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Hepatitis B Immunoglobulin discontinuation in long-term liver transplant patients

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Abstract

Background: Hepatitis B immunoglobulin (HBIG)—as a monotherapy or combined with nucleos(t)ide analogs (NUCs)—has effectively lowered Hepatitis B virus (HBV) reinfection after liver transplantation. However, it is associated with high costs and viral resistance. HBIG-free prophylaxis with novel NUCs (tenofovir, entecavir) composes a viable alternative. We evaluated reinfection rate, histological changes, and outcome associated with HBIG discontinuation.

Methods: A retrospective analysis was performed of patients undergoing liver transplantation due to HBV-induced liver disease at our center since 1988. A controlled HBIG discontinuation was conducted between 2015 and 2017 in 65 patients. Recurrent infection was determined by HbsAg values. Fibrosis and inflammation were evaluated by routine biopsy. The survival of patients after HBIG discontinuation was compared to a control population on HBIG for prophylaxis.

Results: From 1988 to 2013, 352 patients underwent liver transplantation due to HBV-induced liver disease. 169 patients could be included for analysis. 104 (51.5%) patients continued a prophylaxis containing HBIG. HBIG was discontinued in 65 (38.5%) patients in a controlled manner, maintaining an oral NUC. None of those patients showed HBV reinfection or graft dysfunction. No significant changes of inflammation grades (P = .067) or fibrosis stages (P = .051) were detected. The survival of patients after HBIG discontinuation was comparable to the control (P = .95).

Conclusion: HBIG withdrawal under continuation of oral NUC therapy is safe and not related to graft dysfunction, based on blood tests and histology. HBIG-free prophylaxis is not associated with a worse outcome and displays a financial relief as well as a logistic simplification during long-term follow-up.

KEYWORDS

antiviral agents, end-stage liver disease, HBV recurrence, infectious disease

1 | INTRODUCTION

Hepatitis B virus (HBV) infection still represents a major health concern, with a prevalence of 2% in Western countries and 8% in West Africa.[1] Chronic HBV infection shows a high morbidity and mortality due to severe complications such as liver cirrhosis and hepatocellular carcinoma (HCC).[2] Liver transplantation (LT) is the only curative treatment for patients suffering from the end stage of HBV-associated liver cirrhosis.[3] The lack of infectious prophylaxis and simultaneous immunosuppression generated high rates of HBV reinfection in those highly unimmunized patients post-LT due to circulating or extrahepatic HBV particles and increasing the risk of transplant fibrosis or cirrhosis.[4,5]

The introduction of hepatitis B immunoglobulin (HBIG), a polyclonal antibody against the surface antigen of HBV, that binds virions and neutralizes them, reduced the incidence of post-LT HBV infection and improved graft and patient survival back in the nineties.[5] However, monotherapy led to high rates of HBV recurrence due to the development of viral resistance and formation of hepatitis B surface antigen (HbsAg) escape mutants during long-term follow-up. For a long time, combination therapies with HBIG and oral antiviral nucleos(t)ide analogs (NUC), mostly lamivudine, were considered as a standard of care in post-transplant protocols. This therapeutic option was able to prevent recurrent infection in more than 90% of liver recipients. However, HBIG is a severe burden to health economics, requiring parenteral or subcutaneous administration and frequent hospital visits, negatively affecting the patients' quality of life. Moreover, lamivudine has also been associated with the development of viral resistance.[6]

The establishment of modern and more potent third generation NUCs such as entecavir and tenofovir advanced attempts of HBIG-free antiviral treatment as prophylaxis against HBV reinfection. Nevertheless, a standardized protocol has not been established yet, because of limited patient cohorts and short-term follow-ups.

This study aimed to address the potential risk for reinfection after standardized weaning from HBIG in patients who had undergone LT due to HBV-induced liver disease. Secondary endpoints were histopathological changes after HBIG withdrawal as well as on the overall survival.

