ORIGINAL ARTICLE

Personalized subcutaneous administration of hepatitis B surface antibodies without nucleos(t)ide analogs for patients at risk of renal failure after liver transplantation: a prospective single center cohort study

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SUMMARY

Currently, nucleos(t)ide analogs (NAs) in monotherapy are favored as prophylaxis against hepatitis B recurrence after liver transplantation. However, in patients at risk of renal failure, renal safety of NAs is of concern. We investigated the safety and efficacy of subcutaneous (SC) hepatitis B immunoglobulins (HBIG) in monotherapy. This is a single-arm prospective trial in patients transplanted >1 year. We included 43 Caucasian patients. The majority was treated with calcineurin inhibitors, and several patients had other risk factors for renal impairment as well: diabetes mellitus (n = 10/43), arterial hypertension (n = 11/43), and hyperlipidemia (=10/43). At inclusion, 42% (n = 18) had chronic kidney disease ≥ grade 3a. All patients were switched from IV HBIG with or without NAs to SC HBIG without NAs. After one year, the targeted titer was lowered to ≥150 IU/l in patients with low risk of recurrence. Mean follow-up time was 36 ± 5 months. None of the patients had a relapse of HBsAg or HBV DNA. The treatment was well tolerated, safe and the renal function remained unchanged both in patients with (n = 18) or without (n = 25) renal impairment at baseline. The mean HBsAb titer could be decreased from 343 ± 163 to 199 ± 81 IU/l in the low-risk group (n = 17) and 218 ± 71 IU/l in the high-risk group (n = 26). In 86% (n = 37) doses, reductions were possible, which significantly lowered the cost of treatment. SC HBIG without NAs had a 100% success rate in the long-term prevention of HBsAg and HBV DNA reappearance, without deterioration of renal function.

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Introduction

The indication for liver transplantation (LT) due to hepatitis B (HBV) in Europe is 16% and has remained stable over the recent years [1]. Since the introduction of HBV prophylaxis, the long-term outcome for this indication is comparable with outcomes for other indications [1,2]. Until recently, the standard prophylaxis

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was lifelong administration of a combination of hepatitis B immunoglobulins (HBIG) and nucleos(t)ide analogs (NAs) [3]. However, patients with low risk of relapse of HBV post-LT do not need combination therapy and can be treated safely with monotherapy [4–8]. Based especially on cost, there is a tendency to switch to monotherapy with NAs [4,5,8–10]. NAs are cleared by the kidneys and although NAs like tenofovir are usually well tolerated in the treatment for chronic HBV, there is a higher probability of nephrotoxicity in patients at risk of renal impairment, such as patients after LT [11–17]. Indeed after LT, renal dysfunction is one of the most common complication [18–21].

As the regular intravenous (IV) administration of HBIG is inconvenient, some investigators have used intramuscular (IM) injections [22–24]. Recently, subcutaneous (SC) injections were used with high success rates to increase the independency and autonomy of patients [25–28].

In this study, we investigated the value of SC HBIG in monotherapy in the prophylaxis of HBsAg recurrence both in patients with low risk and high risk of HBV recurrence and we focused on the development of nephrotoxicity. In addition, by dosage adjusting based on the HBsAb levels, we explored the optimal dose to reduce the cost.

Patients and methods

Study population

All patients ≥18 years, who had undergone LT more than 1 year before the start of the trial due to HBV, were considered for inclusion. All patients were treated regularly with 10 000 IU IV HBIG whether or not with NAs. To prevent recurrence of HBV after LT, we use the following protocol in our unit: all patients receive a combination of HBIG IV and NA after LT, except if they did not require NA before LT and in this situation only HBIG IV is given; after 1 year, all patients with low risk of recurrence are switched to monotherapy with HBIG IV. At inclusion in the study, the HBsAg and serum HBV DNA were undetectable.

Study design

This is an investigator-driven prospective single-arm trial. Patients who fulfilled the inclusion criteria were switched from IV (Hepacaf®) to SC (Zutectra®) administration of HBIG in monotherapy.

