.29%	2.88%
Time to event after LT [months], median (min, max)	18.5 (13.1, 34.6)	34.6	17.5 (12.5, 22.2)

* Based on all 195 patients (HBV recurrence) or 83 patients with HCC as primary indication for LT (HCC recurrence). CI – confidence interval; HBsAg – hepatitis B surface antigen; HBV – hepatitis B virus; HCC – hepatocellular carcinoma; LT – liver transplantation.

Table 4. Characteristics of patients with HBV recurrence.

Patient no.	Time to HBV recurrence [months]	Determination of HBV recurrence			Risk factors before/at time of LT				Antiviral treatment at time of HBV recurrence			HCC recurrence after LT
		Clinical signs	HBsAg [IU/mL]*	HBV DNA [IU/mL]*	Viral co-infection	HBsAg [IU/mL]	HBeAg [IU/mL]	HBV DNA [IU/mL]	sc HBIg dose/ interval	Anti-HBs [IU/L]	NUC	
1	18.5	None	+	ND	None	+	ND	ND	500 IU/ biweekly	108.2	TDV	Yes
2	23.5	None	+	ND	HDV	+	ND	ND	500 IU/ every 10 days	22.6	ETV	No
3	34.6	Not doc	ND	12	None	2156	ND	20	500 IU/ every 5 weeks	167.9	ETV	No
4	21.8	Not doc	+	ND	None	57	NA	ND	500 IU/ weekly	100.1	TDV	Yes
5	13.1	Not doc	28	ND	HDV	8500	ND	ND	500 IU/ biweekly	29	ETV	No
6	15.0	Not doc	199	ND	HDV	NA	ND	ND	500 IU/ monthly	NA	ETV	No
7	13.2	Not doc	+	NA	None	3159	ND	ND	500 IU/ every 3 weeks	NA	TDV	Yes

* Values at time of first identification of HBV recurrence after LT. ETV – entecavir; HBsAg – hepatitis B surface antigen; HBV – hepatitis B virus; HCC – hepatocellular carcinoma; HDV – hepatitis D virus; IU – international unit; LT – liver transplantation; NA – not available; ND – not detectable; Not doc – not documented; NUC – nucleos(t)ide analog; TDV – tenofovir.

HCC Recurrence

HCC recurrence was seen in 4/83 (4.8%) patients with HCC as primary indication for LT (corresponding to an incidence rate per year of 2.88%; **Table 3**). Time to HCC recurrence ranged between 12.5 and 22.2 months. Patient characteristics included pre-transplant bridging therapy with transarterial chemoembolization in all 4 patients and additional radiofrequency ablation in 1 patient. Downstaging to within the Milan criteria was reported in 1 patient, who also had HDV co-infection.

At the time of HCC recurrence, serum anti-HBs was ≥100 IU/L in 1 patient and below this threshold in 2 patients (value not available for 1 patient). All 4 patients received concomitant NUC therapy. Three of 4 patients also developed HBV recurrence, either approximately 3-4 months prior to HCC recurrence (n=2) or approximately 3 months after HCC recurrence (n=1).

Serum Anti-HBs

Adequate anti-HBs levels were detectable in most patients after the start of s.c. HBIg treatment. Median serum levels in

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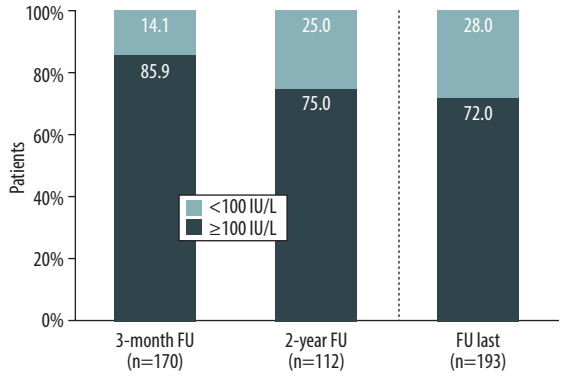

Figure 2. Proportion of patients with serum anti-HBs trough levels at/above or below 100 IU/L under treatment with s.c. HBIg. Percentages are based on patients with quantitative anti-HBs test results available at the respective visits (number in brackets). FU last: last available anti-HBs value documented in a patient (Prepared with Microsoft Office 2016).

those patients with quantitative data available at the 3-month FU, 2-year FU, and FU last were 199 IU/L, 144 IU/L, and 140 IU/L, respectively (**Table 2**). Individual anti-HBs levels were ≥100 IU/L (minimum threshold for effective protection) in over 70% of the patients at the respective documentation time points (**Figure 2**).

