Compliance and tolerability of subcutaneous hepatitis B immunoglobulin self-administration in liver transplant patients: A prospective, observational, multicenter study

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Summary

Background: Subcutaneous self-administration of hepatitis B immunoglobulin (HBIg) prophylaxis is preferred by patients, but compliance with the assigned regimen in routine practice is undocumented.

Material/Methods: A prospective, observational, 18-week, open-label, single-arm, multicenter study assessed compliance and tolerability in maintenance liver transplant patients self-administering subcutaneous HBIg at home according to local practice.

Results: Sixty-one patients were analyzed (median follow-up 18 weeks, range 14.0–27.9 weeks), with 961/1006 injections (95.5%) administered at home during the study. Other than in 4 patients, HBIg was prescribed for weekly administration (500 IU/L, n=39; 1000 IU/L, n=18) at study entry. Eighteen patients (29.5%) were assigned a dose lower than recommended in the Summary of Product Characteristics. The primary variable of compliance failure, defined as ≥1 hepatitis B surface antibody (anti-HBs) serum trough level <100 IU/L, occurred in 4 patients (6.6%; 95% CI 1.8%, 15.9%), of whom were receiving a dose below that recommended for their body weight. Anti-HBs levels exceeded 100 IU/L in all patients at the final visit. Mean (SD) anti-HBs level at the first and final study visits was 248 (97) IU/L and 255 (104) IU/L, respectively. Patient compliance was graded good or very good by physicians in 91.8% of cases. No patients tested positive for HBsAg or HBV-DNA. Four patients experienced ≥1 adverse drug reactions, none of which was serious. No patient discontinued HBIg due to adverse events.
The introduction of hepatitis B immunoglobulin (HBIg) prophylaxis in the early 1990s dramatically reduced the rate of hepatitis B virus (HBV) recurrence following liver transplantation [1]. When co-administered with oral nucleos(t)ide antiviral therapy, passive immunization using HBIg can reduce the risk of HBV recurrence to less than 10% [2,3]. HBIg in combination with an oral antiviral agent is now considered to be the standard of care in this setting. This approach has helped to improve graft survival for HBV-positive liver transplant recipients [4,5], with 5-year survival rates now approaching 76% [6]. Conventional high-dose HBIg therapy, however, is now no longer recommended on the basis of cost, and low-dose or defined-term regimens have been adopted by many centers [7]. Additionally, intramuscular or subcutaneous administration of HBIg in combination with antiviral therapy has been explored as an alternative to the conventional intravenous route, with the aim of reducing HBIg dose and cost. Although randomized trials are lacking, the available evidence indicates that intramuscular therapy offers similar efficacy to intravenous administration in terms of hepatitis B surface antibody (anti-HBs) levels [8–13] and HBV recurrence [10,14], even with substantial reductions in dose [8–10,12]. Intramuscular injection can, however, be painful for patients [15], potentially affecting long-term compliance, and is contraindicated in patients who have coagulopathies or are receiving oral anticoagulants. Furthermore, most intramuscular therapies are not licensed for HBV reinfection prophylaxis and are registered in only a few European countries (e.g., Italy). Subcutaneous HBIg administration is also effective in maintaining the requisite levels of anti-HBs [16] and is preferred by patients [16]. Additionally, the subcutaneous route has the advantage of offering the potential for patients to self-inject at home.

BT088 (Zutectra®, Biotest AG, Dreieich, Germany) is the first HBIg preparation to be approved for subcutaneous administration. A randomized, single-dose trial in healthy volunteers showed that pharmacokinetics were similar following intravenous or subcutaneous administration [17]. Subsequently, an 18-week Phase III clinical trial in 23 liver transplant patients demonstrated that conversion from monthly intravenous HBIg to self-administered subcutaneous therapy maintained the trough anti-HBs concentration at above 100 IU/L [18], a level widely considered to be the minimum threshold for effective protection against HBV reinfection [19]. This finding was confirmed in a single-center study based on a larger cohort of 135 patients followed for 48 weeks [20]. The use of subcutaneous HBIg when administered unsupervised at home under ‘real-life’ conditions, however, has not been examined.

In a prospective, multicenter, observational study, home self-administration of subcutaneous HBIg was evaluated in maintenance liver transplant patients. The objectives of the study were to assess patient compliance with their routine assigned regimen of subcutaneous HBIg self-treatment, as well as tolerability.