Part I: efficacy and tolerance (year one)

The primary aim of this part was to investigate the efficacy and safety of the treatment following the guidelines of the manufacturer at that time. The dose and the interval of HBIG administration were aimed to keep the HBsAb titer above 200 IU/l in all patients to prevent HBsAg and serum HBV DNA recurrence. The first dosages of Zutectra® were in function of the body weight: patients with body weight <75 kg: 500 IU (1 ml)/week (=1 syringe) and patients with body weight ≥75 kg: 1.000 IU (1 ml)/week (=2 syringes on the same day).

After switch to Zutectra®, the titer of HBsAb was monitored at week 4, month 3, and further every 4 months. In case the titer was higher than the target levels at three successive occasions, a dose reduction was executed, and HBsAb titer was checked again at week 4 and month 3. Also, HBV DNA was monitored every 3–4 months or more frequent if the dosage of Zutectra® changed. Both HBsAb and HBsAg were monitored with the Abbott-Architect assay with a detection limit of <10.0 IU/l and <1.0 COI, respectively. HBV DNA was monitored with Abbott real-time HCV, with a detection limit of <10 HBV IU/ml.

If the patient already received the lowest dose of Zutectra® (500 IU/l per week), the interval of administration was switched from weekly to biweekly.

All patients received a questionnaire regarding how they experienced and tolerated the new therapy in comparison with the previous IV HBIG administration. This was quantified by a VAS score at month 8.

During the whole study, serum creatinine and glomerular filtration rate were monitored strictly, and in case of signs of renal impairment, urine sediment and proteinuria were measured. The size of the kidneys was measured by ultrasonography.

Part II: lowering HBV Ab titer in low-risk patients: toward a more cost-effective treatment (year two)

In the second phase of the trial, we investigated whether the dosage of SC HBIG could be lowered in patients with low risk of viral recurrence. These patients consisted of those without a detectable HBV DNA before LT (without NAs), patients with acute liver failure (ALF) due to hepatitis B, or patients with hepatitis Delta (HDV) coinfection. [6] In this group, the target level of HBV Ab was lowered to ≥150 IU/l to keep HBsAg and HBV DNA levels undetectable. In the high-risk group, the target stayed at ≥200 IU/l.

The study was approved by the ethics committee of University Hospitals Leuven.

Results

During the recruitment period from April 2014 to February 2015, 43 patients were included. They were all of Caucasian origin. Overall, the mean time after LT was 9 ± 6 years (percentiles 3–14 years). The HBV DNA status before LT was spontaneously undetectable in 10 of 43 (23.3%) patients, undetectable with NAs in 15 of 43 (34.9%), and still detectable in 18 of 43 (41.9%). The reason for LT was ALF in four of 43 (9%), and five of 43 (12%) patients were co-infected with HDV. This implied that 60.5% of the patients (26/43) were at higher risk of HBV recurrence. Before LT, 15% (6/41) were HBeAg-positive. Sixteen patients (37%) were transplanted for HCC.

The immunosuppression consisted of tacrolimus + mycophenolate 19/43 (44.2%), tacrolimus alone 15/43 (34.9%), cyclosporine + mycophenolate 4/43 (9.3%), mycophenolate + steroids 3/43 (6.9%), and cyclosporine alone 2/43 (4.7%). Monotherapy with a calcineurin inhibitor 1 year after LT was not possible due to renal impairment in 26/43 (60.5%) of the study population. Of the total patient population, 42% (n = 18) had at least grade 3a chronic kidney disease or higher [29]. Proteinuria was observed in 19%: microproteinuria (6/43) and macroproteinuria (2/43). Ten (23.3%) patients had diabetes mellitus, eleven (25.6%) had arterial hypertension (>140/90 mmHg), and ten (23.3%) had hyperlipidemia (total cholesterol >240 mg/dl or LDL >100 mg/dl) with or without statins at the time of inclusion. The mean follow-up period was 3 years.

The characteristics of the patients with (n = 18) or without (n = 25) renal impairment before LT and at the time of inclusion are given in Table 1. Patients within the renal impairment group were significantly older, and the time from transplantation to inclusion was longer.