Chronic and Acute Rejection Episodes

None of the study patients experienced chronic rejection. Only 1 patient (0.5% of 195, a patients with HBV-HCC) experienced an acute rejection episode during the observation period (approximately 7 months after the last LT and approximately 5 months after the start of s.c. HBIg treatment). The episode was characterized by endothelitis, lymphocytic infiltration in the liver, and bile duct damage leading to graft loss.

Safety

A total of 342 AEs were reported in 111/195 (56.9%) patients. The physicians assessed 133 AEs in 52/195 (26.7%) patients as serious, including 7 events with fatal outcome in 6 patients. None of the fatal AEs were assessed as being related to treatment with s.c. HBIg. Twenty-nine AEs with a possible relationship to s.c. HBIg (ADRs) were reported in 16/195 (8.2%) patients; 12 ADRs were serious in 5/195 (2.6%) patients. AEs and/or ADRs were given as the reason for early NIS discontinuation in 9 patients.

The most frequently documented ADRs were asthenia (1.5%), back pain (1.0%), headache (1.0%), nausea (1.0%), pyrexia (1.0%), and rash pruritic (1.0%); all other reported ADRs were single events (**Table 5**). No ADRs regarding hepatobiliary or renal disorders were reported. Median and mean values of all documented safety laboratory parameters of liver and kidney function remained stable during the observation period. One patient experienced an acute graft rejection episode, which was not related to s.c. HBIg treatment.

Table 5. Summary of adverse drug reactions.

	Full analysis set (N=195)
Number of ADRs	
Total (serious+nonserious)	29
Serious	12
Patients with ADRs, n (%)	
Total (serious+nonserious)	16 (8.2)
Serious	5 (2.6)
ADRs by MedDRA PT, n (%)	
Asthenia	3 (1.5)
Back pain	2 (1.0)
Headache	2 (1.0)
Nausea	2 (1.0)
Pyrexia	2 (1.0)
Rash pruritic	2 (1.0)
Single events:	
Arthralgia, blood pressure increased, decreased appetite, discomfort, dizziness, drug ineffective, erythema, fatigue, hepatitis B antibody abnormal, hepatitis B surface antigen, hernia, muscle injury, myalgia, product dose omission issue, pruritus, vomiting	

ADR – adverse drug reaction (adverse event possibly related to treatment with sc HBIg); MedDRA – Medical Dictionary for Regulatory Activities; PT – preferred term.

Treatment Satisfaction (TSQM-11)

Median scores of all 4 TSQM-11 dimensions were equal to or higher at all post-baseline time points compared to those at the baseline visit. **Figure 3** illustrates baseline and 2-year FU median scores. Treatment satisfaction improved significantly ($P<0.05$) in the convenience and overall satisfaction dimensions at all post-baseline time points, and in the effectiveness dimension only at the 2-year FU. Results of the statistical comparisons vs baseline of adverse effects dimension scores were deemed negligible as they were based on the data from only 2 to 6 patients.

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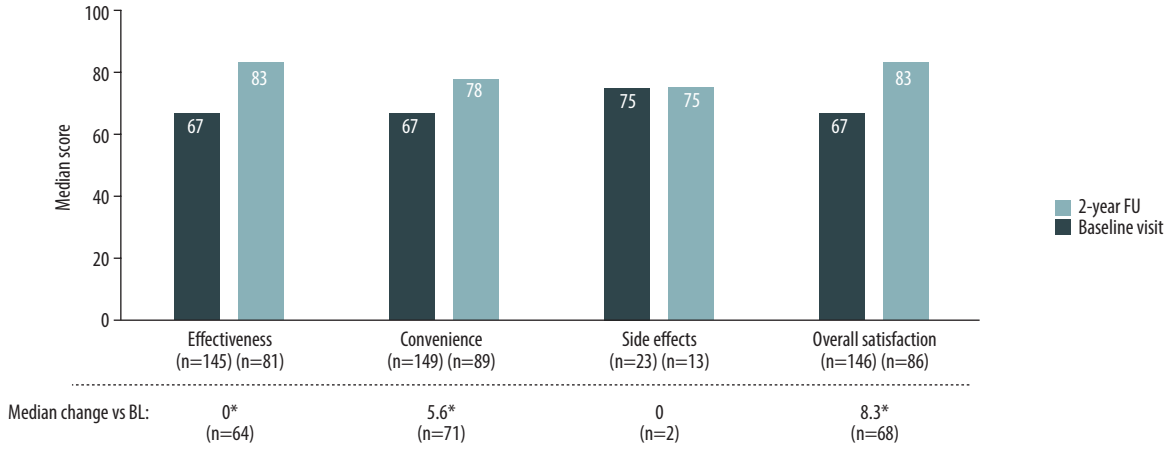

Figure 3. Median scores of the 4 TSQM-11 dimensions at the baseline and 2-year FU visits. Score range: 0 (extremely dissatisfied) to 100 (extremely satisfied). * *P*<0.05 for change vs baseline visit at the 2-year FU (Prepared with Microsoft Office 2016).