2 | METHODS

This study is a retrospective single-center cohort study that included transplanted patients withdrawn from a reinfection prophylaxis with HBIG in a controlled manner since the beginning of 2015. In January 2015, we started to withdraw patients from HBIG at our outpatients' department to improve and modernize the standard of care. Patients were discontinued in chronological way as they were seen in our outpatient's department for routine check examinations. Therefore, the first 65 patients with HBV-related LT on HBIG prophylaxis, seen in sequence at our outpatient's department for a routine check, were withdrawn from HBIG. No evaluation about a high or low risk according current criteria was performed for our patient's selection. Patients, who were withdrawn, were monitored by frequent blood controls measuring serology and HBV-DNA for 6 weeks and prophylaxis with a NUC. Patients on HBIG in combination with a NUC continued prophylaxis with the NUC (lamivudine or entecavir/tenofovir). Patients on a prior monotherapy with HBIG received lamivudine after discontinuation. The study was performed retrospectively according to the Professional Code of the German Medical Association (article B.III.§15) based on the World Medical Association´s Declaration of Helsinki.

Three hundred and seventy-two liver transplantations due to HBV-associated liver disease were performed in 352 patients at our clinic since the year 1988 until 2013. In case of retransplantation, the last LT was considered for analysis. All patients were administered HBIG and a low- or high-potential NUC as part of a standardized prophylaxis protocol against recurrent HBV reinfection after LT. 183 patients were excluded due to former death, loss of follow-up, or HBV reinfection with consecutive HBIG discontinuation before 2015. Of 169 patients, 65 received a controlled discontinuation of HBIG during follow-up ("No HBIG") as described above. 104 patients continued prophylaxis with HBIG ("control") with or without a combined NUC (Figure 1). HBIG was generally administered by iv application every 6 weeks at our outpatient's department.

Data were retrospectively collected from the clinical digital database concerning age, gender, date of HBIG discontinuation, date of death, cause of death, stage of liver graft fibrosis prior to, and after discontinuation of HBIG, modified reinfection prophylaxis, and clinical events after protocol modification. 56 biopsies and histopathological findings prior and after discontinuation of HBIG were evaluated. Biopsies were routinely taken at our center after 1, 3, 5, and 7 years after LT and furthermore every 2-3 years according to the routine check examination. HBIG withdrawal was always initiated after one of those routine check examinations, and the biopsy of the last check examination was determined to be the one before, whereas the next following check examination was counted as the biopsy after HBIG withdrawal. Determination of the grade of fibrosis was based on the classification by Desmet and Scheuer. (0 = no fibrosis, 1 = mild fibrosis, 2 = medium fibrosis, 3 = moderate fibrosis, and 4 = severe fibrosis). Inflammation was graded according to the classification by Desmet (1 = minimal, 2 = mild, 3 = moderate, and 4 = severe).

To determine the effects of the modified reinfection prophylaxis and the occurrences after HBIG discontinuation, medical reports and medical history documents were carefully evaluated. Adverse events were defined as worsening graft function, graft failure, and hepatic complications (eg, increased transaminases, biliary tract infections). The total follow-up in years was defined as the time between the date of the last LT and the 01.06.2019. The period between HBIG administration and discontinuation was given in years and was determined based on LT date and the date of discontinuation. The overall survival for both groups was calculated from the beginning of this study in January 2015 until June 2019.