Material and Methods

Study design and conduct

This was a prospective, observational, open-label, single-arm study undertaken at 6 transplant
centers in Germany during October 2010 to March 2012. Maintenance liver transplant patients who were self-administering subcutaneous HBIG at home were followed for a minimum of 18 weeks. Written informed consent was obtained from all patients following protocol approval from the participating centers, and the study was conducted in compliance with the respective European and/or national regulations and recommendations.

Study population

There were no pre-specified inclusion or exclusion criteria for the study. Selection of patients for home administration of subcutaneous HBIG was at the physician’s discretion. The recommended criteria according to the Summary of Product Characteristics (SmPC) are: male or female patients aged 18 years or older who have undergone liver transplantation for HBV-induced liver failure a minimum of 6 months previously; HBsAg negative and HBV-DNA negative status; and a stable serum level of anti-HBs (300–500 IU/L) while receiving adequate intravenous HBIG at the time of switching to subcutaneous HBIG (measured 14–21 days after last intravenous infusion). The contraindications stated in the SmPC are hypersensitivity to human immunoglobulins or any of its components.

Treatment and monitoring

Subcutaneous HBIG (Zutectra®, Biotest AG, Dreieich, Germany) was purchased, prescribed, and monitored as per local standard practice. Subcutaneous HBIG is available as pre-filled syringes of 1 mL containing 500 IU per syringe. The SmPC recommends a dose of 500 IU/week in patients weighing <75 kg and 1000 IU/week in patients weighing ≥75 kg. If required, the dose can be increased up to 1000 IU/week to maintain an anti-HBs serum level >100 IU/L. Concomitant oral antiviral prophylactic therapy is to be considered, and the SmPC stipulates that patients should be monitored for serum anti-HBs levels regularly. No specific diagnostic or monitoring procedures were required in this observational study.

Before self-administration of subcutaneous HBIG at home, a sufficient surveillance period with stable anti-HBs trough serum levels >100 IU/L and a fixed dosage regimen are recommended. The SmPC also advises that the patient or caregiver should be instructed in injection techniques, the keeping of a treatment diary and measures to be taken in case of severe adverse events. In the event of significant and repeated missed data in the patient diary, the patient should be re-instructed and re-trained.

A treatment diary was provided to patients as part of standard care for subcutaneous HBIG therapy, and the physician was to review the diary at each visit.

Evaluation

Evaluation took place at routine clinic visits according to the local center schedule. At visit 1, baseline data were recorded. Visit 2 was expected to take place during weeks 2–6, and visit 3 (the final visit) took place approximately 18 weeks after inclusion. Other visits during the observational period were optional.

Study objectives

The primary study objective was to demonstrate tolerability and compliance of subcutaneous HBIG, with compliance failure defined as at least 1 anti-HBs serum trough level <100 IU/L, considered to be the minimum threshold for effective protection against HBV reinfection. Trough levels were to be measured prior to and as close as possible to the patient’s next self-injection. Secondary compliance variables were based on patient diary entries, and comprised adherence with agreed clinic visits, adherence with injection dates, and diary documentation. Compliance data based on the patient diary were graded by the physician on a 4-point rating scale (very good, good, moderate, or poor). Tolerability was assessed by adverse drug events reported by the patient at clinic visits or recorded in the treatment diary. Any reported adverse events were assessed by the physician as to whether there was a plausible causal relationship to subcutaneous HBIG treatment (yes/no) and categorized as serious or non-serious. Laboratory assessments included liver enzymes (alanine aminotransferase, aspartate transaminase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, and direct bilirubin), lactate dehydrogenase, blood glucose, urea, serum creatinine, serum protein, albumin, and electrolytes. Significant treatment failure was defined as reappearance of HBsAg and/or HBV-DNA in patients who were HbsAg- and HBV-DNA-negative at the start of therapy. Vital signs and body weight were recorded. Other documented variables included use of concomitant oral antiviral medication, action taken due to
application problems, changes to the HBIg dosing regimen, and the physician’s global assessment of subcutaneous HBIg treatment.

Statistical analysis

The planned number of patients was approximately 60 to ensure that 50 patients with evaluable data would be available for analysis. Data are presented descriptively. Continuous variables are shown as mean (SD) or median (range). All analyses are based on patients who received at least 1 dose of subcutaneous HBIg after the first visit and in whom at least 1 follow-up visit was completed. Anti-HBs serum levels were compared between visits based on patients for whom data were available at the first, second, and third (last) visits. The incidence of the primary variable – compliance failure – was estimated as a percentage with a 95% Clopper-Pearson confidence interval. All statistical analyses were performed using SAS® software (Version 9.2).

