# 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

Peer-reviewed author version

BIELEN, Rob; ROBAEYS, Geert; Schelfhout, Sigrid; Monbaliu, Diethard; Van der Merwe, Schalk; Pirenne, Jacques & Nevens, Frederik (2018) 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. In: TRANSPLANT INTERNATIONAL, 31 (5), p. 503-509.

DOI: 10.1111/tri.13112
Handle: http://hdl.handle.net/1942/26202

# Personalized subcutaneous administration of hepatitis B surface antibodies without nucleos(t)ide analogues for patients at risk for renal failure after liver transplantation

Bielen Rob, MD[1], Robaeys Geert, MD, PhD[1,2], Schelfhout Sigrid [3], Monbaliu Diethard, MD, PhD[4], Van der Merwe Schalk MD, PhD[3], Pirenne Jacques, MD, PhD[4], Nevens Frederik, MD, PhD[3].

[1] Faculty of Medicine and Life Sciences, Hasselt University, Belgium.

[2] Department of Gastroenterology and Hepatology, Ziekenhuis Oost Limburg, Genk, Belgium.

[3] Department of Gastroenterology & Hepatology, University Hospitals KULeuven, Belgium.

[4] Department of Abdominal Transplant Surgery, University Hospitals KULeuven, Belgium.

Corresponding Author: Rob Bielen

Address: Schiepse Bos 6, 3600 Genk

Email: rob.bielen@uhasselt.be

Word count: **2841** (including tables and figure legends)

**KEYWORDS**

Hepatitis B; Liver transplantation; Immunoglobulin; Nephrotoxicity

## 1. Author's contributions

- Bielen Rob: data collection, data analysis and interpretation, drafting the article

- Robaeys Geert: critical revision of the article

- Sigrid Schelfhout: data collection

- Monbaliu Diethard: critical revision of the article

- Van der Merwe Schalk: critical revision of the article

- Pirenne Jacques: critical revision of the article

- Nevens Frederik: conception/design of the project, data analysis and interpretation, drafting the article, critical revision of the article. Guarantor of article.

All authors approved the final version of the article, including the authorship list.

## 2. Disclosures

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

## 3. Funding

The authors received no funding for this work.

**ABSTRACT**

Currently, nucleos(t)ide analogues (NAs) in monotherapy are favored as prophylaxis against Hepatitis B recurrence after liver transplantation. However, in patients at risk for 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±5months. 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±163IU/l 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.

## 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 was lifelong administration of a combination of hepatitis B immunoglobulins (HBIG) and nucleos(t)ide analogues (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 for 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 the present study we investigated the value of SC HBIG in monotherapy in the prophylaxis of HBsAg recurrence both in patients with low 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 in order 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 one 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 was aimed to keep the HBsAb titer above 200 IU/l in all patients in order to prevent HBsAg and serum HBV DNA recurrence. The first dosages of Zutectra® was 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 3 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 <10.0I U/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: towards a more cost-effective treatment (year two)

In the second phase of the trial, we investigated if 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 ≥200IU/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 10/43 (23.3%) patients, undetectable with NAs in 15/43 (34.9%) and still detectable in 18/43 (41.9%). The reason for LT was ALF in 4/43 (9%) and 5/43 (12%) patients were co-infected with HDV. This implied that 60.5 % of the patients (26/43) were at higher risk for 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%: micro proteinuria (6/43) and macro proteinuria (2/43). Ten (23.3%) patients had diabetes mellitus, eleven (25.6%) had arterial hypertension (>140/90mmHg) and ten (23.3%) had hyperlipidemia (total cholesterol >240mg/dl or LDL >100mg/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 $\geq$ 7/10, 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 Figure 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 Figure 1b.

Dose reductions:

In total, 17 patients (39.5%) belonged to the low risk group of HBV recurrence. In Figure 2 the evolution of HBsAb titers are visualized, 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 -1/5 w). 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 since 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 non-transplanted HBV patients, but may induce nephrotoxicity in patients at risk for renal impairment [11-17] The study population was at risk for renal impairment, since 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 (Figure 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. 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 vs. NAs is less clear due to the high associated costs. However, renal impairment after LT occurs even in patients with initial GFR >60 ml/minute as is illustrated in several prospective studies. [5]

It has been advised not to switch to monotherapy in patients at higher risk for 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 non-compliant to long-term oral drug regimens, which increases the risk of viral resistance substantially.[35, 36] Furthermore, non-compliance 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 three 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 for recurrence of HBV. HBIG did not affect renal function in our study cohort at risk for renal dysfunction. Finally, personalized administration of SC HBIG offered a considerate reduction of cost.

## ACKNOWLEDGEMENTS

This study is part of the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the foundation Limburg Sterk Merk, province of Limburg, Flemish government, Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital. Schalk van der Merwe is holds a Flemish senior researcher mandate (FWO klinische mandaat). All authors approved the final version of the article, including the authorship list.