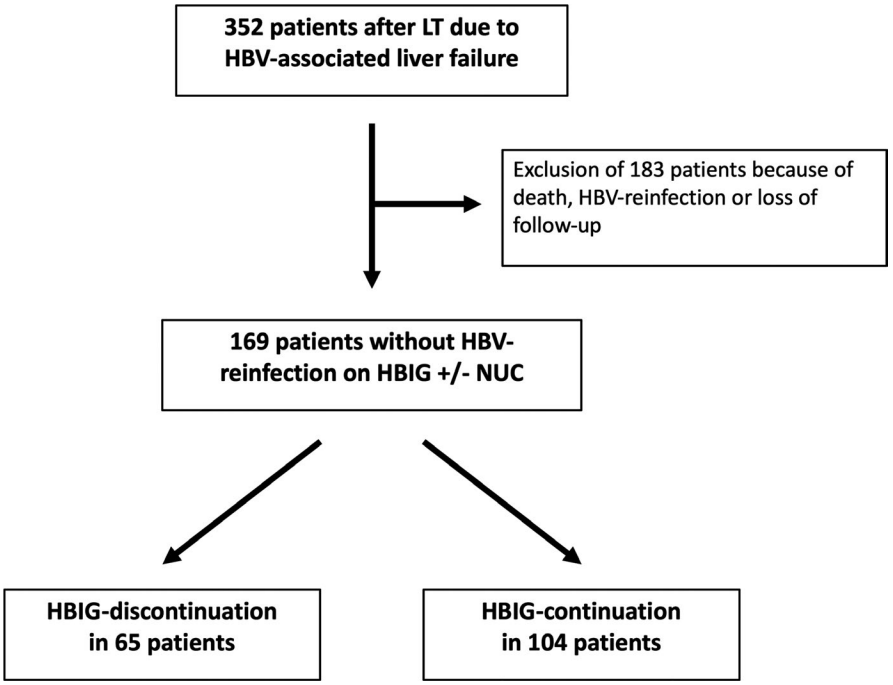

FIGURE 1 Inclusion of patients. 372 liver transplantations in 352 patients were performed at our clinic due to HBV-associated liver disease. 181 patients were excluded due to death or HBV-reinfection. In 65 out of 169 patients, HBIG was withdrawn (since 2015). 104 patients continued with HBIG and or NUC as HBV reinfection prophylaxis

The rate of recurrent infections following HBIG discontinuation was the primary endpoint of our study. Reinfection was defined as a reappearance of HbsAg or HBV-DNA subsequent to HBIG withdrawal. In case of a reactive titer, HBV-DNA-PCR was used as a confirmatory test. Secondary endpoints were the difference in grade of fibrosis and inflammation taken from the histopathological reports of the last routine biopsy prior to, and after HBIG discontinuation as well as the difference in survival between patients with and without HBIG.

Statistical analyses were performed using SPSS version 25 (IBM Statistics 25) for Windows. Metric, non-normalized data such as age, duration of HBIG administration after LT, and time after discontinuation of HBIG are reported as median, minimum, and maximum. Nominal variables are given as frequencies and percentages. The Wilcoxon test was applied and tested for asymptotic significance (2-sided) for two related samples. Cross-tabulations were used for nominal data. Survival was analyzed by the Kaplan-Meier method, and the significance was determined using the log rank test. A *P* value below .05 was considered statistically significant, and the confidence interval was 95%. Figures were established by PowerPoint (Microsoft® PowerPoint for MAC, Version 16.31).

3 | RESULTS

3.1 | Demographic data

From 1988 to 2013, 372 liver transplantations in 352 patients were performed at our clinic due to acute or chronic HBV-induced liver disease. 169 patients could be included into analysis. In 65 (38.5%) patients, HBIG was discontinued in a controlled manner since 2015, followed by regular serological (HbsAg and HBV-DNA) and laboratory controls in a 6-week rhythm. Demographic data are given in Table 1. The median age of patients in the group "No HBIG" was 54 years (22-71), 49 (75.4%) were male and 16 (24.6%) were female. Among the control group, we found a median age of 48 years (11-68), 49 (75.4%) male and 16 (24.6%) female patients. There was a significant difference between both groups concerning the age at LT ($P = .048$) but not for gender ($P > .99$). The median follow-up time since LT was 14 years (5-28) in the "No HBIG" group and 21 years (6-29) "control" group ($P = .19$).

Within the "No HBIG" group, 40 patients (61.5%) underwent LT for HBV-associated liver cirrhosis, while an HCC was found in 17 explants (26.2%). 6 patients (9.2%) presented with HBV-induced acute liver failure. 2 patients (3.1%) had been retransplanted due to an uncontrolled HBV reinfection and severe cholangiopathy in the early 90s. Among the controls, 68 (65.4%) showed HBV-associated liver cirrhosis and 18 (17.3%) a simultaneous HCC. 15 (14.4%) presented with an acute liver failure due to HBV infection, and 3 (2.9%) patients underwent retransplantation on the grounds of HBV reinfection of the graft. There was no significant difference between both groups ($P = .48$) concerning the indication for transplant. Hepatitis D (HDV) coinfection at the time of LT was found in 5 patients (7.9%) of "No HBIG" and in 22 (21.8%) of the control ($P = .03$). There was no HIV coinfection in any groups.

