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의학박사 학위논문

B 형간염 바이러스 부하와 B 형간염 면역글로  
불린의 체내 반감기를 고려한 간이식 후  
B 형간염 예방 프로토콜의 최적화

Individualized optimization of post-transplant hepatitis B  
prophylaxis with hepatitis B Immunoglobulin using  
pharmacokinetic half-life simulation

울산대학교 대학원

의 학 과

정 용 규

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이 논문을 의학박사 학위 논문으로 제출함

2018년 12월

울산대학교 대학원

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2018 년 12 월

## Abstract

**Backgrounds:** Prophylaxis for hepatitis B virus (HBV) recurrence is essential after liver transplantation (LT) in HBV-associated recipients. This study was intended to establish individualized HBV prophylaxis protocol to optimize hepatitis B immunoglobulin (HBIG) administration with application of simulative half-life (SHL).

**Methods:** This study consisted of 5 parts: Part 1 was designed to develop SHL estimation method with 20 patients; Parts 2 and 3 were to assess variability of SHL and to develop a simulation model to apply SHL with 100 patients; Part 4 was to validate simulation model with 114 patients; and Part 5 was a cross-sectional study on current status of HBIG infusion intervals with 660 patients.

**Results:** In Part 1, add-on rise of anti-HBs titer from infusion of 10,000 IU HBIG and means SHL were  $5252.5 \pm 873.7$  IU/L and  $20.0 \pm 3.7$  days respectively, which was 4.4% lower and 2.2% longer than those from actual measurement. In Part 2, the median values of intra-and inter-individual coefficient of variation were 13.5% and 18.5%, respectively. Pre-transplant HBV DNA load and post-transplant antiviral therapy did not affect SHL. In Part 3, a simulation model was developed to determine the interval of HBIG infusion by using SHL. In Part 4, all 114 patients were successfully managed with regular HBIG infusion intervals of  $\geq 8$  weeks and the interval was prolonged to  $\geq 12$  weeks in 89.4% with target trough anti-HBs titer  $\geq 200$  IU/L. In Part 5, 47.4% of our patients received HBIG excessively at a target trough titer of 500 IU/L.

**Conclusions:** SHL estimation using clinically available parameters seems to be reliably accurate comparing with results from actual measurement. We believe that SHL estimation is helpful to establish personalized HBV prophylaxis protocol to optimize HBIG administration.

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## **Abbreviations**

Anti-HBs, antibody to hepatitis B surface antigen; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PK, pharmacokinetic; HNCT, hepatitis B immunoglobulin-nucleos(t)ide analogue combination therapy; LT, liver transplantation; NA, nucleos(t)ide analogue; PK, pharmacokinetic; SHL, simulative half-life; SVR, sustained virological response.



## Introduction

Prophylaxis for hepatitis B virus (HBV) recurrence is essential after liver transplantation (LT) in patients who had been infected with HBV. Many institution-based protocols for post-LT HBV prophylaxis include treatment with hepatitis B immunoglobulin (HBIG) and/or antiviral nucleos(t)ide analog (NA) administration.<sup>(1-4)</sup>

Periodic administration of HBIG is a long-lasting prophylaxis regimen. Although clinically effective, it has several demerits, including high financial cost, cumbersome route of administration, occasional occurrence of HBIG-associated adverse events, and development of resistant viral mutations.<sup>(1,2,5,6)</sup> HBIG monotherapy is primarily based on lifelong maintenance of a high hepatitis B surface antibody (anti-HBs) trough level, which is financially costly and necessitates short intervals of HBIG administration.<sup>(7)</sup> To enhance the prophylactic efficacy and reduce the financial cost, combination therapy with HBIG and NA has been preferred, in which the target trough level of anti-HBs can be significantly lowered. Recently, HBIG-free or HBIG-sparing prophylaxis regimens are also reported to be cost-effective.<sup>(8,9)</sup>

To achieve high cost-effectiveness during HBIG–NA combination therapy (HNCT), the intervals and doses of periodic HBIG administration should be adjusted individually after pharmacokinetic (PK) measurement of the half-life of exogenously administered HBIG. However, in practice, these doses have been crudely determined by the institutional protocols or physicians' personal experience because it is not practical to measure the PK half-life of HBIG in every LT recipient. As a result, HBIG has often been administered more frequently and in higher amounts than required, in a considerably large number of LT recipients.

It is hardly possible to estimate the *in vivo* half-life of exogenous HBIG without meticulous PK studies requiring multiple blood samplings. To replace the actually measured

half-life of exogenous HBIG, we developed a simplified simulative method to estimate the half-life, which we have termed the simulative half-life (SHL). This method requires only clinically available parameters, including gender, body weight, hematocrit, interval period of HBIG administration, and trough anti-HBs titer. Thus, there is no need to perform any other PK measurement in the usual practice at the outpatient clinic.

This study intended to establish an individualized HBV prophylaxis protocol, through optimization of the intervals of HBIG administration, with the application of SHL estimation.

## **Patients and Methods**

### **Study scheme**

This study consisted of five parts as follows: The Part 1 study was designed to develop the SHL estimation method, which included a small-volume (n = 20; cohort 1) PK study to compare the HBIG half-life between the actual PK measurement and SHL estimation; the Part 2 study was to assess the long-term inter-and intra-individual variability of the SHL retrospectively using a single-center cohort (n = 100; cohort 2); the Part 3 study was to develop a simulation model to apply SHL using the the abovementioned single-center cohort (cohort 2); the Part 4 study was to validate the results of the simulation model using another single-center cohort (n = 114; cohort 3); and the Part 5 was a cross-sectional study to reveal the actual status of HBIG infusion intervals in a high-volume single-center cohort (n = 660; cohort 4). This study protocol was approved by the Institutional Review Board at Asan Medical Center (IRB No.2014-0465 and 2018-0739).

### **Patient selection**

Since all study patients should be indicated for HBV prophylaxis using HBIG

administration, the selection criteria for the cohorts 1 to 4 included patient age at LT  $\geq 18$  years; positive for hepatitis B surface antigen (HBsAg) before LT; absence of hepatitis C virus co-infection; regular administration of HBIG with or without NA; no development of hepatocellular carcinoma (HCC) recurrence or de novo malignancy; and regular administration of HBIG and anti-HBs measurement at every visit to the outpatient clinic of our institution.

For Part 1 of the study, we randomly selected 20 patients who passed 1–10 years after LT (cohort 1) because we experienced that the intervals of HBIG administration during long-term follow-up was usually determined after post-transplant 1-2 years. They underwent LT between January 2008 and December 2015 at our institution. They were temporarily admitted due to various causes other than HCC recurrence and liver function abnormality. After informed consent, the peak serum anti-HBs titer was actually measured 6–24 hours after intravenous infusion of 10,000 IU HBIG.

For Parts 2 and 3 of the investigation, we randomly selected 100 patients who passed 7–8 years after LT (cohort 2), thus they underwent LT between January 2010 and December 2011 at our institution. This cohort 2 was used to assess the long-term intra- and inter-individual variability in simulative half-life of exogenous HBIG and to develop a simulation model using SHL.

For Part 4 of this study, we have recruited  $>150$  patients who passed 5 years of LT without any eventful episode and have performed a prospective study to prolong the intervals of HBIG infusion to 12 weeks (94 days) with target trough anti-HBs titer of 200 IU/L since January 2016. Of them, we selected 114 patients who have observed the the study protocol for  $\geq 2$  years (cohort 3) until June 2018 as an interim analysis.

For Part 5 of this investigation, we selected 660 patients who have passed 5–14 years after LT and followed up regularly only at our institution (cohort 4). We excluded the patients who had any considerable co-morbidity except for diabetes mellitus, hypertension and renal

dysfunction. Using this study cohort 4, we conducted a cross-sectional study to reveal the current status of HBIG infusion intervals at our institution, during 3 months between June 2018 and August 2018. We excluded the patients who were included in study cohorts 1-3, so no patient was overlapped in all four study cohorts.