Tolerance

All the patients except one continued the SC injections. This patient reported side effects ("not feeling well") which disappeared after reintroducing the IV administration. All the others continued the use of SC HBIG, without experiencing side effects. The compliance was 100%. The majority of these patients preferred the SC administration and reported a VAS score of ≥7/10,

Table 1. Patient characteristics.

	e-GFR >60 ml/min/1.73 m^2	eGFR <60 ml/min/1.73 m^2	
Number of patients	25	18	
Age at time of inclusion	55 ± 10 years	65 ± 8 years	<0.001
Gender			
Male	19/25 (76.0%)	14/18 (77.8%)	0.594
Female	6/25 (24.0%)	4/18 (22.2%)	
Time from liver transplantation	7 ± 5 years (percentiles 1–14)	11 ± 6 years (percentiles 7–14)	0.020
NA therapy before transplantation	21/25 (84.0%)	10/18 (55.6%)	0.044
Interval of IV HBIG administration	8 ± 2 weeks	8.5 ± 2 weeks	0.729
HCC	11/25 (44.0%)	5/18 (27.8%)	0.223
HBV DNA level (IU/ml) at transplantation	1.601.913 ± 2.364.119	3.030.429 ± 2.697.481	0.388
Patients at high risk of HBV recurrence	17/25 (56.0%)	9/18 (50.0%)	0.191
Comorbidity			
Arterial hypertension†	4/25 (16.0%)	7/18 (38.9%)	0.090
Hyperlipidemia‡	5/25 (20.0%)	5/18 (27.8%)	0.406
Diabetes mellitus	6/25 (24.0%)	4/18 (22.2%	0.594
Proteinuria	4/25 (16.0%)	4/18 (22.2%)	0.328
No CNI monotherapy due to renal impairment in the past*	14/25 (56.0%)	15/18 (83.3%)	0.010

NA, nucleos(t)ide analog; IV, intravenous; HBIG, hepatitis B immunoglobulins; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; CNI, calcineurin inhibitor.

For continuous variables, means and standard deviation are given, and for categorical variables, proportions and percentage are given.

†Arterial hypertension: >140/90 mmHg at inclusion with or without antihypertensive therapy.

‡Hyperlipidemia: total cholesterol >240 mg/dl or LDL >100 mg/dl at inclusion, with or without statins.

*Based on the e-GFR level in ml/min/1.73 m^2 before inclusion.

except 2 who felt more convenient with the IV administration and reported a VAS score of, respectively, 3 and 4 but continued the SC HBIG. Two patients died during follow-up (one due to neutropenic sepsis after chemotherapy for HCC and one due to pancreatic cancer). One patient moved to Italy. Immunosuppressive therapy remained unchanged.

Renal function

The evolution of renal function in function of time is given in Fig. 1a. The renal function and the degree of proteinuria remained stable during the follow-up period of 3 years, both in patients with or without renal impairment at inclusion in this study, as is illustrated in Fig. 1b.