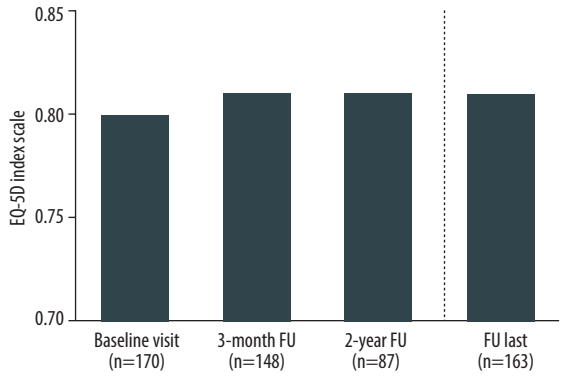

Figure 4. Medians scores of the EQ-5D index (total score). An index of 1.00 corresponds to a perfect health state (Prepared with Microsoft Office 2016).

Quality of Life (EQ-5D)

Self-assessed quality of life was relatively high at treatment start and remained stable throughout the observation period as indicated by median EQ-5D index and VAS scores (**Figure 4**). There were no statistically significant changes from baseline at any post-baseline time point (index: $P \geq 0.075$; VAS: $P \geq 0.1794$).

Figure 5 shows the frequencies of perceived problems at the start and the patients' individual end of the documentation period in all 5 dimensions. The proportions of patients with no problems (level 1) were marginally higher at last FU compared to the baseline visit in each dimension. Patients most frequently experienced no problems in the dimensions 'mobility', 'self-care', 'usual activities', and 'anxiety/depression', with the highest proportion of patients with level 1 answers in the self-care dimension at all time points (>90% of the patients). Some problems (level 2) were most frequently reported in the 'pain/discomfort' dimension (between 44.7% and 50.6%).

Discussion

HBIg combined with NUC therapy has reduced the risk of post-transplant HBV reinfection to <5% [8]. As there is no standardized definition of HBV recurrence, usually 1 or more of the following criteria are applied in published research: reappearance of HBsAg, detectable serum HBV DNA, increase in transaminase levels, or observation of HBV-related graft damage. Depending on the definition used, HBV recurrence rates may vary considerably. In 303 patients under treatment with HBIg and NUC over a median of 12 months, HBV recurrence rates were 1.0% or 0.3% depending on whether recurrence was defined as either HBsAg or HBV DNA positivity [20]. In the current NIS, the annual rate of HBV recurrence was 0.29% if HBV DNA detectability was used as the only criterion compared to 2.01% using a stricter definition (HBsAg and/or HBV DNA positivity). The observed HBV and HCC recurrence rates were lower compared to those found in other recent studies with NUC+HBIg combination therapy or NUC monoprophylaxis [14,21,22] (**Table 6**). The highest recurrence rates were reported under NUC monotherapy. In line with this are the results of a recent meta-analysis showing that HBIg in combination with NUC provides better protection against HBV than therapy with either with HBIg or NUC alone [23].

Treatment with second-generation NUCs achieves considerable suppression of viral replication but usually not a complete viral eradication [1]. A transient HBsAg reappearance after LT may not necessarily indicate HBV recurrence or lead to clinically

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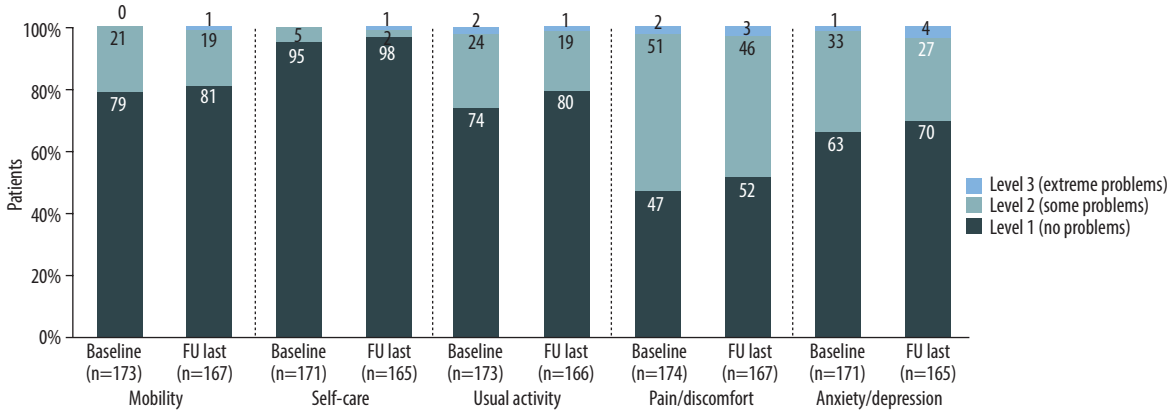