### **Institutional protocol for post-LT HBV prophylaxis**

At our institution, HBIG of 10,000 IU was infused during the anhepatic phase, daily during the first week, once weekly for the next one month, and once monthly thereafter. After the first 1 year of LT, the interval period between regular HBIG infusions was gradually prolonged toward 8-12 weeks on a patient-by-patient basis to maintain a trough serum anti-HBs titer  $\geq 500$  IU/L. There are two highly purified HBIG types available in Korea (HepaBig, Green Cross Co., Seoul, Korea; and Hepabulin, SK Plasma Co., Seoul, Korea), which safely enable rapid intravenous infusion of 10,000 IU within 30-60 minutes after dilution. A high-genetic barrier NA (entecavir or tenofovir) has often been added as an HNCT, especially, in LT recipients showing rapid HBIG consumption or risk of HCC recurrence.<sup>(10,11)</sup>

### **Simulative PK study to assess half-life of exogenous HBIG**

The purpose of Part 1 of this study was to develop PK formulae of half-life, using only clinically available parameters, through simulative PK analyses.

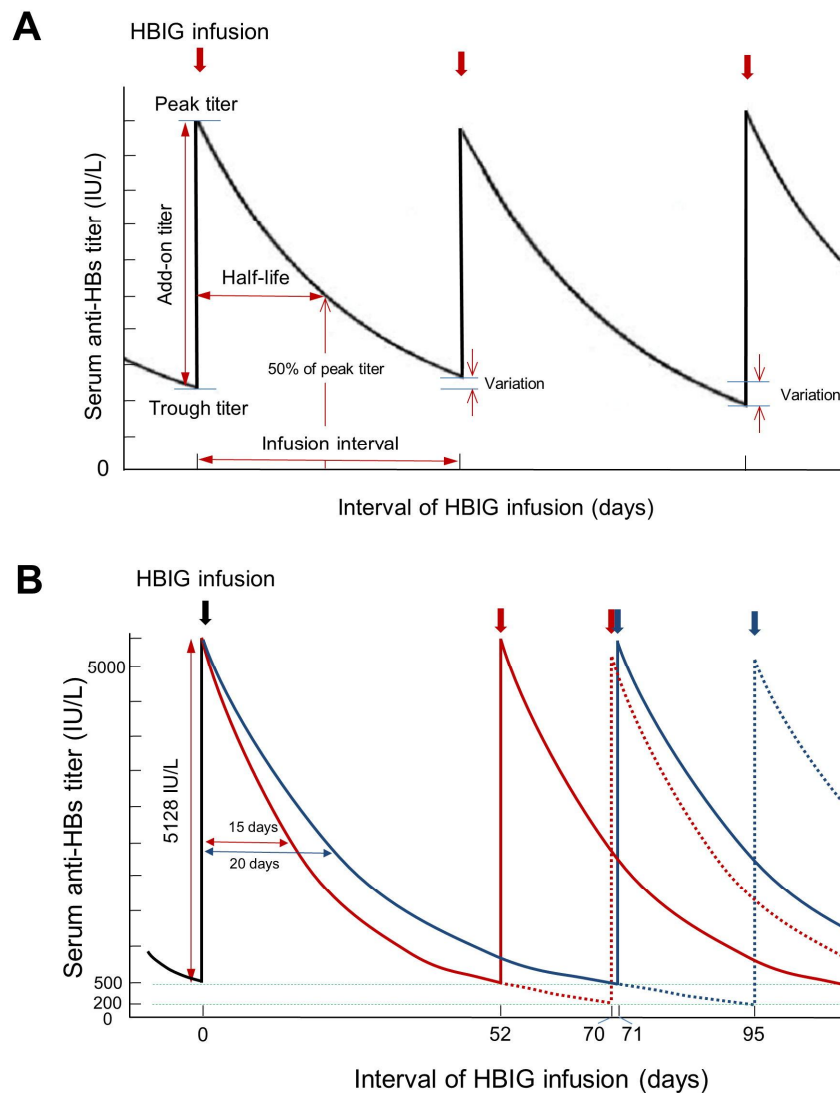
The peak anti-HBs titer shortly after HBIG infusion is not measured in routine clinical practice, but it can be roughly estimated as follows because HBIG is primarily distributed within the blood and only a small proportion is dispersed into the interstitial fluid: "Amount of HBIG infused (IU) is divided by blood volume (L)". Total body water = 60% (male) or 50% (female) of body weight; Extracellular fluid = total body water / 3; Interstitial fluid = total body water  $\times$  0.25; Intravascular blood = extracellular fluid - interstitial fluid. Thus the

initial formula was simplified as follows: “Add-on peak titer of anti-HBs (IU/L) = Amount of HBIG infused (IU) / (body weight [Kg] × 0.6 for male [or 0.5 for female] / 12)”. Thus the peak anti-HBs titer shortly after HBIG infusion is the sum of pre-existing trough titer and add-on peak titer from HBIG infusion (Fig. 1A).

We assessed the accuracy of this initial formula, by comparing with the actually measured peak anti-HBs titers, in 20 patients. As a result, we found that there was a large discrepancy between the actual and simulative peaks titers, and the size of titer difference appeared to be comparable to the hematocrit value. Since the whole blood is consisted of plasma and blood cells, we extracted the volume proportion of red blood cells (hematocrit) and plasma volume was recalculated as follows: “Plasma volume = Blood volume × (100 – hematocrit [%]) / 100”. Therefore, the final formula was modified as follows: “Add-on peak titer of anti-HBs (IU/L) = Amount of HBIG infused (IU) / (body weight [Kg] × (100 – hematocrit [%]) × 0.6 for male [or 0.5 for female] / 1200)).

Measurement of the half-life of exogenous HBIG was simulated by plotting the formula-based peak titer at day 0 and trough titer after certain infusion intervals, and these points were traced by an exponential decay curve. A half-life was determined as the period showing 50% of peak titer according to the exponential decay curve, using the following formula: “ $t_{1/2} = t \times \ln 2 / \ln(C_0 / C_t)$ ”, where  $t$  is the infusion interval;  $\ln$  is loge;  $t_{1/2}$  is the half-life;  $C_t$  is the target trough titer, and  $C_0$  is the peak titer. The HBIG infusion interval for a target trough titer can then be determined since the peak titer and half-life are already derived. This calculation can be solved by using general calculation software, such as Microsoft Excel or the online half-life calculator (<http://www.calculator.net/half-life-calculator.html>).

Considering the usual institutional protocol for HBIG infusion, the resulting SHL estimation appears to apply to the recipients passing the first 1 year after LT. The mean or lowest value from at least three consecutive SHL may be helpful to compensate the intra-individual variability.



**Fig. 1.** Simulation of anti-HBs pharmacokinetics with calculation of half-life (**A**) and application of simulative half-life (**B**).

#### **Application of SHL to determine the administration interval of HBIG**

The formula to determine the interval of HBIG administration was as follows: “ $t = t_{1/2} \times \ln(C_t / C_0) / \ln 2$ ”, where  $t$  is the infusion interval;  $\ln$  is loge;  $t_{1/2}$  is the half-life;  $C_t$  is the target trough titer, and  $C_0$  is the peak titer. This formula is directly converted from the abovementioned formula for half-life estimation. We used both 500 IU/L and 200 IU/L as the target trough titers in this study (Fig. 1B).

The peak titer was sum of the target trough titer and add-on titer after administration of 10,000 IU HBIG. We used the actual trough titer of a certain time point only for estimation of SHL. Once SHL is determined, the actual trough titer was no longer valid for determination of the interval of HBIG administration because it would be automatically moved toward the target trough titer after passing a few sessions of HBIG administration.

The parameters to determine the interval of HBIG administration for a certain target trough titer are the body weight, gender, hematocrit, actual trough anti-HBs titer and interval between two consecutive sessions of HBIG administration, thus additional blood sampling for specific PK study is unnecessary.

