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ORIGINAL ARTICLE

Efficacy and safety of subcutaneous human HBV-immunoglobulin (Zutectra®) in liver transplantation: an open, prospective, single-arm phase III study

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Keywords
hepatitis B, hepatitis B immunoglobulin, liver transplantation, re-infection prophylaxis, subcutaneous application.

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The authors have declared no conflicts of interest.

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Summary

Hepatitis B re-infection prophylaxis is crucial for graft and recipient survival for transplanted patients and is administered routinely after liver transplantation for hepatitis B. Aim of the current study was the investigation of efficacy, safety and feasibility of home-treatment of a novel human hepatitis B immunoglobulin BT088 (Zutectra®) after weekly subcutaneous application in liver-transplanted patients. A total of 23 patients (5 female, 18 male, median age 51 years) were enrolled and switched from monthly IV to weekly SC hepatitis B immunoglobulin administration. During a period of 18 weeks (optional 24 weeks) anti-HBs levels, signs of re-infection, adverse events and feasibility of self-administration were studied. After 8 weeks of training patients showing good compliance and stable antibody titres were allowed to start self-administration at home. All patients maintained a safety level of >100 U/l anti-HBs. No failure was noted, no re-infection occurred. A total of 10 treatment-emergent events were assessed as related to study drug application (injection-site haematoma, headache, abdominal pain, fatigue and haematuria). High numbers of self-administration (287 vs. 122 by staff) demonstrated general feasibility of SC administration. Weekly subcutaneous administration of BT088 (Zutectra® – registered trade mark in the EU) is effective, safe and presents an easy-to-apply treatment option for combined hepatitis B virus re-infection prophylaxis in liver transplant patients (Eudra CT Number: 2005-003737-40).

Introduction

Patients undergoing liver transplantation because of hepatitis B virus (HBV) infection-related liver disease are at highest risk for developing HBV re-infection of the transplanted organ leading to graft failure and high patient mortality (1). Therefore, life-long combined oral antiviral and immune prophylaxis by intravenous (IV) administration of hepatitis B immunoglobulines (HBIg) is known to be a potent option to decrease re-infection rates in this population dramatically to a level of 0–10% (2). Increasing expenses as well as the need to administer HBIg intravenously at the hospital have led to investigate more cost-effective and simple treatment options. Several studies have investigated combined re-infection prophylaxis with low-dose monthly intramuscular (IM) HBIG and lamivudine showing promising low-recurrence rates (3,4). IM administration appeals to be a cost-saving alternative to iv administration but still has some limitations. For instance, this administration route is contraindicated in patients suffering from coagulopathies or patients with oral anticoagulation. Moreover IM administration is

considered to be more painful than subcutaneous (sc) administration and therefore would have an effect on the patient's well-being leading to a lack of compliance. Furthermore, IM HBIG is not licensed for prophylaxis of HBV re-infection after orthotopic liver transplantation (OLT). In recent studies, protocols were evaluated for HBIG discontinuation showing promising results concerning short-term outcomes (5,6) but on the long-term follow-up increasing recurrence rates (11–17%) were described (7). However, data on HBIg-free prophylaxis protocols are limited and need to be investigated more intensely. The SC administration route would be preferable for various clinical settings to improve safety and decrease costs because of the possibility of self-administration by the patient at home (8). Patients with liver failure secondary to hepatitis B will greatly benefit from convenient administration of a SC preparation of HBIg, especially in view of potentially life-long treatment requiring frequent injections. However, after IM and SC application bioavailability of anti-HBs may be different (9); as levels of anti-HBs after IM administration show a different pharmacokinetic profile than after IV administration. In previous studies, these administration routes provided sufficient anti-HBs titres above 100 IU/l to protect against re-infection in liver transplant patients (10). A study by Faust *et al.* (11) showed that IM application is an effective and safe option to avoid re-infection in liver-transplanted patients.