All of those 65 patients with HBIG discontinuation and 102 out of 104 (98.1%) patients of the control received HBIG during the anhepatic period of transplantation ($P = .52$).

All patients received 10 000 units HBIG during the anhepatic period of transplantation, followed by the combination of HBIG and NUC in the most cases. 34 patients (32.7%) of the control group and 7 (10.8%) patients of "No HBIG" received HBIG monotherapy for prophylaxis after LT, 62 (59.6%) of "control" and 46 (70.8%) of "No HBIG" HBIG in combination with lamivudine and 8 (7.8%) of

TABLE 1 Demographic characteristics of patient cohort (n = 171) on age, sex, follow-up time, HBIG administration after LT, LT indication, HDV coinfection, type of reinfection prophylaxis, re-LT, reinfection rate, and mortality

	No HBIG (n = 65)	control (n = 101)	
Median Age at LT in years; (Min.–Max.)	54 (22-71)	48 (11-68)	0.048
Gender; n (%)			0.99
male	49 (75.4%)	78 (75.0%)	
female	16 (24.6%)	26 (25.0%)	
Median follow-up in years since LT; (Min.–Max.)	14 (5-28)	21 (6-29)	0.18
Indication for LT; n (%)			0.48
HBV–acute liver failure	6 (9.2%)	15 (14.4%)	
HBV–cirrhosis	40 (61.5%)	68 (65.4%)	
HBV–hepatocellular carcinoma	17 (26.2%)	18 (17.3%)	
Retransplantation at HBV-Reinfection	2 (3.1%)	3 (10.7%)	
HDV-Coinfection; n (%)	5 (7.9%)	22 (21.8%)	0.03
HBIG during LT; n (%)	65 (100%)	102 (98.1%)	0.52
Long-term HBV-Prophylaxis; n (%)			0.01
HBIG monotherapy	6 (9.2%)	34 (32.7%)	
HBIG + lamivudine	59 (90.8%)	62 (59.6%)	
HBIG + entecavir or tenofovir	12 (18.5%)	8 (7.8%)	
Median HBIG-therapy post LT in years; (Min.–Max.)	11 (3-26)	21 (0-29)	0.32

Abbreviations: HBIG, hepatitis B immunoglobulin (n = 169); HBV, hepatitis B virus; HDV, hepatitis D virus; LT, liver transplantation.

"control" and 12 (18.5%) of "No HBIG" HBIG combined with entecavir or tenofovir (P = .01). HBIG had been administered for a median time period of 11 years (3-26) in the group of discontinuation and 21 years (0-29) in the control group (P = .318). The shortest treatment period was 36 months (3 years), and the longest one was 316 months (26 years).

3.2 | Evaluation of histopathology

Liver biopsies of 64 patients prior to and 56 biopsies after HBIG discontinuation were evaluated according to the stage of fibrosis and grade of inflammation (Figure 2). With regard to fibrosis, stages from 0 (no fibrosis) to 3 (severe fibrosis) were detected. Prior to HBIG discontinuation, 15 patients (22.7%) were diagnosed with fibrosis stage 0, 35 patients (53.0%) with stage 1, 12 patients (18.2%) with stage 2, and 2 (3.0%) with stage 3. After HBIG discontinuation, 16 patients (24.7%) were diagnosed with fibrosis stage 0, 24 patients (36.4%) with stage 1, 11 patients (16.7%) with stage 2, and 5 (7.6%) with stage 3 (Figure 1). 43.9% of the patients remained constant concerning the stage of fibrosis whereas 21.2% developed an increase and 19.7% a decrease of fibrosis stage. According to the Wilcoxon rank test, there was no statistically significant difference in the distribution of fibrosis stages before and after HBIG discontinuation (P = .051). 32 patients (48.5%) showed inflammation grade 0, 12 (18.2%) grade 1, 18 (27.3%) grade 2, and 2 (3.0%) grade 3 prior to HBIG discontinuation (Figure 2). After HBIG discontinuation, 30 patients (45.5%) showed inflammation grade 0, 10 (15.2%) grade 1, and 16 (24.2%) grade 2 with no significant change in the distribution (P = .067, Figure 2). 43.9% of the patients had no change in the grade of inflammation, 13.6% declined, and 27.3% improved.