### **Statistical analysis**

To quantify the variation in HBIG SHL, the mean with standard deviation (SD) of consecutive measurements were used. Considering that the patients usually visited the outpatient clinic every 2-3 months for HBIG infusion during the study period, the number of sample sessions per patient was  $\geq 10$  in the Part 2 study. Intra- and inter-individual variabilities were reported as mean with SD and coefficient of variation (CV); wherein the CV is the ratio of the SD in trough titer to the mean trough titer (expressed as percentage) as follows: “ $CV = SD / \text{Mean} \times 100\%$ ”.<sup>(12)</sup>

To avoid bias from wide fluctuation of trough anti-HBs titer, the lowest trough anti-HBs titer among the latest 3 measurements were used for calculation of SHL in Part 4 and 5 studies. Two logarithms were used in this study. Base-10 logs ( $\log_{10}$ ) were simply expressed as log and natural logs ( $\log_e$ ) were expressed as ln.

All numerical data are reported as means with standard deviations or as medians with ranges. Continuous variables were compared using Student’s t-test or analysis of variance (ANOVA). A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 22; IBM, New York, NY).

## Results

### **PK study to assess the accuracy of simulative anti-HBs peak titer and SHL (Part 1 study)**

The profiles of 20 patients (study cohort 1) are summarized in Table 1, and their anti-HBs PK data are provided in Table 2.

The actual trough and peak titers of anti-HBs were  $617.5 \pm 354.1$  IU/L and  $6262.3 \pm 1224.4$  IU/L respectively with a mean infusion interval of  $69.3 \pm 15.6$  days. Infusion of 10,000 IU HBIG increased the add-on anti-HBs titer by  $5644.8 \pm 1191.6$  IU/L. The mean actual half-life of HBIG was estimated to be  $19.6 \pm 3.1$  days.

With the application of initial simulative estimation, the add-on rise of anti-HBs titer from 10,000 IU HBIG was  $3337.2 \pm 704.7$  IU/L, which was 37.4% lower than that of the actual measurement. With the addition of the trough titer, the peak anti-HBs titer was increased to  $3964.7 \pm 941.3$  IU/L. This discrepancy between the simulative and actually measured peak anti-HBs titers resulted in prolongation of the half-life to  $24.2 \pm 5.1$  days, which was 23.6% longer than that obtained from the actual measurement.

After 10,000 IU HBIG administration, the discrepancy between the actual and simulative titer rises was 37.4%, which appeared to be similar to the mean hematocrit value (36.7%). To minimize this difference, we used the plasma volume instead of the whole blood volume, after subtracting the volume proportion of hematocrit. With the application of the simulative estimation using the plasma volume, the add-on rise of anti-HBs titer from 10,000 IU HBIG was  $5252.5 \pm 873.7$  IU/L, which was only 4.4% lower than that from the actual measurement. When adding the trough titer, the peak anti-HBs titer was estimated to be  $5870.0 \pm 1077.4$  IU/L. This correction resulted in a mean SHL of  $20.0 \pm 3.7$  days, which was only 2.2% longer than that from the actual measurement. Thus, this hematocrit-corrected simulative estimation using plasma volume was applied in the subsequent studies.



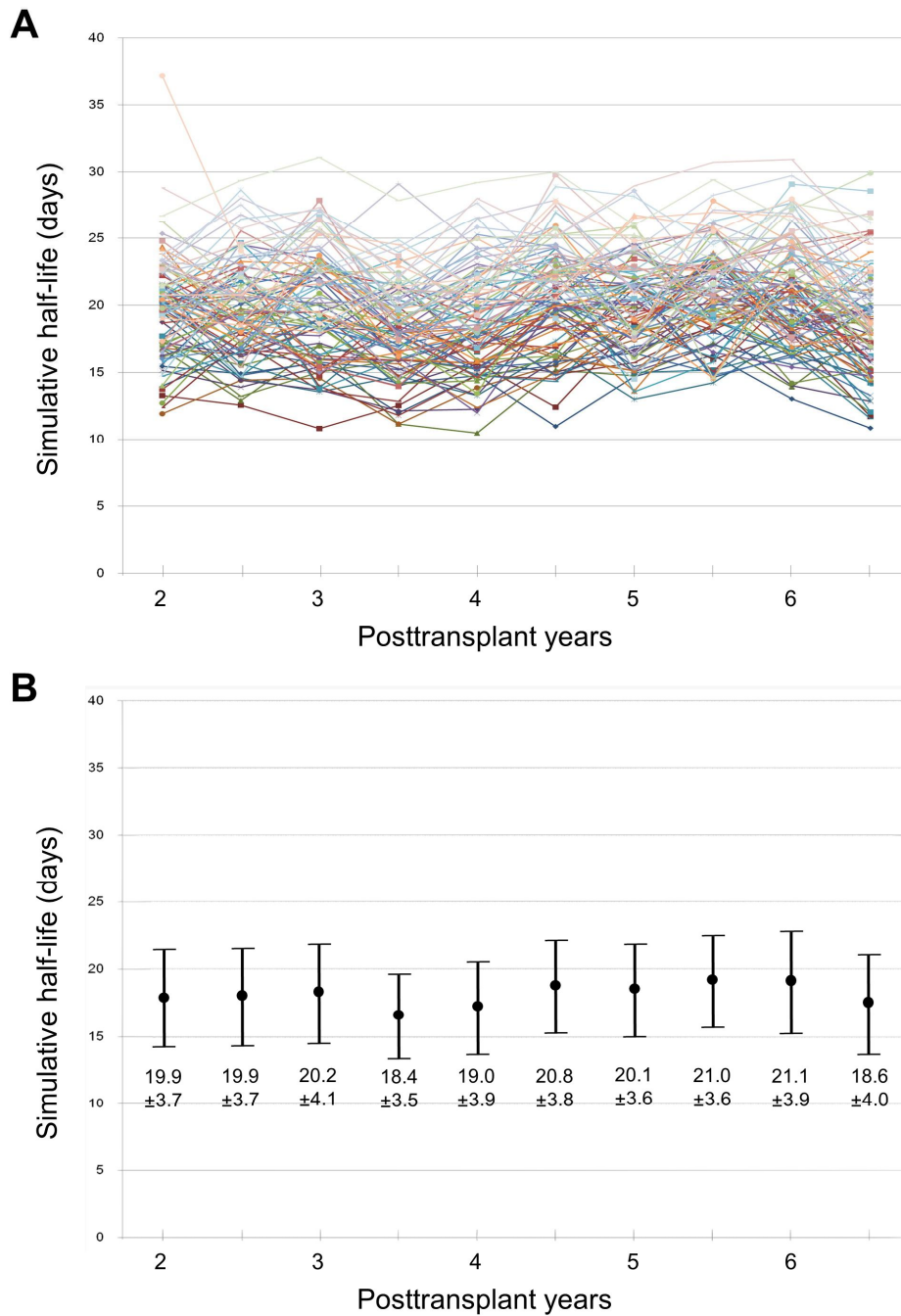
### **Assessment of long-term intra-and inter-individual variability of SHL (Part 2 study)**

The profiles of 100 randomly selected recipients who passed 7–8 years after LT (study cohort 2) are reviewed in Table 1. All patients underwent regularly administered HBIG infusion and measurement of trough anti-HBs titer, every time. The serial changes in SHL over 5 years, from the post-transplant 2nd to 6th year, are depicted in Fig. 2A.

The SHL in 10 consecutive measurement sessions of every patient ranged from  $18.4 \pm 3.5$  to  $21.1 \pm 3.9$  days, with a mean of  $14.0 \pm 3.4\%$  and median of  $13.5\%$ , as CV of intra-individual variability. The overall mean SHL of each patient ranged from  $18.4 \pm 3.5$  to  $21.1 \pm 3.9$  days, with a mean of  $19.0 \pm 1.3\%$  and median of  $18.5\%$ , as CV of inter-individual variability in 100 patients (Fig. 2B). The mean overall SHL of  $19.9 \pm 2.8$  days in Part 2 was comparable with that of  $20.0 \pm 3.7$  days in Part 1 ( $p = 0.27$ ).

We assessed the influence of pre-transplant HBV DNA load on SHL. The mean SHL was  $20.1 \pm 4.4$  days, in 25 patients showing HBV DNA of undetectable level ( $<15$  IU/mL or 84 copies/mL);  $20.4 \pm 2.6$  days, in 40 patients showing HBV DNA  $\leq 4$  log IU/mL; and  $19.7 \pm 2.9$  days, in 35 patients showing HBV DNA  $>4$  log IU/mL ( $p = 0.23$ ), respectively.