Hepatitis B immunoglobulin (BT088), a novel HBIg with high specific anti-HBs activity (500 IU/ml) and the first HBIg approved for SC application in a prefilled syringe was developed by Biotest AG, Dreieich Germany. Results of a preclinical study in rabbits to investigate local tolerability of BT088 showed that the new preparation was well tolerated after a single SC injection. Results of an open, randomized parallel phase I study investigating safety and pharmacokinetic properties of BT088 after SC or IM application in 30 male and female healthy volunteers with a single dose of 30 IU/kg body weight presented pharmacokinetic characteristics which were comparable with data of human HBIg after IV administration (12). Mean anti-HBs serum concentrations increased to maximum values on day 4 after dosing and the mean elimination half-live was 3–4 weeks. The administration of BT088 was well tolerated and safe. This phase I pharmacokinetic study demonstrated the feasibility of maintaining anti-HBs levels >100 IU/l with SC and IM administration of BT088 HBIg and further showed that the elimination half-life (3–4 weeks) is as predicted with naturally occurring immunoglobulin as with IV administered HBIG (Hepatect® CP – registered trade mark in the EU, Biotest) (13,14). An open, prospective phase III trial to investigate the infection prophylaxis in neonates is currently ongoing. Main objective in this open, prospective single-arm phase III trial was to demonstrate the efficacy of the SC application of the new human HBIg BT088 in patients after liver transplantation for hepatitis B. Secondary objectives comprised the number of hepatitis B-related (re-) infections and safety data as well as the feasibility of the SC self-administration at home.

Materials and methods

Overall study design

In the initial study design, it was planned that the patients were switched from their standard IV HBIg either to a weekly SC or IM application of BT088 with doses of 500 IU/week. During the course of the study, three of seven patients treated according to the initial study design showed clear trend of decreasing anti-HBs titres. Therefore, the initial study was stopped and a protocol amendment was implemented to allow a dosage adjustment up to 1000 IU/week to ensure sufficient anti-HBs concentrations (≥100 IU/l).Thus, the weekly standard dose of Zutectra® was 500 IU (1 ml) BT088 for patients with body weight <75 kg and 1000 IU (2 ml) for patients with body weight ≥75 kg. The study design included the possibility to adapt the dose individually, e.g. in case of higher antibody consumption. As the IM administration of 2 ml BT088 into the deltoid muscle could impair the patient's well-being and consecutively compliance, the IM study arm was cancelled and only the SC study arm retained. It was considered that local pain would impose a limitation to the quality of life (QoL) in a population of patients for whom long-term if not lifelong administration was foreseen on a weekly basis. Even overlooking the volume limitation, the requirement for medically trained staff for IM dosing would make this mode of administration inappropriate in a homecare setting in contrast to SC application that allows self-administration at home and improves the patients' well-being.

Self-administration at home was only allowed for patients compliant with the injection technique and presenting sufficiently high trough serum anti-HBs concentrations.

Study description

Trough levels of the serum HBs antibody concentrations were determined weekly prior to each application for the first 4 weeks followed by regular intervals fortnightly until day 127. For investigation of efficacy of BT088, clinical data – including hepatitis B-related infections – were documented in the same patients during the follow-up.

Between August 2006 and March 2008, 23 OLT patients were enrolled (18 male and 5 female at the

median age of 51 years) undergoing postoperative combined prophylaxis with HBIg and lamivudine.

Main inclusion criteria were male and female patients (age 18–75 years), ≥3 months after liver transplantation, long-term prophylaxis against hepatitis B re-infection with an anti-HBs level of 300–500 U/l after the last administration of HBIg, stable graft function and negativity for HBsAg and HBV-DNA [measured by a central laboratory using AxSYM HBsAg ELISA Assay (Abbott GmbH & Co. KG, Wiesbaden, Germany), detection limit 10 mIU/ml] and HBV-DNA [Cobas Taqman HBV-DNA RT-PCR Assay, detection limit 6 IU/ml (Roche Molecular Systems Inc., Pleasanton, CA, USA) and HBV-DNA 3.0 Assay (bDNA), limit 357 IU/ml (Bayer Healthcare, Tarrytown, NY, USA)]. Particular inclusion and exclusion criteria are shown in Tables 1 and 2.