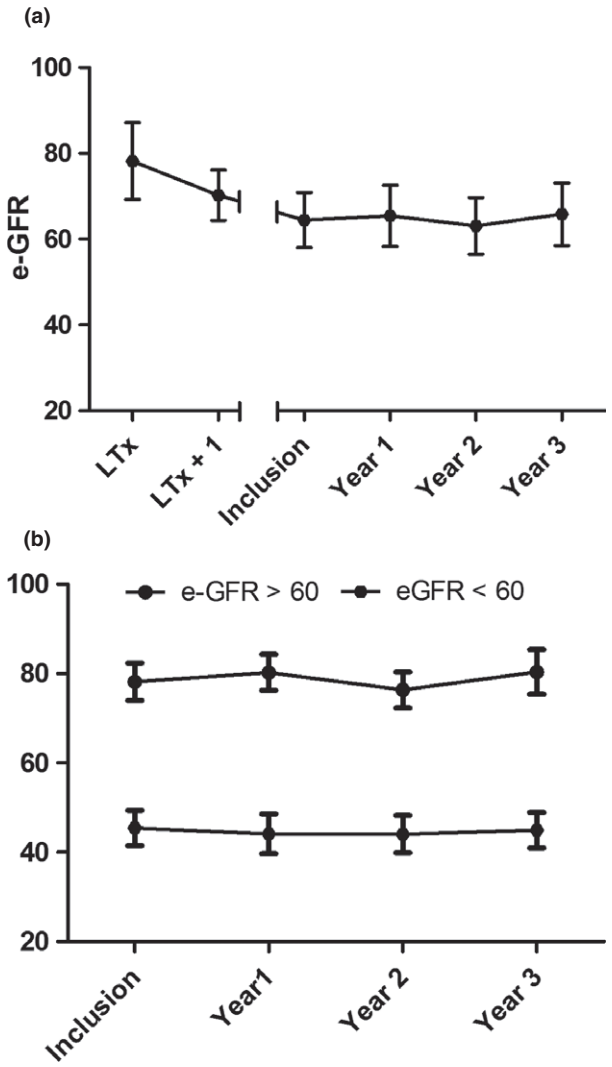

Figure 1 (a and b) There was a steady decline in renal function after liver transplantation, most pronounced during the first year after transplantation. After the start of this trial, the e-GFR level (ml/min/1.73 m^2) remained the same during the follow-up period of 3 years, both in the groups with impaired renal function and normal renal function before inclusion.

Dose reductions

In total, 17 patients (39.5%) belonged to the low-risk group of HBV recurrence. In Fig. 2, the evolution of HBsAb titers is visualized, and five patients dropped temporarily below 150 IU/l in the low-risk group. Ten patients had a temporarily decline below 200 IU/l in the high-risk group. This was corrected by adjusting the dosage interval. None of the patients had a relapse of HBsAg or HBV DNA (Table 2). In 38 patients (86%), dose reductions were possible. The mean frequency of injections reduced from 1 per week (2/w–1/w) to 1 time per 2 weeks (range 2/w–1/5w). Finally, the total dose used per patient per month dropped from 2.769 ± 985 IU/month to 1234 ± 660 IU/month (−55%) ($P = 0.001$).

Discussion

This prospective trial confirmed the safety and efficacy of SC administration of HBIG during a long-term follow-up. In none of the patients, we observed HBsAg positivity or HBV DNA reactivation. Based on patient self-reporting, this treatment was better tolerated compared to IV HBIG administration and was more convenient and caused less discomfort to patients compared to IM administration.

Whether prophylaxis with HBIG should remain the standard therapy is a matter of debate. Data from other regions in the world support the use of NAs in monotherapy in prevention of HBV recurrence after LT [4,5,8–10]. This has become an attractive alternative to HBIG as the price of these medications has been substantially lowered. However, a major concern with the use of NAs is the fact that these compounds are cleared by the kidneys, and renal dysfunction is a frequent complication following LT [18,20,21]. NAs like tenofovir are well tolerated by nontransplanted HBV patients but may induce nephrotoxicity in patients at risk of renal impairment [11–17]. The study population was at risk of renal impairment, as the majority of patients were treated with calcineurin inhibitors, and several of them had comorbidities such as diabetes, arterial hypertension, and hyperlipidemia. Furthermore, a progressive decline in creatinine clearance was observed since the moment of liver transplantation (Fig. 1a). In fact, in our cohort at baseline, 42% ($n = 18$) of the patients had already ≥grade 3a chronic kidney disease. During the 3-year follow-up, renal function was not affected by the HBIGs.

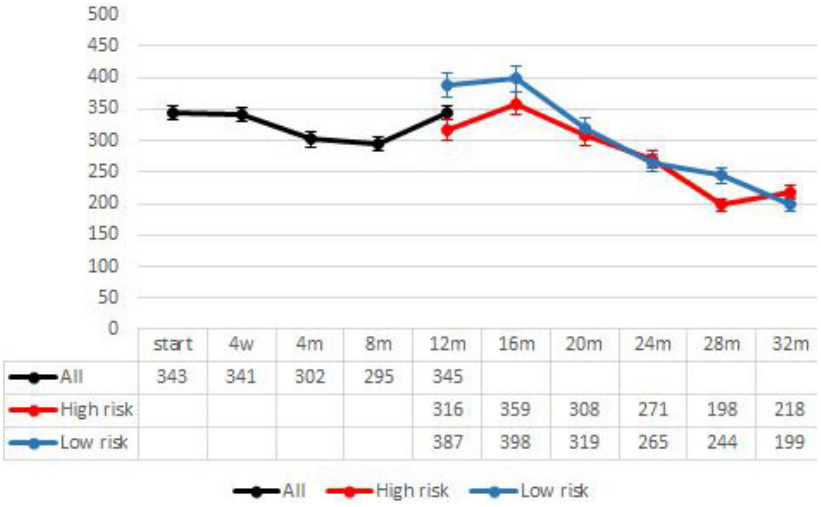

Figure 2 The average titer (±SEM) of HBV surface antibody during the follow-up period. After year 1, this was split up into a low-risk and high-risk groups.