We also assessed the influence of concurrent post-transplant NA administration on SHL. The mean SHL was  $19.6 \pm 2.7$  days in 64 patients receiving HNCT, and  $20.7 \pm 3.9$  days in 36 patients receiving HBIG monotherapy ( $p = 0.14$ ), respectively.

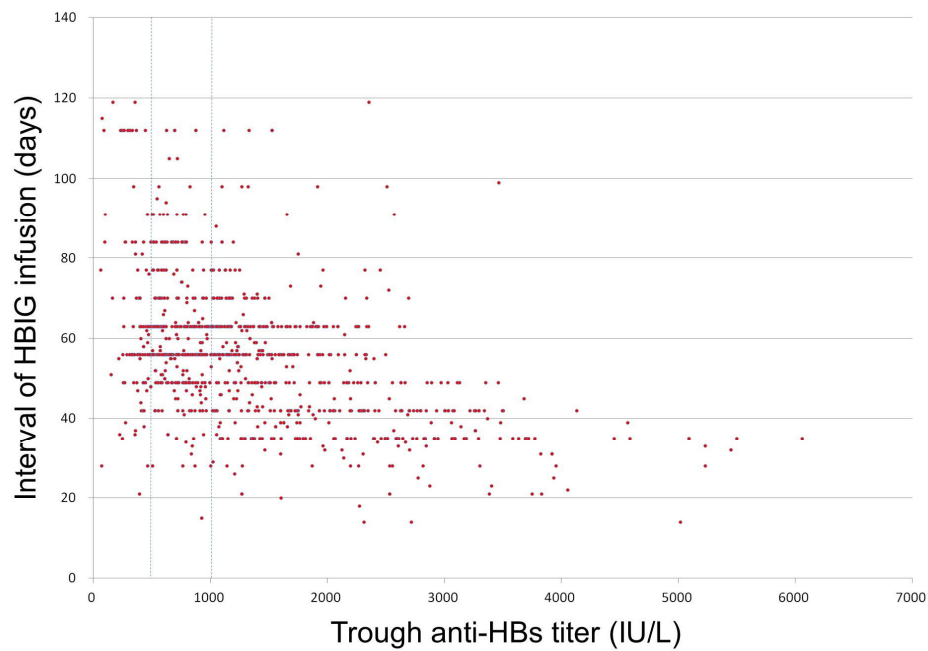


**Fig. 2.** Serial changes of simulative half-life of exogenously infused HBIG in the 100 patients of study cohort 2 showing individual data (A) and collective data (B).

### Development of clinical simulation model using SHL (Part 3 study)

The trough anti-HBs titer and intervals of HBIG infusion of overall 1000 measurement sessions in 100 patients (study cohort 3) are depicted in Fig. 3. Only 111 measurement

sessions (11.1%) showed a trough anti-HBs titer <500 IU/L, and 439 measurement sessions (43.9%) showed an anti-HBs titer  $\leq 1000$  IU/L. Considering that the institutional target level of trough anti-HBs titer was set at 500 IU/L, and some reserve in anti-HBs titer (additional 250 IU/L) is permitted, these results suggest that a majority of our patients have received HBIG infusion more frequently than required.



**Fig. 3.** Scatter plot showing the association between the trough anti-HBs titer and HBIG infusion intervals in the 100 patients of the study cohort 2.

For clinical application, we developed a clinical simulation model, to effectively adjust the interval of HBIG infusion. For example, a male patient with a body weight of 65 kg and hematocrit of 40% has a plasma volume of 1.95 L, so the add-on peak titer of anti-HBs after infusion of HBIG 10,000 IU is 5128 IU/L. If the target trough anti-HBs titer is 500 IU/L and SHL is 15 versus 20 days, the infusion interval becomes 52 versus 70 days, respectively. If the target trough titer is 200 IU/L and SHL is 15 versus 20 days, the infusion interval

becomes 71 versus 95 days, respectively (Fig. 1B).

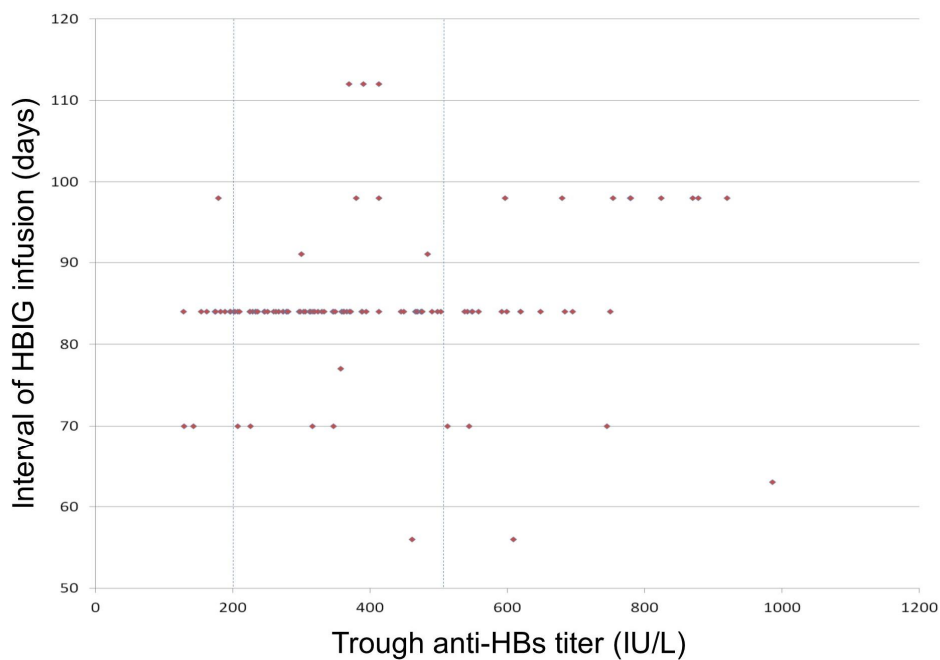
In the 100 patients of the study cohort 2, the actual trough anti-HBs titers, according to the mean HBIG infusion intervals and SHL, were  $1236.8 \pm 758.0$  IU/L (median 1045) and  $20.0 \pm 8.6$  days for a 50-day interval (47–53 days);  $1105.1 \pm 508.7$  IU/L (median 1018) and  $21.3 \pm 3.5$  days for a 60-day interval (57–63 days);  $1022.0 \pm 550.6$  IU/L (median 866) and  $21.3 \pm 3.8$  days for a 70-day interval (57–63 days);  $918.0 \pm 469.7$  IU/L (median 713) and  $22.2 \pm 3.3$  days for an 80-day interval (77–83 days);  $712.0 \pm 292.1$  IU/L (median 582) and  $21.3 \pm 4.3$  days for a 90-day interval (87–93 days); and  $642.4 \pm 307.8$  IU/L (median 480) and  $21.6 \pm 3.3$  days for a 100-day interval (97–103 days), respectively. These actual data supported that time-dependent consumption of exogenous HBIG roughly followed the simulation model using SHL.

#### **Validation of the simulation model using SHL (Part 4 study)**

We performed a prospective study to prolong the intervals of HBIG infusion to 12 weeks (94 days), with a target trough anti-HBs titer of 200 IU/L. The study protocol included slow progressive prolongation of the interval of HBIG infusion toward 12 weeks, with concurrent use of NA. If the trough anti-HBs titer is in the 200–500 IU/L range, we keep the interval unchanged; if it is below 200 IU/L, the interval is shortened by 1–2 weeks until 8 weeks, and if it is above 500 IU/L, the interval is prolonged by 1–2 weeks until 16 weeks. More than 150 patients have been recruited, to date. For this interim study, we selected 114 patients who observed the study protocol for  $\geq 24$  months (study cohort 3). During the follow-up period, progressive prolongation of the interval of HBIG decreased the trough anti-HBs titer, accordingly to the target trough titer. The profiles of these 114 patients are summarized in Table 1. The lowest trough anti-HBs levels among the latest three measurements were used for calculation of SHL.