Results

Patient population

In total, 61 patients were enrolled in the study. All patients received at least 1 dose of subcutaneous HBIg and attended a minimum of 1 follow-up visit, and were included in the analysis. The mean (SD) observation period was 18.3 (2.2) weeks (median 18 weeks, range 14.0–27.9 weeks).

The median age of the population was 57.0 (range 26.0–75.0) years; 22 patients were aged over 60 years. The majority of patients were male (72.1%). The median time from liver transplantation to first study visit was 5.7 (range 0.2–19.0) years (Table 1). The indication for transplantation was HBV-induced cirrhosis in 82.0% of patients. Concomitant hepatocellular carcinoma was present in 37.7% of patients (Table 1). Six patients had undergone 1 previous liver transplant.

The characteristics of patients and the assigned treatment regimens differed from those recommended in the SmPC for home administration of subcutaneous HBIg in 31 cases (50.8%). In 29 patients (47.5%), using a fixed-dose intravenous regimen, anti-HBs serum levels were lower than 300–500 IU/L at the time of conversion to subcutaneous administration. Four patients did not meet the criterion of a sufficient surveillance period with stable anti-HBs trough serum levels >100 IU/L with a fixed-dosage regimen.

Table 1. Baseline characteristics (n=61).

| Age, years | Mean (SD) | 55.8 (9.6) |
| Male gender, n (%) | 44 (72.1) |
| Body mass index, kg/m² | 26.4 (4.5) |
| Indication for liver transplantation, n (%)* | 50 (82.0) |
| HBV-induced cirrhosis | 23 (37.7) |
| HBV-induced hepatocellular carcinoma | 6 (9.8) |
| HBV-induced acute liver failure | 5 (8.2)** |
| Retransplantation | 3 (4.9) |
| Other | 14 (23.0) |
| Co-infection | 2 (3.3) |
| Previous transplant, n (%) | 6 (9.8) |
| Time from liver transplant to first study visit, years | 6.2 (4.8) |
| Median (range) | 5.7 (0.2–19.0) |

* More than one indication was possible; ** one additional patient underwent retransplantation but this was not listed by the investigator as the indication for liver transplantation.

Four patients had not undergone liver transplantation due to HBV-induced liver failure at least 6 months previously (3 were less than 6 months post-transplant and 1 was transplanted for a non-HBV indication but received an HBV-positive graft).

Treatment

After starting subcutaneous HBIg, the median time to first home administration was 8 days (range 0–148 days). The median duration of home administration prior to study entry was 117 days, with a maximum of 370 days. Five patients (8.2%) were not self-administering HBIg at home at the time of study entry; the maximum delay from study entry to start of home administration was 27 days.

The dosing regimens prescribed by the treating physicians at the first and last study visit are summarized in Table 2. Overall, 57 patients (93.4%) were administered weekly injections, most frequently 500 IU/L (n=39, 63.9%). In 18 patients (29.5%), the dose assigned by the physician at first study visit was lower than that recommended in the SmPC. Three patients weighing <75 kg received a dose of less than 500 IU/week, and 15 patients weighing ≥75 kg received less than 1000 IU/week. For 1 patient prescribed a dose of 500 IU each week at study entry, the dose was...
increased by the physician to 1000 IU per week. In 2 patients, the dose was lowered to 500 IU every second week. Three patients who initially received 1000 IU per week were switched to 500 IU weekly. By the final visit, the mean (SD) dose was 589 (272) IU/week.

In 4 patients, the physician temporarily discontinued subcutaneous HBlg administration. As described below (see Compliance), treatment was interrupted in 2 patients when anti-HBs level was 169 IU/L and 114 IU/L, respectively, then restarted after it decreased to below 100 IU/L. In the other 2 cases, treatment was interrupted due to high anti-HBs serum level (570 IU/L and 420 IU/L), which had decreased to 117 IU/L and 102 IU/L, respectively, at the final study visit.

In total, 1006 injections were recorded in the patient diaries (mean 16.5 injections per patient), of which 961 (95.5%) were administered at home. Of these 961 injections, 924 (96.1%) were administered by the patient and 47 (4.9%) by a family member. In 1 patient, the site of injection was changed, but there were no other changes made due to application problems during the observation period.