3.3 | Outcome and survival

In 58 out of 65 (89.2%)—no clinical events were reported following HBIG discontinuation. However, in 7 (10.8%), unusual adverse events occurred (Table 2). One patient (1.5%) was diagnosed with a hepatitis E virus infection and later developed pneumonia. 3 patients (4.6%) showed elevated transaminases or cholestasis parameters. But, none of the patients suffered complications due to recurrent

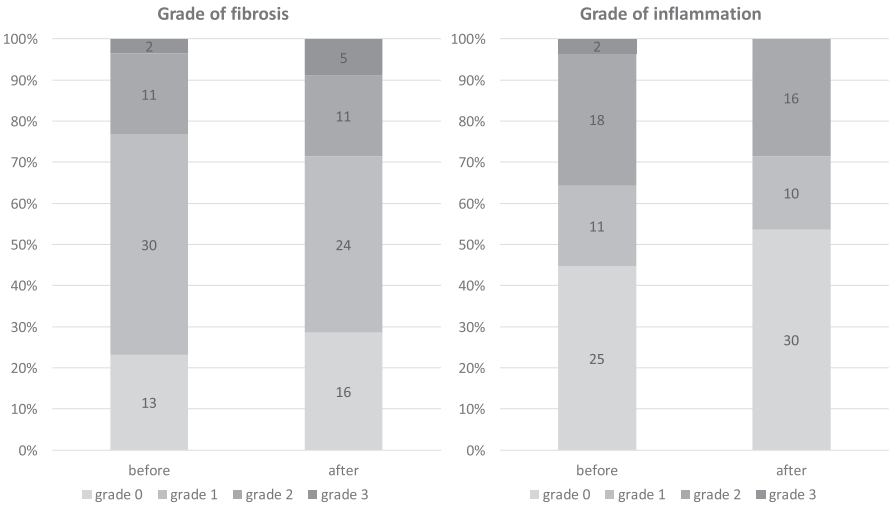

FIGURE 2 Evaluation of histopathology. Graph displays percentage of different gradings concerning fibrosis and inflammation before and after HBIG withdrawal. (fibrosis: n = 64 before discontinuation; n = 28 after discontinuation; inflammation: n = 63 before discontinuation; and n = 27 after discontinuation)

TABLE 2 Schematic display of complications after HBIG discontinuation

	No HBIG (n = 65)	control (n = 104)	*P*-value
Reinfection rate; n (%)	-	-	-
Adverse events	-	-	-
Mortality; n (%)	7 (10.8%)	13 (12.5%)	.99
HCC recurrence	-	1 (1.0%)	
Malignancy	-	1 (1.0%)	
Infection	-	2 (1.9%)	
Cardiovascular	4 (57.1%)	2 (1.9%)	
Multiorgan Failure	2 (28.6%)	5 (4.8%)	
Unknown	1 (14.3%)	2 (1.9%)	

Abbreviations: HBIG, hepatitis B immunoglobulin; HCC, hepatocellular carcinoma (n = 169).

HBV infection. 7 patients (10.8%) died during the observation period in the discontinuation group, none of them due to a recurrent HBV infection. The most common cause of death was heart failure (57.1%). Another patient passed away after septic multiorgan failure. Table 2 provides a more in depth look into the various causes of death. In the control group, 13 patients died during the period from 2015 until 2019, most of them because of septic multiorgan failure and cardiovascular disease. There was no significant difference between both groups ($P > .99$). There was no significant difference in survival among patients with (49.1 months CI 95% 46.8-51.3) and without HBIG (60.0 months CI 95% 48.3-52.5, $P = .95$, Figure 3). No one out of 65 patients showed a positive HbsAg titer during the median follow-up period of 51 (4-53) months. Thus, no patient developed recurrent infection after HBIG discontinuation (0%). In 3 patients, the last HbsAg was reactive. However, the negative HBV-DNA-PCR ruled out recurrent infection.