The infusion intervals of HBIG were 8–9 weeks in 3 patients (2.6%) and their trough anti-

HBs level and mean SHL were  $685.3 \pm 270.7$  IU/L and  $19.8 \pm 4.6$  days, respectively; 10–11 weeks in 10 patients (8.8%), and their trough anti-HBs level and mean SHL were  $352.7 \pm 196.9$  IU/L and  $18.2 \pm 3.5$  days, respectively; 12 weeks in 84 patients (73.7%), and their trough anti-HBs level and mean SHL were  $359.5 \pm 144.1$  IU/L and  $20.7 \pm 3.0$  days, respectively; 13–14 weeks in 16 patients (14.0%), and their trough anti-HBs level and mean SHL were  $615.2 \pm 239.4$  IU/L and  $27.6 \pm 4.5$  days, respectively; and 16 weeks in 1 patient (0.9%), and the trough anti-HBs level and mean SHL were 369 IU/L and 27.4 days, respectively. Prolongation of the intervals of HBIG infusion  $\geq 12$  weeks was successfully achieved in 101 patients (88.6%). The distribution of infusion intervals and lowest trough anti-HBs levels are depicted in Fig. 4.

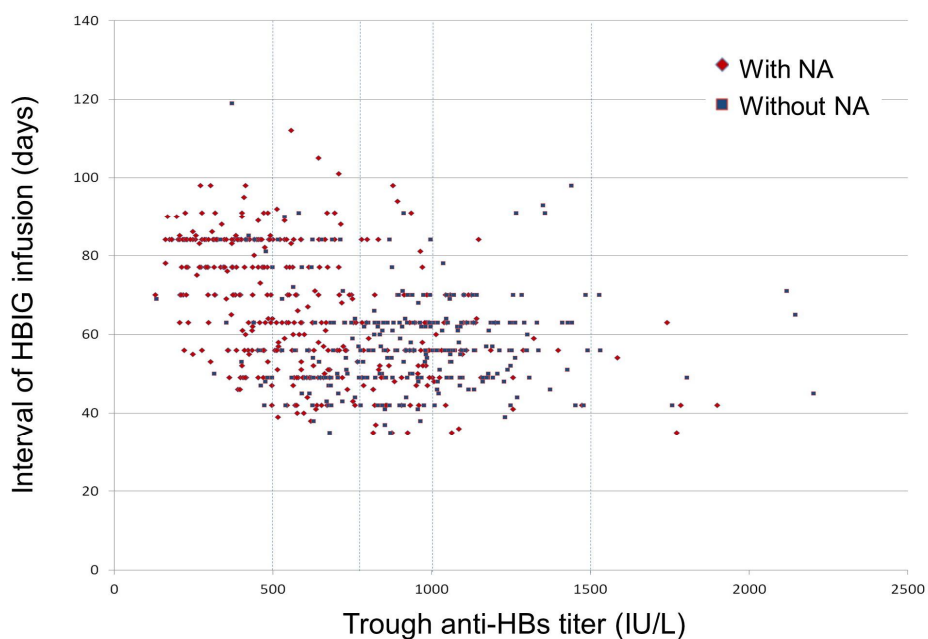


**Fig. 4.** Scatter plot showing the association between the trough anti-HBs titer and HBIG infusion intervals in the 114 patients of the study cohort 3.

#### **Cross-sectional study on empirical determination of HBIG infusion intervals (Part 5)**

We performed a cross-sectional study, to reveal the current status of HBIG infusion

intervals in our institution during the recent 3 months. We selected 660 patients who have passed 5–14 years after LT and been regularly followed-up only at our institution (study cohort 4). Nine transplant surgeons of our institution independently determined the interval of HBIG infusion on a patient-by-patient basis under the simplified principle, to maintain a trough serum anti-HBs titer  $\geq 500$  IU/L. The profiles of these 660 patients are summarized in Table 1. The lowest trough anti-HBs levels among the latest three measurements were used for calculation of SHL. The distribution of infusion intervals and lowest trough anti-HBs levels are depicted in Fig. 5.



**Fig. 5.** Scatter plot showing the association between the trough anti-HBs titer and HBIG infusion intervals after stratification according to concurrent use of nucleos(t)ide analogue (NA) in the 660 patients of the study cohort 4.

The mean trough anti-HBs level was  $751.1 \pm 340.0$  IU/L and simulative add-on anti-HBs level was  $5842.5 \pm 1169.6$  IU/L, for which, the peak anti-HBs level was  $6572.6 \pm 1283.4$  IU/L. Since the mean infusion interval was  $62.5 \pm 15.0$  days, the resulting mean SHL was  $19.5 \pm 4.4$

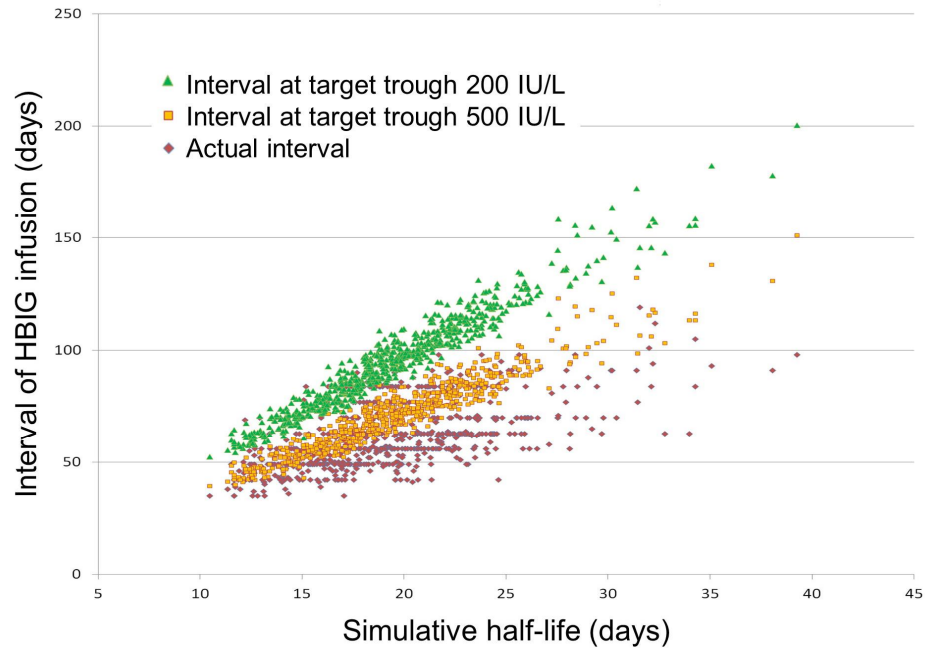
days.

After stratification, according to concurrent use of NA as HNCT ( $n = 374$ ) and HBIG monotherapy ( $n = 286$ ) groups, the mean trough anti-HBs levels were  $609.1 \pm 302.5$  IU/L in the HNCT group and  $934.6 \pm 295.3$  IU/L in the HBIG monotherapy ( $p < 0.001$ ), respectively; the mean infusion intervals were  $66.2 \pm 15.9$  and  $57.8 \pm 12.2$  days, respectively ( $p < 0.001$ ); and the mean SHLs were  $19.3 \pm 4.2$  and  $19.8 \pm 4.3$  days, respectively ( $p = 0.13$ ). These findings implicate HBIG was less frequently administered in the HNCT group than in the HBIG monotherapy group.