Patients were converted from the monthly IV standard HBIg treatment to weekly SC HBIg (BT088, market name Zutectra®; Biotest AG, Dreieich, Germany) 14–21 days after the last IV dosage to ensure adequate anti-HBs coverage during the transition from IV to SC dosing. The study period comprised 18 weeks with an optional extension for another 6 weeks (in case of patients interest, stable anti-HBs titres and compliance with the injection technique) building a total study duration of 24 weeks. HBIg was applied via the SC route weekly for 18 (24) weeks; after the closing visit on day 127 (168) the respective standard IV HBIg dosing scheme was resumed. After 8 weeks of training on self-administration, patients showing good compliance and stable antibody titres (trough levels of ≥150 IU/l) were allowed to start self-administration at home. A minimum serum anti-HBs level of ≥100 IU/l had to be maintained to complete the study.

Table 1. Main inclusion criteria of the study.

- Male and female patients (age 18–75 years)
- ≥3 months after liver transplantation
- HBsAg negative
- Regular long-term HBIg prophylaxis (combined re-infection prophylaxis) with stabilized HBIg dosage and administration intervals
- Stable liver function
- After the last IV administration of HBIg baseline serum HBs antibody concentration ≥300–500 IU/l should be achieved prior to the first dosing of BT088 at visit 2

HBIg, hepatitis B immunoglobulin.

Table 2. Main exclusion criteria of the study.

- Pregnancy or unreliable contraceptive measures or lactation period (women only)
- Known intolerance to immunoglobulins or comparable substances (e.g. vaccination reaction)
- Known intolerance to proteins of human origin
- Selective absolute IgA deficiency
- Positive HIV or HCV test
- Unexplained elevation of liver enzymes
- Ongoing acute rejection episode
- Renal insufficiency (dialysis) or other serious organ dysfunctions
- Life expectancy below 6 months
- Administration of plasma preparations or other immunoglobulins during the conduct of the trial
- Patients who are known to be HBV-DNA positive

IgA, immunoglobulin A; HBV, hepatitis B virus; HCV, hepatitis C virus.

The study was performed according the legal requirements of the German Drug Law (ABG) and the EU Clinical Trials Directive (2001/20/EC) taking into account the principles of Good Clinical Practice (ICH GCP) and the Declaration of Helsinki (revision 1996). Each patient provided written informed consent before enrolment in the study.

In collaboration with the academic investigators, the study design, collection and analysis of data were performed by Biotest AG, Germany. Blood samples were measured centrally in a central laboratory (Dr. Spranger und Partner, Ingolstadt, Germany),

Investigational product

BT088 (Zutectra®) is a purified human HBIg preparation obtained from plasma from selected and/or immunized donors having antibodies against hepatitis B surface antigen (anti-HBs) fractionated according to a modified cold ethanol plasma fractionation method by Biotest AG, Dreieich, Germany. It is a sterile solution for SC injection containing 150 mg/ml human plasma protein with at least 96% IgG and 500 IU/ml anti-HBs antibody. The product is considered a further development of an already approved HBIg preparation for IV administration (Hepatect® CP) with the difference being that the IV product is less concentrated. BT088 (Zutectra®) is presented in 1 ml pre-filled glass syringes. Final purification using cation exchange chromatography, nanofiltration, concentration and purification by ultra- and diafiltration, adjustment of protein concentration and pH, and subsequent filtration formulation and filling the product into 1-ml syringes result in the drug product Zutectra® which should be stored and transported refrigerated at 2–8 °C.

The second batch of BT088 which was introduced during the study after the expiry of the first batch included the additional nanofiltration step.

Study objective

Primary efficacy parameter

The trough levels (C_{trough}) of serum anti-HBs antibodies, determined at the end of a dosing interval directly before

the next administration represented the primary efficacy objective.