## REFERENCES

1 Burra P, Germani G, Adam R, *et al.* Liver transplantation for HBV-related cirrhosis in Europe: an ELTR study on evolution and outcomes. *J Hepatol* 2013; **58:** 287-96.

2 Pauwelyn K, Cassiman D, Laleman W, *et al.* Outcomes of long-term administration of intravenous hepatitis B immunoglobulins for the prevention of recurrent hepatitis B after liver transplantation. *Transplant Proc* 2010; **42:** 4399-402.

3 Katz LH, Tur-Kaspa R, Guy DG, Paul M. Lamivudine or adefovir dipivoxil alone or combined with immunoglobulin for preventing hepatitis B recurrence after liver transplantation. *Cochrane Database Syst Rev* 2010**:** CD006005.

4 Fung J, Cheung C, Chan SC, *et al.* Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. *Gastroenterology* 2011; **141:** 1212-9.

5 EASL Clinical Practice Guidelines: Liver transplantation. *J hepatol* 2016; **64**: 433-485.

6 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:** 1321-34.

7 Wang P, Tam N, Wang H, *et al.* Is hepatitis B immunoglobulin necessary in prophylaxis of hepatitis B recurrence after liver transplantation? A meta-analysis. *PLoS One* 2014; **9:** e104480.

8 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:** 353-62.

9 Gane EJ, Patterson S, Strasser SI, McCaughan GW, Angus PW. Combination of lamivudine and adefovir without hepatitis B immune globulin is safe and effective prophylaxis against hepatitis B virus recurrence in hepatitis B surface antigen-positive liver transplant candidates. *Liver Transpl* 2013; **19:** 268-74.

10 Radhakrishnan K, Chi A, Quan DJ, Roberts JP, Terrault NA. Short Course of Postoperative Hepatitis B Immunoglobulin Plus Antivirals Prevents Reinfection of Liver Transplant Recipients. *Transplantation* 2017; **101:** 2079-82.

11 Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. *Hepatology* 2009; **49:** S185-95.

12 Lok AS. Drug therapy: tenofovir. *Hepatology* 2010; **52:** 743-7.

13 Marcellin P, Zoulim F, Hezode C, *et al.* Effectiveness and Safety of Tenofovir Disoproxil Fumarate in Chronic Hepatitis B: A 3-Year, Prospective, Real-World Study in France. *Dig Dis Sci* 2016; **61:** 3072-83.

14 Lampertico P, Chan HL, Janssen HL, Strasser SI, Schindler R, Berg T. Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. *Aliment Pharmacol Ther* 2016; **44:** 16-34.

15 Kayaaslan B, Guner R. Adverse effects of oral antiviral therapy in chronic hepatitis B. *World J Hepatol* 2017; **9:** 227-41.

16 Fung S, Kwan P, Fabri M, *et al.* Tenofovir disoproxil fumarate (TDF) vs. emtricitabine (FTC)/TDF in lamivudine resistant hepatitis B: A 5-year randomised study. *J Hepatol* 2017; **66:** 11-8.

17 Petersen J, Heyne R, Mauss S, *et al.* Effectiveness and Safety of Tenofovir Disoproxil Fumarate in Chronic Hepatitis B: A 3-Year Prospective Field Practice Study in Germany. *Dig Dis Sci* 2016; **61:** 3061-71.

18 Ojo AO, Held PJ, Port FK, *et al.* Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; **349:** 931-40.

19 Ruiz R, Barri YM, Jennings LW, *et al.* Hepatorenal syndrome: a proposal for kidney after liver transplantation (KALT). *Liver Transpl* 2007; **13:** 838-43.

20 Morard I, Mentha G, Spahr L, *et al.* Long-term renal function after liver transplantation is related to calcineurin inhibitors blood levels. *Clin Transplant* 2006; **20:** 96-101.

21 De Simone P, Metselaar HJ, Fischer L, *et al.* Conversion from a calcineurin inhibitor to everolimus therapy in maintenance liver transplant recipients: a prospective, randomized, multicenter trial. *Liver Transpl* 2009; **15:** 1262-9.

22 Faust D, Rabenau HF, Allwinn R, Caspary WF, Zeuzem S. Cost-effective and safe ambulatory long-term immunoprophylaxis with intramuscular instead of intravenous hepatitis B immunoglobulin to prevent reinfection after orthotopic liver transplantation. *Clin Transplant* 2003; **17:** 254-8.

23 Marzano A, Marengo A, Andreone P, *et al.* Pharmacokinetics and efficacy of intravenous or intramuscular hepatitis B immunoglobulins in prophylaxis of hepatitis B after liver transplantation. *Minerva Med* 2010; **101:** 373-83.