The trough anti-HBs level was  $<500$  IU/L in 181 patients (27.4%); 500–749 IU/L in 164 (24.9%); 750–999 IU/L in 163 (24.7%); 1000–1499 IU/L in 140 (21.2%); and  $\geq 1500$  IU/L in 12 patients (1.8%), respectively. Considering the reserve for fluctuation of trough anti-HBs level (empirically up to 250 IU/L), only 164 patients (24.9%) exactly met the target level; 181 patients (27.4%) did not reach the target level; and 315 patients (47.7%) showed an excessively higher titer than the target level. Given the target trough anti-HBs level was 500 IU/L (peak anti-HBs titer becomes the sum of 500 IU/L and add-on peak titer from HBIG 10,000 IU infusion), and individual SHL was applied, the mean HBIG infusion interval was estimated to be  $70.9 \pm 16.6$  days in these 660 patients (Fig. 6). Thus, a mean interval of 10 weeks can be applied to achieve a trough anti-HBs level of 500 IU/L. Comparing with the actual infusion intervals, 355 patients (53.8%) can be indicated for interval prolongation by  $\geq 7$  days, and 89 patients (13.5%) can be indicated for interval shortening by  $\geq 7$  days.

Given the target trough anti-HBs level was 200 IU/L, and individual SHL was applied (peak anti-HBs titer becomes the sum of 200 IU/L and add-on peak titer from HBIG 10,000 IU infusion), the mean HBIG infusion interval was estimated to be  $95.2 \pm 22.0$  days (Fig. 6). Hence, a mean interval of 13 weeks can be applied to achieve a trough anti-HBs level of 200 IU/L. Comparing with the actual infusion intervals, 623 patients (94.4%) can be indicated for interval prolongation by  $\geq 7$  days, and only 1 patient (0.2%) can be indicated for interval

shortening by  $\geq 7$  days.



**Fig. 6.** Scatter plot showing the association between the simulative half-life of HBIG and intervals of HBIG infusion according to the target anti-HBs titers in the 660 patients of the study cohort 4.



**Table 1.** Collective profiles of patients who were included in the study cohort 1 to 4

	<b>Cohort 1</b>	<b>Cohort 2</b>	<b>Cohort 3</b>	<b>Cohort 4</b>
Case number	20	100	114	660
Age at LT (year)	59.9±10.2	52.3±6.5	51.3±7.4	51.7±8.9
Gender (n)				
Male	18 (90.0%)	72 (72.0%)	92 (80.7%)	504 (76.4%)
Female	2 (10.0%)	28 (28.0%)	22 (19.3%)	156 (23.4%)
Primary diseases (n)				
HBV-associated LC	20 (100%)	95 (95.0%)	110 (96.5%)	633 (95.9%)
HBV-associated ACLF	0 (0%)	5 (5.0%)	4 (3.5%)	27 (4.1%)
Pre-transplant HBsAg positivity (n)	20 (100%)	100 (100%)	114 (100%)	660 (100%)
Pre-transplant HBeAg positivity (n)	7 (35.0%)	38 (38.0%)	42 (36.8%)	257 (38.9%)
MELD score	18.3±3.5	18.6±4.4	19.6±5.4	19.7±9.8
Concurrent HCC (n)	7 (35.0%)	46 (46.0%)	51 (44.7%)	283 (42.9%)
Mean body weight (Kg)	63.0±10.3	66.7±10.7	65.3±10.3	64.1±10.1
Mean hematocrit (%)	36.7±5.9	41.2±5.4	41.8±4.6	42.3±4.9
Pre-transplant NA use (n)				
Yes	12 (60.0%)	74 (74.0%)	75 (65.8%)	392 (59.4%)
No	8 (40.0%)	26 (26.0%)	39 (34.2%)	268 (40.6%)
Pre-transplant HBV DNA (IU/L)				
Undetectable	7 (35.0%)	25 (25.0%)	34 (29.8%)	184 (27.9%)
≤4log IU/mL	8 (40.0%)	40 (40.0%)	46 (40.4%)	239 (36.2.0%)
>4log IU/mL	5 (25.0%)	35 (35.0%)	34 (29.8%)	237 (35.9%)
Type of LT (n)				
LDLT	17 (85.0%)	89 (89.0%)	104 (91.2%)	610 (92.4%)
DDLT	3 (15.0%)	11 (11.0%)	10 (8.8%)	50 (7.6%)

Type of HBV prophylaxis (n)				
HBIG-NA combination therapy	13 (65.0%)	64 (64.0%)	110 (96.5%)	374 (56.7%)
HBIG monotherapy	7 (35%)	36 (36.0%)	4 (3.5%)	286 (43.3%)
Antiviral agents after LT (n)				
Tenofovir	6 (30.0%)	26 (26.0%)	16 (14.0%)	149 (22.6%)
Entecavir	6 (30.0%)	38 (38.0%)	94 (82.5%)	217 (32.9%)
Adefovir	1 (5.0%)	0 (0%)	0 (0%)	2 (0.3%)
lamivudine	0 (0%)	0 (0%)	0 (0%)	6 (0.9%)

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ACLF, acute-on-chronic liver failure; DDLT, deceased donor liver transplantation; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LC, liver cirrhosis; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, model for end-stage liver disease; NA, nucleos(t)ide analogue.

**Table 2.** Profile of 20 patients who underwent pharmacokinetic study on HBIG infusion and consumption (study cohort 1)

		Anti-HBs																					
		Actual measurement				Simulation using whole blood volume				Simulation using plasma volume													
No.	Sex	Age at LT (years)	Post-LT (months)	Body weight (kg)	Whole blood volume (L)	Hematocrit (%)	Plasma volume (L)	Antiviral agent	Actual trough titer (IU/L)	Actual peak titer (IU/L)	Actual Titer rise after infusion (IU/L)	Infusion interval (days)	Actual half life (days)	Simulation titer rise (IU/L)	Simulation peak level (IU/L)	Simulation Titer rise difference (%)	Simulation half life (days)	Simulation Half life difference (%)	Simulation titer rise (IU/L)	Simulation peak titer (IU/L)	Simulation Titer rise difference (%)	Simulation half life (days)	Simulation Half life difference (%)
		A	B	B - A = C	D	A, B, D → E	F	A + F = G	(C - F) / C	A, G, D → H	(E - H) / C	I	(C - I) / C	A + I = K	A, K, D → L	(E - L) / C							
1	M	51	24	60	3.00	34.2	1.97	None	1286	6085	4799	44	19.6	3333	4819	30.5	23.1	-17.9	5066	-5.6	6352	19.1	2.6
2	M	47	25	60	3.00	42.1	1.74	Tenofovir	471	6496	6025	54	14.3	3333	3804	44.7	17.9	-25.2	5757	4.4	6228	14.5	-1.4
3	M	42	25	70	3.50	43.7	1.97	None	715	7886	7171	73	21.1	2857	3572	60.2	31.5	-49.3	5075	29.2	5790	24.2	-14.7
4	M	51	26	49	2.45	36.0	1.57	Adefovir	473	5853	5380	53	14.6	4082	4555	24.1	16.2	-11.0	6378	-18.5	6851	13.7	6.2
5	M	75	26	49	2.45	30.7	1.70	Entecavir	872	6544	5672	49	16.9	4082	4954	28.0	19.6	-16.0	5890	-3.8	6762	16.6	1.8
6	M	52	27	82	4.10	48.8	2.10	Tenofovir	578	7477	6899	70	19.0	2439	3017	64.6	29.4	-54.7	4764	31.0	5342	21.8	-14.7
7	M	57	28	71	3.55	36.1	2.27	None	722	4383	3661	52	20.0	2817	3539	23.1	22.7	-13.5	4408	-20.4	5130	18.4	8.0
8	M	67	28	58	2.90	38.4	1.79	Entecavir	275	6681	6406	85	18.5	3448	3723	46.2	22.6	-22.2	5598	12.6	5873	19.3	-4.3
9	M	52	32	71	3.55	39.0	2.17	Tenofovir	116	7132	7016	98	16.5	2817	2933	59.9	21.0	-27.3	4618	34.2	4734	18.3	-10.9
10	M	62	37	52	2.60	28.0	1.87	None	1054	6403	5349	62	23.8	3846	4900	28.1	28.0	-17.6	5342	0.1	6396	23.8	0.0
11	F	68	45	43	1.79	31.2	1.23	Entecavir	1290	7312	6022	56	22.4	5581	6871	-11.1	23.2	-3.6	8112	-34.7	9402	19.5	12.9
12	M	69	46	63	3.15	40.2	1.88	Entecavir	220	4787	4567	84	18.9	3175	3395	30.5	21.3	-12.7	5309	-16.2	5529	18.1	4.2
13	M	70	49	67	3.35	37.8	2.08	Entecavir	221	5142	4921	87	19.2	2985	3206	39.3	22.6	-17.7	4799	2.5	5020	19.3	-0.5
14	M	49	54	81	4.05	46.5	2.17	None	447	7741	7294	84	20.4	2469	2916	66.1	31.1	-52.5	4615	36.7	5062	24	-17.6
15	F	59	54	70	2.92	31.9	1.99	Entecavir	779	7033	6254	74	23.3	3429	4208	45.2	30.4	-30.5	5035	19.5	5814	25.5	-9.4
16	M	77	55	64	3.20	33.6	2.12	None	711	8501	7790	80	22.4	3125	3836	59.9	32.9	-46.9	4706	39.6	5417	27.3	-21.9
17	M	54	58	67	3.35	41.0	1.98	None	918	5249	4331	55	21.9	2985	3903	31.1	26.3	-20.1	5059	3.6	5977	20.4	6.8
18	M	60	84	53	2.65	34.6	1.73	Tenofovir	670	5207	4537	74	25.0	3774	4444	16.8	27.1	-8.4	5770	-27.2	6440	22.7	9.2
19	M	61	91	62	3.10	28.7	2.21	Tenofovir	71	4690	4619	87	14.4	3226	3297	30.2	15.7	-9.0	4524	2.1	4595	14.5	-0.7
20	M	75	97	68	3.40	30.4	2.37	Tenofovir	461	4644	4183	64	19.2	2941	3402	29.7	22.2	-15.6	4226	-1.0	4687	19.1	0.5
Mean±SD		59.9 ±10.2	45.6 ±22.8	63.0 ±10.3	3.10 ±0.55	36.7 ±5.9	1.95 ±0.27		617.5 ±354.1	6262.3 ±1224.4	5644.8 ±1191.6	69.3 ±15.6	19.6 ±3.1	337.2 ±704.7	3964.7 ±941.3	37.4 ±19.0	24.2 ±5.1	-23.6 ±15.4	525.5 ±873.7	4.4 ±21.9	5870.0 ±1077.4	20.0 ±3.7	-2.2 ±9.7