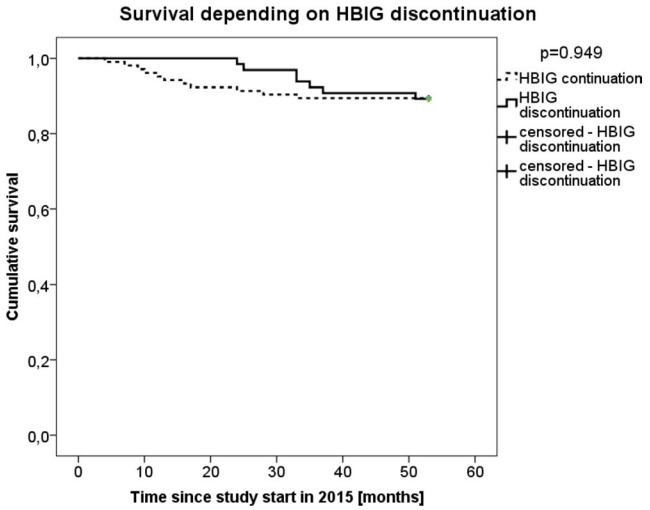

FIGURE 3 Survival depending on HBIG discontinuation. Kaplan-Mayer-Analysis: estimated survival between the group of patients with HBIG continuation and discontinuation was without significant difference ($P = .949$). Time is given from the beginning of the study in 2015 (n = 169)

Following the discontinuation of HBIG, all patients were treated with oral NUCs as part of the antiviral prophylaxis. 39 patients (65%) received lamivudine, while 21 patients (35%) were treated by other high-potential NUCs (entecavir or tenofovir). 5 deceased patients took lamivudine and 2 deceased patients entecavir.

4 | DISCUSSION

HBIG withdrawal from prophylaxis protocols against HBV recurrence after LT has been a substantial topic of research for a long time. Before the implementation of antiviral medication, the reinfection rate was almost 100% and the two-year survival approximately 50%.[6-10] The administration of HBIG and modern antivirals significantly raised survival rates over 75% and decreased HBV recurrence to <10%.[6,7,10-14] The single application of HBIG bares the risk of HBV recurrence in up to 60% due to escape variants of HBV.[15,16] Different studies supported the hypotheses that HBIG exerts an immune pressure on HBV, which induces mutations in the genome and HBV surface antigen, if the genome is present after LT.[17,18] Despite the reported effectiveness of a combined application of high-dose HBIG and NUCs, the use of HBIG became more and more controversial not only because of viral resistance. A cost-effectiveness analysis of 2006 summed up the yearly treatment costs of HBIG from $50 000 to $70 000.[19] A combination of lamivudine and intravenous HBIG costs up to $526 000 after 5 years, while a combination of lamivudine and intramuscular HBIG would be $139 000.[19] Translating these data to the patients included in our study, the costs for a combination therapy of intravenous HBIG and a NUC would amount up to 1.15 Million dollars. Australian researchers have compared HBIG costs to those of adefovir or lamivudine in 2008 and supposed HBIG-free reinfection prophylaxis as a cheaper treatment with similar efficacy. Furthermore, HBIG-based prophylaxis lowers the patient's quality of life, as intravenous application requires medical staff and regular visits. In contrast, patients with intramuscular injections achieved a higher quality of life, but an oral reinfection prophylaxis is the most comfortable and flexible alternative.[20,21]

However, the discussion about antivirals to use for mono- or combination therapies is still ongoing and combined prophylaxis against HBV reinfection based on HBIG have been a standard protocol in various transplant centers for a long time. There are numerous studies to support HBIG discontinuation and monotherapy with oral antivirals. However, existing data are still limited, mostly because of small patient numbers. A randomized study by Buti et al showed in 32 patients that monotherapy with lamivudine had been as effective as the combination therapy with lamivudine and HBIG.[22] Gane et al could also show that either a short perioperative application of HBIG followed by an antiviral prophylaxis without regular HBIG applications, as well as a complete perioperative abstaining of HBIG, did not lead to HBV recurrence during a follow-up of 22 months (n = 26 and n = 18).[23] Therapies based on highly potential NUCs such