24 Gane EJ, Angus PW, Strasser S, *et al.* Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. *Gastroenterology* 2007; **132:** 931-7.

25 Thürmann PA SJ, Haffner S, Tenter U, Grieger F, Sonnenburg C. . Pharmacokinetics and safety of a novel anti-HBs enriched immunoglobulin in healthy volunteers after subcutaneous and intramuscular administration. *Eur J Clin Pharmacol* 2006; **62:** 511–2.

26 Singham J, Greanya ED, Lau K, Erb SR, Partovi N, Yoshida EM. Efficacy of maintenance subcutaneous hepatitis B immune globulin (HBIG) post-transplant for prophylaxis against hepatitis B recurrence. *Ann Hepatol* 2010; **9:** 166-71.

27 Yahyazadeh A, Beckebaum S, Cicinnati V, *et al.* Efficacy and safety of subcutaneous human HBV-immunoglobulin (Zutectra) in liver transplantation: an open, prospective, single-arm phase III study. *Transpl Int* 2011; **24:** 441-50.

28 Di Costanzo GG, Lanza AG, Picciotto FP, *et al.* Safety and efficacy of subcutaneous hepatitis B immunoglobulin after liver transplantation: an open single-arm prospective study. *Am J Transplant* 2013; **13:** 348-52.

29 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013; 3: 1–150.

30 Liu H, Xu J, Zhou L, *et al.* Hepatitis B virus large surface antigen promotes liver carcinogenesis by activating the Src/PI3K/Akt pathway. *Cancer Res* 2011; **71:** 7547-57.

31 Salpini R, Surdo M, Warner N, *et al.* Novel HBsAg mutations correlate with hepatocellular carcinoma, hamper HBsAg secretion and promote cell proliferation in vitro. *Oncotarget* 2017; **8:** 15704-15.

32 Qu LS, Liu JX, Zhang HF, Zhu J, Lu CH. Effect of serum hepatitis B surface antigen levels on predicting the clinical outcomes of chronic hepatitis B infection: A meta-analysis. *Hepatol Res* 2014.

33 Liu F, Wang XW, Chen L, Hu P, Ren H, Hu HD. Systematic review with meta-analysis: development of hepatocellular carcinoma in chronic hepatitis B patients with hepatitis B surface antigen seroclearance. *Aliment Pharmacol Ther* 2016; **43:** 1253-61.

34 Wang ML, Tang H. Nucleos(t)ide analogues causes HBV S gene mutations and carcinogenesis. *Hepatobiliary Pancreat Dis Int* 2016; **15:** 579-86.

35 Kamezaki H, Kanda T, Arai M, *et al.* Adherence to medication is a more important contributor to viral breakthrough in chronic hepatitis B patients treated with entecavir than in those with Lamivudine. *Int J Med Sci* 2013; **10:** 567-74.

36 Chotiyaputta W, Hongthanakorn C, Oberhelman K, Fontana RJ, Licari T, Lok AS. Adherence to nucleos(t)ide analogues for chronic hepatitis B in clinical practice and correlation with virological breakthroughs. *J Viral Hepat* 2012; **19:** 205-12.

## TABLES

**Table 1: Patient characteristics**

| | e-GFR >60ml/min/1.73m² | eGFR <60ml/min/1.73m² | |
|---|---|---|---|
| **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 (1) | 4/25 (16.0%) | 7/18 (38.9%) | 0.090 |
| Hyperlipidemia (2) | 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 |

For continuous variables, means and standard deviation, for categorical variables proportions and percentage are given. NA: nucleos(t)ide analogue, IV: intravenous, HBIG: hepatitis B immunoglobulins HCC: hepatocellular carcinoma. HBV: hepatitis B virus, CNI: calcineurin inhibitor.

(1) Based on the e-GFR level in ml/min/1,73m² before inclusion

(2) Arterial hypertension: >140/90mmHg at inclusion with or without antihypertensive therapy

(3) Hyperlipidemia: total cholesterol >240mg/dl or LDL > 100mg/dl at inclusion, with or without statins

**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 analogue 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.

## FIGURE LEGEND

Figure 1a and 1b:

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/1.73m$^2$) 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.