HBlg was combined with nucleos(t)ide analogues as reinfection prophylaxis in 41 patients (67.2%) during the observation period, comprising lamivudine (n=27), tenofovir (n=8), adefovir (n=3), and entecavir (n=3).

Compliance

Anti-HBs serum level was available at the first, second, and third (final) visit for all but 1 patient. Among these 60 patients, the mean (SD) level at these visits was 248 (97) IU/L, 266 (110) IU/L, and 255 (104) IU/L, respectively, representing a mean difference of 18 (78) IU/L between the first and second visits, and 7 (97) IU/L between the first and final visits (Figure 1). The mean (SD) time between measurement of trough anti-HBs serum level and the next self-injection was 6.8 (7.6) days (median 6.0, range 1.0–61.0 days).

The primary variable of compliance failure, defined as at least 1 anti-HBs serum trough level <100 IU/L, occurred in 4 patients (6.6%; 95% CI 1.8%, 15.9%) during the observation period. An anti-HBs serum level <100 IU/L was observed once in 3 patients and twice in 1 patient. At the final study visit, the anti-HBs serum level exceeded 100 IU/L in all patients, including
these 4 individuals. In 3 of the patients with low anti-HBs-levels, the initial dose of HBIg was only 500 IU/L per week despite body weight exceeding 75 kg (ie, dosing was inadequate according to body weight). In 1 of these patients, the dose was increased to 1000 IU/L and anti-HBs level then exceeded 100 IU/L. In the other 2 patients, the level fell below 100 IU/L during a period of temporary treatment discontinuation. Following reintroduction at a dose of 500 IU/L per week, both patients again achieved anti-HBs serum trough levels above 100 IU/L, despite being below the recommended dose. Nevertheless, the physician discontinued treatment in 1 of these cases. In the final patient, weighing 120 kg, the anti-HBs level decreased from 142 IU/L at baseline to 63 IU/L approximately 1 month later, even through the recommended dose of 1000 IU/L per week was administered. The site of injection was changed to the thigh, and a single dose of intravenous HBlg (2000 IU) was administered. All subsequent serum trough levels of anti-HBs exceeded 100 IU/L, with a value of 116 IU/L at the final visit.

Compliance data from the patient diaries was graded by physicians and categorized according to the lowest score at the second or the final visit. Compliance with scheduled clinic visits and injection dates were graded very good or good in approximately 90% of patients (Table 3). Compliance with diary documentation was very good or good in 72.1% of patients (Table 3). No patient required any re-instruction or re-training during the observation period.

Tolerability

During the observation period, 33 patients (54.1%) reported 98 adverse events, most frequently headache (8 reports in 6 patients), nasopharyngitis (n=5), oropharyngeal pain (n=4), and biliary ischemia (n=4). Four patients experienced a total of 6 suspected adverse drug reactions (ie, adverse events considered by the physician to be related to subcutaneous HBlg). These were nasopharyngitis, muscle spasms, oropharyngeal pain, hematoma, and abnormal renal function, each of which was reported in 1 patient. One adverse drug reaction was reported by the physician as ‘HBsAg serum level <100 IU/L’, measured during laboratory testing. This low level was not associated with any clinical adverse drug reaction or reinfection. Eleven patients (18.0%) experienced a total of 14 serious adverse events, none of which was considered to be related to subcutaneous HBlg. No patient discontinued HBlg treatment temporarily or permanently due to adverse events.

Three patients (4.9%) developed laboratory values outside the normal range during the observation period; these were considered by the investigator to be clinically relevant but not related. One patient experienced an increase in LDL-cholesterol, 1 patient had a reduction in urea levels, and 1 patient developed decreased urea and increased serum creatinine. Blood pressure, heart rate, and body weight showed no relevant changes.

Efficacy

Data on HBsAg status were available for 57 patients at the first visit and at the final visit, all of whom were negative. HBV-DNA status was recorded in 59 patients at the first visit and 50 at the final visit, and all results were negative.

Physician experience

The physicians’ global assessment of treatment with subcutaneous HBlg was very good, good, and moderate in 11, 49, and 1 case (18.0%, 80.3%, and 1.6%), respectively. In no cases was the assessment poor or very poor.