as entecavir, adefovir, and combination therapies of lamivudine and tenofovir achieved similar results.[24-27] Fung et al reported about 265 patients on entecavir prophylaxis without reinfection, during a follow-up period of 8 years.[24,25] The study further stated that not only in Hong Kong, where a moderate HBV prevalence (5%-7%) is registered, but also in the USA, with a HBV prevalence of <2% same results could be achieved.[1,18,28] However, even if some study protocols embraced a prospective character and randomization, reported patient numbers are still small beside the trial of Fung et al and a standardized universal guideline is still missing.[26,27] We were able to provide retrospective data on another 65 patients who were withdrawn in a controlled manner and evaluated for reinfection rate, graft dysfunction, histopathological changes, and outcome. As we had withdrawn the first 65 in a chronological order from the beginning of 2015 by clinical routine, we did not perform a specific selection of patients according to an individual risk profile which might have been done in a prospective trial. It has previously been observed that patients with cirrhosis as well as HCC, immunosuppression (eg, HIV), HBeAg positive status, HDV seronegative status, and high HBV virus load at the time of LT are considered to be at a higher risk for HBV recurrence after LT.[29-31]

We present a very heterogenous group of patients from the real world with a diverse risk profile. HBV recurrence among our withdrawn patients, even in those with a higher risk profile as described above, was not observed. A specific analysis of each risk factor at this point would not be reasonable due to a relatively small number of patients in every subgroup (regarding HCC, HDV coinfection). This might be performed after discontinuation of the total cohort and a higher number of patients have been recruited. Theoretically, there is no reasonable explanation for the higher tendency for HBV reinfection in patients with HCC as assumed.

After HBIG discontinuation, all patients continued with a NUC (either lamivudine or entecavir/tenofovir) of the former combination therapy. In case of a HBIG monotherapy that indeed was historically efficient in a smaller proportion of patients, the mode of prophylaxis was changed to lamivudine mono. Most patients maintained a stable graft function. However, complications not related to HBV reinfection were present in a small proportion of patients comparable to the control. HBIG continuation and withdrawal did not show any significant differences in survival, and the overall mortality rate of the total cohort was low. Former studies showed high survival rates of 85% after a period of 9 years after consequent antiviral prophylaxis.[18,22,24]

Additionally, we report about a save discontinuation of 5 patients with an HDV coinfection. HDV coinfection is still discussed as a risk factor for HBV recurrence after LT especially in the absence of adequate prophylaxis or proper adjustment of HBIG.[32-37] Cholongitas et al could show HBV/HDV recurrence in 5.8% of 34 patients after HBIG discontinuation and proposed that HBIG sparing prophylaxis could be safe during the long-term follow-up but might depend on the period of time of HBIG administration after LT.[38] Therefore, HBIG-free prophylaxis in patients with HDV coinfection might be safe especially if a highly potent NUC is used prophylactically. Further controlled studies are necessary to deliver a scientific proof and standard recommendation.

Furthermore, we attempted to deliver histological data on the dynamics associated with HBIG discontinuation. 43.9% remained stable concerning the grade of fibrosis or inflammation. There was an improvement of the stage of fibrosis in 19.7% and of the grade of inflammation in 27.3%, whereas 21.2% showed an aggravated fibrotic stage and 13.6% an impaired inflammation grade after HBIG discontinuation, but without significance. One reason might be that the follow-up period (51 (4-53) months) after HBIG discontinuation was currently too short to show histopathological changes, because the process of fibrogenesis is generally slow. Secondly, as the biopsy was performed percutaneously by a core needle, the amount of tissue is small and the area it was taken from might have varied to the former biopsy. However, these results support those of another retrospective analysis by Fung et al showing that only 17% of the liver grafts on a HBIG-free mono-therapeutic prophylaxis post LT displayed signs of fibrosis. Moreover, patients with a positive HbsAg and a negative HBV-DNA showed a very low rate of fibrosis.[39]