Trough levels of serum anti-HBs were determined for 18 (24) weeks to assess if serum concentrations ≥100 IU/l were achieved after SC treatment. At the screening examination, weekly prior to each application of BT088 for 4 weeks until day 29, followed by regular intervals fortnightly until day 127 (closing visit) prior to the infusion of standard HBIg. Sampling times for the facultative study extension were day 148 and day 169 (closing visit).

The failure rate after 18 weeks and the respective 95% confidence interval were calculated using the Clopper Pearson method. A failure was defined by two possible outcomes: (i) anti-HBs concentrations <100 IU/l at last visit or (ii) serum HBs antibody concentrations tending to decrease below a value of 100 IU/l during the weekly SC dosing schedule, resulting in premature withdrawal of the patient from the study by the investigator.

Secondary efficacy parameter

The secondary efficacy parameter was the number of patients with hepatitis B-related infections as assessed by monitoring of clinical signs, liver function and measurement of HBsAg.

At each visit, clinical signs of hepatitis B infection were monitored regularly and concomitant medications were recorded in the CRF (case report form) [correction made here after online publication, 16 February 2011. 'corticotropin-releasing factor' changed to 'case report form']. Measurements of HBsAg had to be performed at the initial visit, on days 1, 29, 57, 85 and at the closing visit on day 127 (additional closing visit for the facultative extension on day 169). In case of clinical or paraclinical signs of re-infection, HBV-DNA measurement had to be performed additionally.

Safety parameters

Safety and tolerability issues were addressed by (i) occurrence of adverse events, (ii) rate of premature withdrawals, (iii) changes in clinical laboratory parameters and changes in vital signs.

Adverse events were analysed for treated patients. Incidences of adverse events were given stratified for seriousness, intensity, relationship to trial medication, countermeasures and outcome. For evaluation of safety, a physical examination including assessment of heart rate, blood pressure and body temperature was performed at the initial visit, on days 1, 29, 57, 85 and at the closing visit on day 127(169) to detect any possible adverse events or other changes in the course of the patients clinical condition. The patients were asked about adverse events at all visits and kept a diary which was surveyed at each visit to document changes of well-being and concomitant medications during the course of the trial. Safety laboratory parameters including haematology [WBC (white blood cell count), RBC (red blood cell count), haematocrit and platelets] and clinical chemistry [ALAT (alanine aspartate transferase), ASAT (aspratate amino transferase), γ-GT (gamma glutamyl transferase), AP (alkaline phosphatase), bilirubine, total protein, albumin, LDH (lactate dehydrogenase), creatinine, sodium, chloride, potassium, calcium, urea, glucose, Quick, partial thromboplastin time, IgM, IgG and IgA] were recorded at the initial visit and on day 1 before the injection, as well as on other visits given by the study design – the immunological parameters at the same time points, except for day 57. Urine analysis for glucose, protein, pH, nitrite, ketone bodies, urobilinogen, bilirubin, qualitative for blood and leucocytes was performed.

Feasibility parameter

Feasibility criteria evaluated until week 18 were percentage of self-administration, time to first self-administration and time to complete self-administration. In the beginning of the trial patients underwent a training period and practised the SC injection technique. The study staff supervised the study drug administration and documented if the patient completed the self-administration independently or if assistance was provided. During the time of home self-administration, the patient's diary was surveyed regularly by the medical staff. For transportation, the centres provided the patients approved cooling bags to keep the cool chain intact. Moreover, patients were instructed to store the syringes in a home refrigerator (2–8 °C).

Statistics

Descriptive statistical evaluations were performed. No formal inferential tests were carried out. Descriptive statistics on all parameters collected for trough serum anti-HBs levels (C_{trough}), safety or tolerability were carried out. Within a repeated measurement model the values for C_{trough} in dependence of the time were analysed. For each patient, it was assessed if there was a trend in the values of C_{trough} over time. The failure rates after 18 and 24 weeks of treatment and the respective 95% confidence intervals were calculated using the Clopper Pearson method.