## Discussion

The primary reason for undertaking this study was our recognition that the post-transplant HBV prophylaxis protocols in Korea were already moved toward HNCT, but the protocol for HBIG infusion was not correspondingly changed in many Korean LT centers, including our institution.

HBV prophylaxis protocols have primarily originated with HBIG monotherapy. Thus, HNCT has begun to simply add an NA to HBIG monotherapy, with or without lowering the target trough anti-HBs titer. In the real-world practice in Korea, a majority of LT centers have still adopted high-dose HBIG prophylactic therapy, with or without NA, because there is no consensus or practical guideline to lower the target trough anti-HBs titer, primarily due to the meager medical cost, with the patients paying only 70–140 US dollars per 10,000 IU HBIG (5–10% of total cost). We believe that the target trough anti-HBs titer would have been lowered previously if the medical cost for HBIG infusion had not been so low in Korea.

HNCT is well known to be more effective than HBIG monotherapy or HBIG-free NA monotherapy. Considering the high efficacy of HNCT, it must be reasonable to make the target trough anti-HBs titer lower than that of HBIG monotherapy. Consequently, it is necessary to develop a practical method to readjust the target trough anti-HBs titer logically, in LT recipients regularly administering HBIG. In the current LT setting in Korea, prolongation of HBIG infusion interval is more convenient to the patients than a reduction in the amount of HBIG infusion. For this reason, we only investigated the intervals of HBIG infusion in this study because adjustment of HBIG amount can be easily performed later, through simple modification of the add-on peak titer.

Since the *in vivo* half-life of HBIG varies widely with occasion or time, as well as person, it is difficult to reliably make the trough anti-HBs titer close to the target level. Hence, a considerable number of patients have shown much higher trough titer than the target level, as

verified in this study, which implies that HBIG has been administered too much or too frequently than required. It had been previously thought that the anti-HBs titer was proportional to the efficacy of preventing HBV recurrence, thereby explaining the much higher anti-HBs titer than the target trough level, but such a concept is no longer valid in the current clinical field of LT. After passing the very early post-transplant period of active HBV neutralization by HBIG, an excessively high anti-HBs titer is not as effective as expected because HBIG consumption is very highly accelerated or HBIG is no longer effective if HBV-resistant mutants develop. In contrast, high genetic-barrier NAs are very effective to suppress HBV replication,<sup>(8)</sup> but it still carries the risk of development of drug-resistant mutants. Thus, HNCT is the most effective prophylactic regimen, so far.

From the viewpoint of cost-effectiveness, the simple addition of NA to HBIG monotherapy increases medical cost, making it necessary to decrease the financial burden, through reduction of excessively infused HBIG. However, any change in the real-world clinical practice requires robust evidence because it is often related to the safety of patients. Thus, we focused on designing a practical method to safely prolong the interval of HBIG infusion, which can lead to a reduction in the total amount of HBIG infused. Prolongation in the interval of HBIG infusion means that the patients visit the outpatient clinic less frequently, creating a patient-friendly as well as a cost-effective outcome.

An *in vivo* PK study of HBIG administration in each patient is ideal, but not practical. We searched for a practical method to replace the cumbersome PK study, by which we developed the concept of SHL estimation. To our knowledge, HBIG administration, according to its personalized half-life, has not been reported before. In Part 1 of the present study, we demonstrated that there was only a difference of 4.4% between the estimated and actually measured add-on rise of anti-HBs titer after infusion of 10,000 IU HBIG. This small discrepancy meant the SHL was only 2.2% longer than that of the actual measurement. The ranges of such differences were considerably small, so we believed that SHL estimation

could be reliably used in Parts 2–5 of this research.

In Part 2, we focused on the intra- and inter-individual variabilities of HBIG consumption in patients who passed the first 1 year after LT. Analysis of the SHL revealed a mean of  $14.0\pm 3.4\%$  for intra-individual CV and  $19.0\pm 1.3\%$  for inter-individual CV. These results imply that there are non-negligible patient-to-patient discrepancies in HBIG consumption, but intra-individual time-to-time fluctuation was rather smaller than patient-to-patient disparities, and so we suggest that individualized SHL is reliably applicable lifelong. A Korean prospective multicenter study determined that the trough anti-HBs titer stabilized after 16 weeks of LT, according to the usual protocol described in the method section of this study.<sup>(10)</sup> Therefore, individualized adjustment of intervals for HBIG infusion toward a certain target trough titer can be reliably determined by adoption of SHL at 1 year after LT.

We also investigated the potential factors that can affect SHL. We assessed the influence of pre-transplant HBV DNA load, but there was no association between the long-term SHL and pre-transplant HBV DNA load. This finding is not consistent with our previous study, in which high pre-transplant HBV load was associated with rapid HBIG consumption requiring a shortened interval of HBIG infusion and high incidence of HBV recurrence. We think that there is a definite difference in selection of the study patients, in which our present study did not include the patients with recurrence of HBV or HCC, but our previous study included the whole single-center cohort including the patients suffering from HBV or HCC recurrence. In a Korean multicenter analysis, blood HBV DNA was detectable at 1 week after LT in 13 of 79 patients, and their pre-transplant HBV DNA was  $823,143\pm 1,506,950$  IU/mL, which was marginally higher than other 66 patients showing no HBV DNA positivity at post-transplant 1 week.<sup>(10)</sup> One of them showed persistent blood HBV DNA positivity up to 8 weeks.<sup>(10)</sup> However, after passing the very early post-transplant period requiring high-dose HBIG, the trough anti-HBs titer became stabilized. These findings indicate that it is beneficial to perform pre-transplant NA treatment actively to reduce the HBV viral load because HBIG

with/without NA at the time of LT operation cannot eradicate viral load in the circulating blood or extrahepatic sites. However, once occult HBV viral load is fully suppressed by HBIG after passing the very early post-transplant period, it may not accelerate HBIG consumption unless HBV reactivation develops. At first, we wondered whether concurrent post-transplant NA administration might be associated with prolonged SHL, but we found that there was no significant difference in SHL between HBIG monotherapy and HNCT in patients without HBV reactivation, as shown in Parts 2 and 5 of this investigation.