Figure 5. Frequencies of the 3 levels of perceived problems for each of the 5 dimensions of the EQ-5D at baseline (study start) and last FU. Percentages are based on the number of patients with data available for the respective dimension at the respective time point (shown in brackets) (Prepared with Microsoft Office 2016).

Table 6. HBV and HCC recurrence rates after LT under various prophylactic regimens.

Author, year [ref]	Patients, N/n (total/HCC)	Prophylactic treatment	Median duration of follow up, (total/HCC) [months]	HBV recurrence (based on HBsAg and/or HBV DNA) N (%)/AR	HCC recurrence n (%)/AR	Comments
Fung et al, 2017 [21]	242/97	NUC only (entecavir)	59/51	36 (14.9)/3.03%	13 (13.4)/3.15%	Only patients with HBsAg clearance post LT included patients with re-transplantation and/or LAM-resistance excluded
Beckebaum et al, 2018 [14]	371/147	HBIg+NUC	84/67	16 (4.3)/0.65%	14 (9.5)/1.7%	Patients outside the Milan Criteria excluded
Lens et al, 2018 [22]	338/113	HBIg+NUC	72/71.8	37 (11.0)/1.83%	15 (13.3)/2.17%	Patients with short- and long-term HBIg treatment
Current study	195/83	sc HBIg+NUC	24/20.5	7 (3.6)/2.01%	4 (4.8)/2.88%	High variability regarding time to first sc HBIg treatment after LT – from days to years

AR – annual rate; HBIg – hepatitis B immunoglobulin; HCC – hepatocellular carcinoma; LAM – lamivudine; LT – liver transplantation; N – all study patients (total); n – subgroup of patients with HCC at time of LT; NUC – nucleos(t)ide analog.

relevant signs of HBV reinfection [1,20,24,25]. However, post-transplant positivity of HBsAg has been associated with a higher risk of HCC recurrence in transplanted HCC patients [26]. A retrospective chart review showed that HBV-recurrent patients were 3.6 times more likely to develop HCC recurrence than non-HBV-recurrent patients [27]. Vice versa, HCC recurrence was identified as an independent risk factor for HBV recurrence [28]. In our study, 3/4 patients with HCC recurrence also experienced HBV recurrence. All 4 HCC recurrent patients had received pre-transplant bridging therapy and at least 1 patient was downstaged to within Milan criteria. Other factors associated with a higher risk of HBV recurrence include pre-transplant HCC, especially outside the Milan criteria [29-31], the viral load at time of transplantation [32], co-infection with human immunodeficiency virus [33], pre-transplant HBeAg positivity [5], and immunosuppressive therapy [1]. All 7 HBV-recurrent patients in our NIS presented with at least 1 of the above-mentioned risk factors.

In previous clinical trials and 1 previous observational study of s.c. HBIg with/without antiviral therapy, none of the patients (total n=158) developed HBV recurrence based on HBsAg or

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HBV DNA seropositivity during the respective treatment periods of up to 12 months [11-13]. The treatment period of the current study was considerably longer and all cases of HBV recurrence were observed during the second treatment year. Furthermore, dosing of s.c. HBIg in our NIS was overall considerably lower than in the previous studies with s.c. HBIg. In the 18-week observational study in 61 patients, approximately 93% or 87% of the patients received weekly injections of 500 IU or 1000 IU at the first and final study visits, respectively, and the mean weekly s.c. HBIg dose was 589 IU at the final visit [13]. In these studies, anti-HBs levels were above 200 IU/L at all time points [12,13]. In the current NIS, a wider variety of dosing regimens were observed, with a mean monthly dose of 1171 IU averaged over the entire treatment period. The lower dosing is reflected in the decline of median anti-HBs levels and an increase in the proportion of patients with levels below 100 IU/l (eg, 14% at the 3-month FU and 28% at last FU). Nevertheless, the majority of patients (≥70%) with quantitative data available reached adequate anti-HBs levels at all documentation time points, indicating compliance with and suitable dosing of s.c. HBIg in these patients.