Figure 2:

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

Figures

Figure 1a

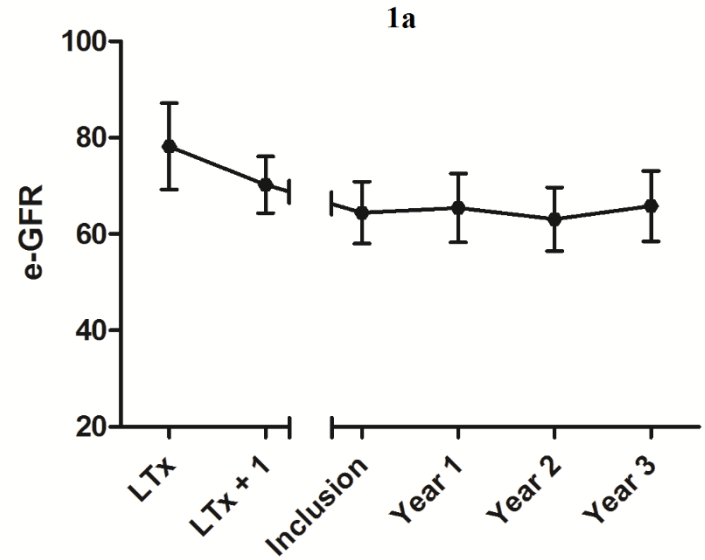



Figure 1b

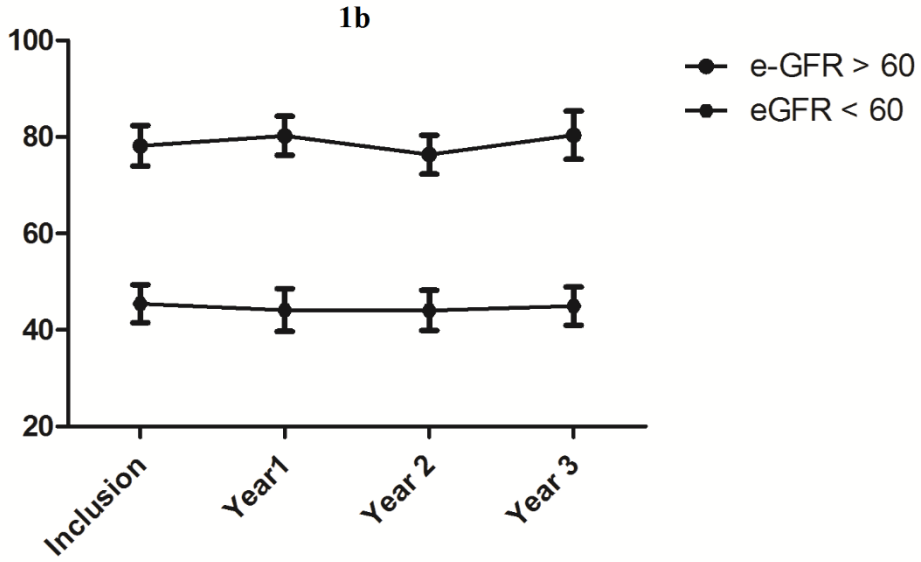
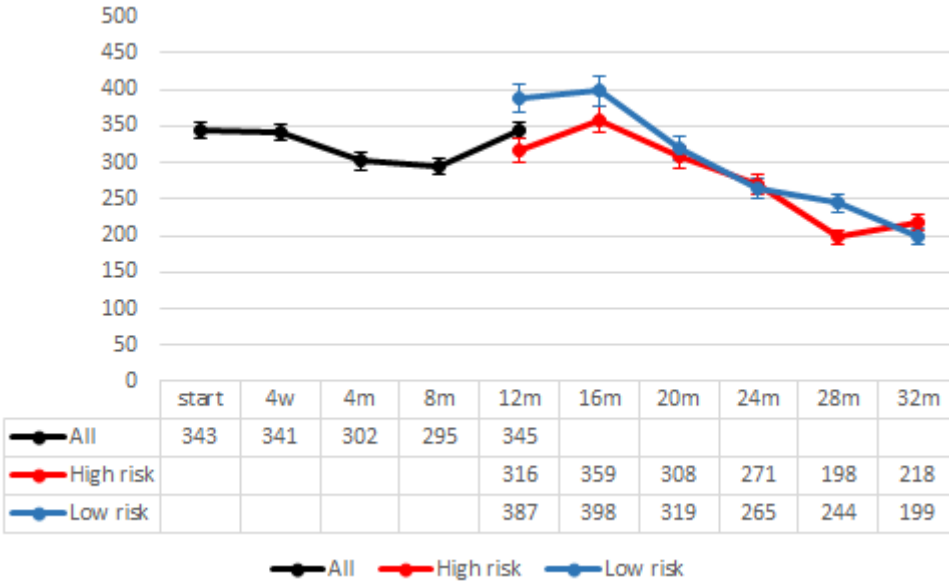


Figure 2




| | start | 4w | 4m | 8m | 12m | 16m | 20m | 24m | 28m | 32m |
|---|---|---|---|---|---|---|---|---|---|---|
| All | 343 | 341 | 302 | 295 | 345 | | | | | |
| High risk | | | | | 316 | 359 | 308 | 271 | 198 | 218 |
| Low risk | | | | | 387 | 398 | 319 | 265 | 244 | 199 |