Table 2. Outcome during SC HBIG administration.

Mean follow-up time	36 ± 5 months
Number of patients with HBsAg−	39/39 (100%)
Number of patients with HBV DNA−	39/39 (100%)
Mean dosage of SC HBIG/w (IU/l)	
Start	692 ± 246
End	304 ± 167
Mean interval of SC HBIG administration	
Start	1/w (range: 2/w–1/w)
End	1/2w (range: 2/w–1/5w)
Appreciation of the patient (VAS score)	8/10

HBsAg−, hepatitis B surface antigen-negative; HBV DNA−, hepatitis B deoxyribonucleic acid-negative; SC HBIG, subcutaneous hepatitis B immunoglobulins; IU/l, international units per liter; VAS, visual analog scale.

None of the total of 44 patients had a relapse of HBsAg or HBV DNA, but two patients died during follow-up, one patient was lost to follow-up, and one patient was reintroduced on IV HBIG.

Therefore, a strategy using HBIGs instead of NAs may be safer in high-risk post-transplant patients to prevent renal failure. Obviously, this should be further investigated in randomized trials. In patients with normal renal function, the advantage of HBIG in monotherapy versus NAs is less clear due to the high associated costs. However, renal impairment after LT occurs even in patients with initial GFR >60 ml/min as is illustrated in several prospective studies [5].

It has been advised not to switch to monotherapy in patients at higher risk of HBV recurrence [5]. In our study, 60.5% belonged to this group, but also in these patients keeping the HBsAb above 200 IU/l with monotherapy, HBIG prevented recurrence of HBV disease. Whether the levels of HBsAb used in this study of >150 IU/l in the low-risk patients and >200 IU/l in the high-risk patients are necessary also needs to be further investigated.

Another matter of debate is the importance of HBsAg recurrence. This occurs in NA monotherapy [7,9]. It has been demonstrated that this large protein is oncogenic [30,31]. In this study, 37% of the patients were transplanted for HCC. Therefore, prophylaxis should not only suppress HBV replication but should ideally also neutralize HBsAg production. This strategy is supported by different meta-analyses [32,33]. It has been suggested that the long-term use of NAs is one of the driving forces for mutations in the HBsAg gene and that these mutations possess potential carcinogenic properties [34]. However, this mutation process is based on the development of drug resistance and mutations in the HBV reverse transcriptase (RT) region of the polymerase gene and might be of less importance with the newer generation of NAs. Nevertheless, up to 20% of the patients are noncompliant to long-term oral drug regimens, which increases the risk of viral resistance substantially [35,36]. Furthermore, noncompliance cannot be monitored easily with the use NAs and is often only detected after recurrence of HBsAg positivity. In our study, we monitored the HBsAb levels, reflective of treatment adherence. As only two patients dropped temporarily below the target levels, adherence was considered to be high.

The convenience of self-administration was already demonstrated in earlier trials and confirmed in this trial [26–28].

Titration of the HBsAb titer resulted in a significant dose- and cost reduction. In several patients, the dosage

could be lowered to once per 3 weeks. This lowered the monthly cost far below the cost of HBIG IV.

In conclusion, we confirmed that SC HBIG in monotherapy is highly effective during long-term follow-up after LT, and in this group of patients, the use of NAs is not required even in those at higher risk of recurrence of HBV. HBIG did not affect renal function in our study cohort at risk of renal dysfunction. Finally, personalized administration of SC HBIG offered a considerate reduction in cost.

Authorship

RB: involved in data collection, data analysis and interpretation and drafting the manuscript. GR, DM, SVdM and JP: made critical review of the manuscript. SS: collected the data. FN: involved in conception/design of the project, data analysis and interpretation, drafting the manuscript and critical revision of the manuscript. Guarantor of article. All authors approved the final version of the manuscript, including the authorship list.

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Conflict of interest

Professor Frederik Nevens participated in an advisory board of Biotest AG. All other authors declare no conflict of interest.

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