Apart from its key role in the prevention of viral reinfection, HBIg may also exert beneficial immune-modulatory effects in liver transplant patients, eg, by inhibiting the differentiation and maturation of dendritic cells involved in allograft rejection [34,35]. The incidence of acute rejection was very low (0.5%) in this study.

The analysis of safety data supported the favorable safety profile of s.c. HBIg established in previous studies [11,12]. The incidence of events with assumed relationship to s.c. HBIg was low (8.2%) and similar to the rate observed in a previous observational study with s.c. HBIg (6.6%) [13]. No new safety signal was identified. The most frequent ADRs observed in clinical investigations so far are injection site reactions (≥1/100 to <1/10) [15], which were not an issue in this NIS. It remains unclear whether they did not occur or, as a well-known and common adverse effect of (self-) injection, were simply not documented.

A favorable adverse effect profile contributes positively to treatment satisfaction, adherence and, ultimately, therapy success. Treatment satisfaction was good throughout the observation period and improved significantly from the baseline visit regarding convenience and overall satisfaction. Most of the patients (>80%) had received i.v. or i.m. HBIg before starting s.c. HBIg treatment over varying periods of time. The switch from these modalities to the potentially more convenient s.c. injections may have contributed to the improvements in the convenience dimension. A recent observational study in patients who had undergone LT 1 year before study entry and switching from i.v. or i.m. HBIg to s.c. HBIg, showed positive effects of the s.c. route on adverse effects, negative feelings, and patient autonomy [36].

The subjectively perceived quality of life may be comparatively high in patients after coming through critical illness and successful LT. The results of the EQ-5D instrument revealed good quality of life at the start of s.c. HBIg treatment, which could be maintained over the entire observation period. Patients most frequently reported problems in the domains 'pain/discomfort' and 'anxiety/depression'. These findings are in line with the results of a longitudinal study in 30 liver transplant recipients showing that these 2 domains contributed to a worse self-perceived health status 1 year after transplantation [37].

Observational studies are prone to some weaknesses, including lack of a comparator group and certain types of bias. In about half of the study patients, the interval between LT and start of s.c. HBIg treatment was longer than 4 years. Thus, there may have been a selection bias towards patients whose condition after transplantation was stable over a long period. The study did not capture whether patients were negative for HBV DNA and HBsAg immediately before the start of s.c. HBIg treatment or whether at that time a stable anti-HBs level of ≥300-500 IU with previous i.v. HBIg was achieved as stipulated in the SmPC [15]. Results of serological tests prior to LT were documented retrospectively without a strict specification of the time point of measurement in relation to the time of LT. Thus, not all of these results may refer to measurements performed in close temporal proximity to the LT. This may explain why approximately 8% of the patients were documented with negative HBsAg prior to LT. However, in a previous retrospective analysis of HBIg treatment in liver transplant patients, a similar proportion of patients was documented with negative HBsAg before LT [14]. Missing data in observational studies may cause under- or overestimation of outcomes. For most study variables, the rate of missing or incomplete data was low. An exception were the serological test results of HBV-related markers. As determination of HBV recurrence was based on the evaluation of HBsAg and/or HBV DNA serum levels, the number of patients with actual HBV recurrence may have been underestimated based on these criteria. On the other hand, other documented data did not suggest any further potential cases of HBV recurrence. For example, physicians were asked to document at each visit whether HBV recurrence occurred since the last visit. Such measures are only possible in prospective studies.

Increasing financial pressure in almost all national health systems results in strenuous efforts for cost reduction. Considerable cost savings have been demonstrated upon switching prophylaxis against HBV from i.v. HBIg to s.c. HBIg in liver transplant patients [38]. Moreover, based on a patient's individual risk profile, individualized treatment regimens may also have positive

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effects on both health and cost outcomes. In our study, we observed a clear tendency for the use of individualized and flexible dosing regimens in daily practice.

Conclusions

Overall, the results of this prospective NIS support the evidence that self-administered s.c. HBIg in combination with NUC therapy is efficacious in the long-term prophylaxis of HBV recurrence in liver transplant patients under real-life conditions. The low HBV recurrence rate was comparable to those found in previous studies with s.c. HBIg/NUC combination therapy and better than those seen under either HBIg or NUC monoprophylaxis. S.c. HBIg was well tolerated over the 2-year treatment period. Its convenience of use may have contributed to the high overall treatment satisfaction and acceptance by the patients. In the light of increased individualization of treatment regimens, identification of high-risk patients and continuous monitoring of viral markers and anti-HBs levels during HBIg therapy seem essential for the prevention of HBV reinfection.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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