Populations of analysis

The safety set consists of all patients who received at least one dose of study medication. The intention-to-treat set (ITT) consists of all patients of the safety set, where the pharmacokinetic data are considered to be sufficient. The per-protocol (PP) set consists of all patients of the ITT set, who finished the study according to the protocol or

who terminated the study because of an event related to the study medication.

Results

Patient disposition

The safety set includes 30 patients who had stable virological, immunological and biochemical characteristics after liver transplantation, e.g. (HBsAg-cleared and HBV-DNA-negative). The ITT set included 23 patients, five female and 18 male. Seven patients who started the study in 2006 according to the initial study design (randomization to SC or IM administration) were excluded. The PP set included 22 patients because one patient with a major protocol violation (IV infusion with other HBIg product) was excluded. A total of 16 patients entered the 6-week extension of the study. Details on the patient population are shown in Fig. 1.

Patient demographics of the ITT set are shown in Table 3. Causes for transplantation were acute and chronic liver disease caused by HBV as well as associated impairments including re-transplantation after OLT for HBV as listed in Table 4. Previous and concomitant virostatic therapy as well as immunosuppression are depicted in Tables 5 and 6, respectively.

Primary efficacy results

All patients adhered to the schedule for measuring serum HBs antibody concentration after application of BT088 on day 1. The mean linear and log-linear serum HBs antibody concentrations measured during the course of the study for the ITT set are displayed in Fig. 2. The log-linear values represent the natural logarithm of the measured antibody concentrations (linear values). Over the course of the study, the mean linear serum HBs antibody concentrations achieved after SC treatment were relatively constant within a range of 350–400 IU/l. At every time point of the study period, the serum HBs antibody concentration in each patient was >100 IU/l. The available data on HBs antibody concentration for the excluded seven patients were also within the therapeutic range

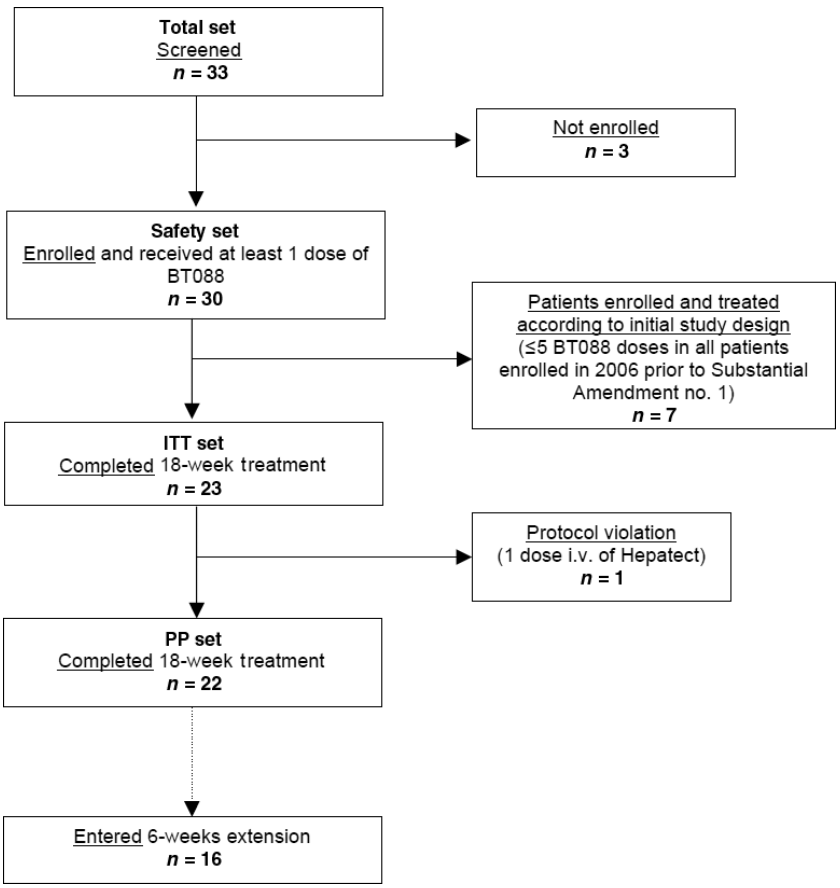

Figure 1 Patients' disposition. This figure demonstrates the different populations analysed during the study including withdrawals according the study design.