Discussion

In this prospective, multicenter, observational study, all patients who self-administered
subcutaneous HBIG at home under routine clinical management had anti-HBs serum concentrations above the protective trough level of 100 IU/L at the final study visit, with no treatment failure or HBV reinfection. Compliance with subcutaneous self-administration was good and treatment was well-tolerated, with no interruption or discontinuation of treatment due to adverse events. These findings are consistent with the results from a single-center study of subcutaneous HBIG therapy in which patient selection criteria, dosing regimen, and monitoring frequency were all specified by protocol [20].

In this real-life population, half of the patients did not fully meet the criteria for initiation of subcutaneous HBIG as recommended in the prescribing information, most frequently due to absence of a stable anti-HBs serum level of 300–500 IU/L while receiving adequate intravenous HBIG prior to conversion. Moreover, almost one-third of patients received a dose below that recommended in the SmPC based on their body weight. Despite this, the mean level of anti-HBs for the total study population was 254.3 IU/L at the final visit, well above the threshold of 100 IU/L that is widely believed to protect against HBV reinfection. Among the 4 patients with 1 or more serum levels below 100 IU/L prior to the final visit, 3 received an initial dose lower than recommended, and in these patients either the low serum level only developed during temporary interruption of treatment or it increased to above 100 IU/L after the dose was increased. Importantly, all patients remained negative for HBV-DNA and HBsAg during the 18-week observation period, including those who received less than the recommended dose. In the absence of any protocol-specified dosing algorithm, physicians did not adjust the dose upwards if the anti-HBs titer was in the 100–150 IU/L range, as was specified in a previous protocol-led study [20]. In that trial, the strategy was found to result in over-treatment [20]. The less aggressive approach to dosing compared to the SmPC, which was seen in this observational study, appeared to maintain efficacy without use of excessive doses.

All patients could successfully self-inject with no need for re-training during the study period, administering either 1 or 2 pre-filled syringes of HBIG according to the prescribed dose, as has been described previously [20]. The high rate of compliance with self-administration, as assessed objectively by anti-HBs serum levels and subjectively by the patient diaries, suggests that the standard instructions given at the centers were adequate. Monitoring based on anti-HBs level appears appropriate, prompting a dose increase in a previously under-dosed patient and a change in injection site in another patient.

The incidence of suspected adverse drug reactions was low (6.6%), and no serious adverse events were considered by the investigators to be related to HBIG treatment. There was no reinfection reported, although some HBIG levels were below 100 IU/L. There was only 1 injection site-related adverse drug event (a hematoma) and no patient reported injection site pain. No adverse event led to temporary or permanent discontinuation of treatment, consistent with results of a previous analysis [20].

An observational design was selected to allow the use of subcutaneous HBIG to be assessed under real-life conditions, including physician-led decisions on patient selection and training, and on dosing and monitoring. While this offers the advantage of evaluating compliance and outcomes under routine conditions, we recognize that there was no control arm and that physician assessments of diary entries were subjective, with no central review. However, the objective measurement of anti-HBs serum levels and the presence or absence of HBVDNA and HBsAg provided a robust measurement of compliance with home administration, if the dose was adjusted adequately by the physician. Adverse event reporting was based on patient feedback at clinical visits and via diaries, instead of using standard clinical trial reporting procedures.

**Conclusions**

These results demonstrate that self-administration of subcutaneous HBIG (500 IU/L) at home maintains an adequate anti-HBs serum concentration to protect against HBV reinfection in maintenance liver transplant recipients. The rare and short-lived instances of low anti-HBs levels were mainly due to temporary interruption of treatment by the physician or administering a dose lower than that recommended for the patient’s body weight. It would seem advisable to adhere to weight-based dosing recommendations when switching from intravenous to subcutaneous administration, and to monitor anti-HBs levels regularly to allow for HBIG dose adjustments based on trough levels. This is particularly important in the event of temporary treatment discontinuation, to avoid exposure to risk of reinfection. Compliance with subcutaneous HBIG home self-administration...
is good, achieves effective prophylaxis, and offers convenience for the patient, with potential cost savings for the health care provider.

Conflicts of interest

CGK, HS, TG, FB, and SZ have no conflicts of interest to declare. MNS has received speaker’s honoraria and travel grants from Biotest. VC and SB have received speaker’s honoraria, travel grants, and research funding from Biotest. AWD and GN are employees of Biotest.

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