In relation to the previously mentioned mutations of the HBV genome, the extent in which a long-term oral antiviral monotherapy with NUCs leads to an increased resistance of the virus remains critical. Especially lamivudine has been associated with the induction of novel HBV mutations, thus explaining the time dependent possibility of reinfection. Bartholomew et al showed recurrence in 3 patients, who received lamivudine as reinfection prophylaxis. The DNA sequencing of these patients yielded a mutation in YMDD locus of the HBV-DNA polymerase.[40] Thus, more potent NUCs such as entecavir and tenofovir were taken into consideration. Matteo et al evaluated reinfection, renal side effects, and patient survival of patients on monotherapy with entecavir or tenofovir for a follow-up period of 5 years. The study demonstrated no HBV reinfection, no major clinical events or side effects, and no deaths, providing strong evidence that a monoprophylaxis with entecavir and tenofovir is safe and effective and not associated with viral resistance or reinfection.[41] In our study, lamivudine monotherapy showed no significant differences in survival when compared to other highly potent NUCs. Despite former studies on the lower efficacy of lamivudine in comparison to for example entecavir, we would administer lamivudine and escalate to entecavir or tenofovir in case of serological changes due to good tolerance and cost-effectiveness.[42]

The question about the duration of HBIG use is still discussed.[4,32,43,44] We have discontinued HBIG after a median administration period of 11 (3-26) years, and all patients received a perioperative dosage during surgery. Recent studies showed effectiveness of short-term application for 5 days in combination with an antiviral long-term therapy as well as perioperative infusions in combination with entecavir.[32,45,46] Hu et al provided promising data on a prophylaxis with entecavir and on-demand HBIG.[32,47] Therefore, the HBIG-free approach can be advocated.[32] Intraoperative infusion of HBIG, especially in patients still being positive for HBs-Ag at the moment of LT in combination with a potent NUC, is reasonable steps in prevention of HBV reinfection. In our view, the long-term

application of HBIG cannot be recommended generally, but critically reserved for high risk patients for HBV reinfection.

On the other hand, the meaning of HBV reinfection has substantially changed from the early 90s with no possibilities to handle the reinfection to the era with efficient NUCs being able to successfully control HBV replication thus avoiding uncontrolled inflammation, fibrogenesis, and graft loss.

The limitation of the present study is the relatively short follow-up after HBIG discontinuation with a median follow-up of 51 months, on the other hand being long enough to state, that no clinical, biochemical, virological, and histological event associated with HBV occurs.

Lacking histological changes in 56 cases before and after HBIG discontinuation may be a part of the short follow-up. However, we reported previously that a slight progression of fibrosis was observed in a cohort of 112 patients without formal HBV reinfection receiving NUC and HBIG as prophylaxis long term after LT that can be attributed to various factors unrelated to HBV. This is a retrospective study on HBV-prophylaxis modes, of course with all limitations of a single-center approach.[6] As we included only patients who were discontinued after 2015 in a non-randomized manner with an obviously stable graft function and excluded all patients with HBV recurrence and major HBV-associated complications before 2015, there might be bias in the analyses. Nevertheless, we did not find HBV recurrence or severe graft dysfunction or HBV-related complications during follow-up. A longer observation period, as well as prospective and randomized approach from the beginning of the post-transplant period, may be useful to find a more definitive answer.

HBIG withdrawal under continuation of oral NUCs does not implicate any health disadvantages and is secure and effective for liver transplant patients during long-term follow-up. HBV reinfection does not occur in NUC-based monoprophylaxis and does not lead to any significant impairment of graft histology and patient survival after LT.

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CONFLICT OF INTEREST

All authors declare that they do not have any conflict of interest related to the presented work.

AUTHOR'S CONTRIBUTION

E. Dobrindt, D. Eurich, and J. Pratschke were involved in the conception of the work. A. Saipbaev and A. Gillespie supported the acquisition of the data, whereas E. Keshi and Y. Salim performed the final analysis of the data. E. Dobrindt, W. Schöning, and R. Öllinger helped for interpretation of the data. E. Dobrindt, A. Saipbaev, E. Keshi, and W. Schöning drafted the final manuscript. D. Eurich, J. Pratschke, A. Gillespie, and R. Öllinger critically revised the first draft for important intellectual content. All authors approved the final version before publication and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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