In Part 3 of this work, we developed a clinical simulation model to adjust the interval of HBIG infusion effectively. The required parameters were gender, body weight, hematocrit, SHL, and target trough anti-HBs titer. Through 1000 measurement sessions in Part 2 of this research, we learned the mean SHL might be around 20 days, with an intra-individual CV of  $14.0\pm 3.4\%$  and inter-individual CV of  $19.0\pm 1.3\%$ . Based on our long-term experience, we have set the interval of HBIG infusion at 8–12 weeks for a target trough anti-HBs titer of 500 IU/L, which often resulted in the actual trough anti-HBs titer between 500 and 1000 IU/L.

Although the target trough anti-HBs titer was set at 500 IU/L, the actual level in clinical practice was usually higher than the target level. To enhance the cost-effectiveness of HBV prophylaxis, we intended to lower the target trough anti-HBs titer toward 200 IU/L, in Part 4 of this research. We observed that 114 patients were successfully managed with a regular HBIG infusion at  $\geq 8$ -week intervals, which could be prolonged to  $\geq 12$  weeks in 101 patients (88.6%). Considering that only 11.1% of measurement sessions showed anti-HBs trough titers  $< 500$  IU/L (Part 2 of this work), we believe that a majority of our patients are indicated for prolongation of HBIG infusion intervals. If the target trough anti-HBs titer is set at 200 IU/L, the interval of HBIG infusion will be prolonged in nearly all of our patients.

In Part 5 of this investigation, we analyzed the actual intervals of HBIG infusion in 660 patients who passed 5 years after LT. We found that only 24.9% exactly met the target anti-HBs trough titers  $\geq 500$  IU/L, with a reserve of an additional 250 IU/L. Another 27.4% did

not meet the target level, and 47.7% exceeded the target level. Comparing with the actual infusion intervals, simulative analyses revealed that 53.8% of the patients could be indicated for interval prolongation by  $\geq 7$  days, and 13.5% could be indicated for interval shortening by  $\geq 7$  days, respectively, when setting the anti-HBs trough titer at  $\geq 500$  IU/L. If the target anti-HBs trough titer is lowered to 200 IU/L, 94.4% of the patients could be indicated for interval prolongation by  $\geq 7$  days while only 0.2% could be indicated for interval shortening by  $\geq 7$  days.

There are a few recent studies about HBIG-free and HBIG-sparing HBV prophylaxis regimens.<sup>(8, 9)</sup> Theoretically, HBIG-free NA prophylaxis cannot prevent intraoperative HBV infection of naïve graft hepatocytes unless sustained virological response (SVR) is achieved before LT operation. Thus, it may be reasonable to attempt HBIG-free NA prophylaxis only to the patients who show SVR before LT. In a report of entecavir monotherapy from the University of Hong Kong, 206 of 242 (85%) patients showed HBsAg seroclearance, and HBsAg seroclearance occurred within 1 year in 90% of the patients.<sup>(8)</sup> The HBsAg reappearance rate was 13% at 3 years. The 265 patients, including 99 patients having undetectable HBV DNA at LT, showed an HBsAg seroclearance rate of 92% and an HBV DNA undetectable rate of 100%, at 8 years. At 1 year of LT, the HBsAg seroclearance rates were 98%, 92%, 81%, and 60% for HBV DNA at LT of undetectable levels,  $\leq 4$  log,  $>4-6$  log, and  $>6$  log IU/mL, respectively ( $p < 0.001$ ). The authors also commented that additional HBIG administration setting would invariably lead to a decreased rate of HBsAg. From the viewpoint of prophylactic efficacy and cost-effectiveness, if pre-transplant SVR is not achieved, NA prophylaxis with concurrent HBIG administration, at least for a short period, is beneficial to minimize perioperative HBV infection of the graft hepatocytes.<sup>(9)</sup>

Considering the high effectiveness of NA prophylaxis, there is no reason to maintain the trough anti-HBs titer as high as that in HBIG monotherapy. Maintenance dosing for HBIG infusion is highly variable across LT centers worldwide.<sup>(13)</sup> The target levels for trough anti-



HBs titer decreases with time after LT: generally, the anti-HBs titer levels were maintained at greater than 500 IU/L during 1–3 months; at greater than 250 IU/L until 6–12 months; and at greater than 50 to 100 IU/L, after that. Some studies using low-dose HBIG had successful HBV prophylaxis with target trough anti-HBs titers of 100 or 50 IU/L.<sup>(14–16)</sup> The optimal trough anti-HBs titer needed to prevent recurrence in the medium- and long-term follow-up is unknown, but probably reduced if NA therapy is combined with HBIG. A meta-analysis with 19 studies, including 1484 patients, indicated HBIG administration was helpful to reduce HBV recurrence and virus mutants, and subgroup analysis showed that in patients with positive pre-transplant HBV DNA status, HBIG was necessary to reduce the HBV recurrence rate.<sup>(17)</sup> In contrast, in patients with negative HBV DNA, HNCT gained no significant advantages.<sup>(17)</sup>

This study has some limitations. First, three of the five study parts were performed retrospectively. Second, it is a single-center study, although the study cohorts were sizeable. Third, we intentionally excluded the patients who showed HBV recurrence, for simplification of the study design, and so risk factor analysis for HBV recurrence was not carried out.

In conclusion, SHL estimation, using clinically available parameters, seems to be reliably accurate when compared with the results from the actual measurement. We believe that SHL estimation is helpful to establish an individualized HBV prophylaxis protocol, to optimize the interval of HBIG administration. Further prospective and multicenter studies are necessary to validate the clinical role of SHL estimation

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## 국문 요약

HBV 관련 수혜자의 간이식 후 HBV 재발 예방은 매우 필수적이다. 이 연구의 목적은 simulative half-life(SHL)을 적용하여 B형 간염 면역글로불린(HBIG) 투여를 최적화하여 개별화된 HBV 예방 프로토콜을 수립하기 위한 것이다. 연구는 5 부분으로 구성되어 있다. Part 1은 20명의 환자를 대상으로 SHL 추정 방법을 개발하기 위해 고안되었다. Part 2와 3은 SHL의 가변성을 평가하고 100명의 환자를 대상으로 SHL을 적용하는 시뮬레이션 모델을 개발하는 것이다. Part 4에서는 114명의 환자를 대상으로 시뮬레이션 모델을 검증하는 것이었다. Part 5에서는 660명의 환자를 대상으로 현재의 HBIG 주입 간격에 대한 cross-sectional 연구이다.

Part 1에서는 10,000IU HBIG 주입 시 anti-HBs titer는 상승하였고, SHL은  $5252.5 \pm 873.7$  IU/L,  $20.0 \pm 3.7$  days 였고, 실제 측정과 비교하여, 4.4% 낮고, 2.2% 길었다. Part 2에서 개인 내 및 개인 간 변동 계수의 median value는 각각 13.5%, 18.5% 였다. 이식 이전의 HBV DNA load 및 이식 후 항 바이러스 치료는 SHL에 영향을 미치지 않았다. Part 3에서 SHL을 사용하여 HBIG 주입 간격을 결정하기 위한 시뮬레이션 모델을 개발하였고, Part 4에서 114명의 환자 모두 HBIG 주입 주기가 8주 이상으로 성공적으로 관리되었으며, HBs titer 가 200이상의 경우 89.4%에서 12주 이상으로 연장되었다. Part 5에서 우리 환자의 47.4%는 500 IU/L 목표보다 HBIG 를 과도하게 투여 받았다.

임상적으로 측정 가능한 파라미터를 이용한 SHL 추정은 실제 측정의 결과와 비교하여 신뢰성 있게 정확해 보인다. 우리는 SHL 평가가 HBIG 투여를 최적화하기 위해 개인화된 HBV 예방 프로토콜을 확립하는데 도움이 된다고 믿는다.