Table 3. Patient demographics (intention-to-treat set, $n = 23$).

Demographic variable		
Age [years], mean (SD)		50.8 (10.4)
Height [cm], mean (SD)		171.2 (9.2)
Weight [kg], mean (SD)		74.7 (15.3)
BMI [kg/m^2], mean (SD)		25.5 (4.2)
Time between liver transplantation and first injection of BTD88 [years], mean (SD)		5.1 (3.1)
Time between last administration of standard HBIg and first administration of BT088 [days], mean (SD)		20.3 (22.2)
Gender [*n*] (%)	Female	5 (21.7)
	Male	18 (78.3)
Ethnic origin [*n*] (%)	Caucasian	23 (100.0)
Smoking [*n*] (%)	Never	16 (69.6)
	Occasional	4 (17.4)
	Daily	3 (13.0)
Alcohol [*n*] (%)	Never	20 (87.0)
	Occasional	3 (13.0)

BMI, body mass index; HBIg, hepatitis B immunoglobulin.

Table 4. Reasons for transplantation (ITT set, $n = 23$).

Reason	*n*	%*
Chronical HB-cirrhosis	18	78.3
Acute liver failure	6	26.1
Co-infection	3	13.0
Retransplantation	1	4.3
Other	5	21.7

n, number of patients.
Several reasons per patient are possible.
*Calculation of percentages based on the total number of patients in the intention-to-treat (ITT) set.

Table 5. Previous/concomitant virostatics (ITT set, $n = 23$).

ATC code description	*n*	n_D	%*
Lamivudine	15	15	93.8
Tenofovir	1	1	6.3
Valaciclovir hydrochloride	1	1	6.3
Valganciclovir hydrochloride	1	1	6.3

n, number of patients; n_D, number of medications.
*Calculation of percentages based on the total number of patients in the intention-to-treat (ITT) set.

(>100 IU/l). No premature terminations caused by adverse events or because of lack of efficacy occurred. The majority of patients were treated with 500 IU. Nine patients received a constant dose of 500 IU weekly. In five patients, a constant dose of 1000 IU/week was administered. Three patients received a higher (1000 IU) and four patients received a lower dose (500 IU) than required by the study amendment. In two of these patients, dose was reduced or increased during the course of the study. In four patients, an increase of the dosage of 1000 IU was conducted by the responsible investigators without a tendency of decreasing antibody titres. In two patients, a dose increase was conducted because of decreasing antibody titres and in only one of these patients a temporary dose increase to 1500 IU was administered. However, no patient had an increase of the dose because of a drop of the HBs antibody level below the defined minimum level of 100 IU/l.

Table 6. Previous/concomitant immunosuppressives (ITT set, $n = 23$).

ATC code description	*n*	n_D	%*
Tacrolimus	15	39	65.2
Mycophenolate mofetil	8	13	34.8
Ciclosporin	7	20	30.4
Sirolimus	1	1	4.3

n, number of patients; n_D, number of medication.
*Calculation of percentages based on the total number of patients in the intention-to-treat (ITT) set.

Failure during study period

Using the Clopper Pearson method, the failure rate after 18 weeks was 0% for patients of the ITT set (95% CI: [0%, 14.8%]). A failure rate of 0% was also found for the facultative extension phase (week 24) (95% CI: [0%, 20.6%]).

Secondary efficacy results

No patient (0/23) showed a hepatitis B re-infection (HBsAg positive) throughout the complete study period.

Safety results

A total of 139 adverse events occurred; 135 were treatment-emergent adverse events (four were present at baseline) and were reported in 24/30 patients (80.0%). The investigators assessed 24 events as not related to the study medication, 101 events as unlikely to be related. Seven adverse events were possibly related (headache, haematuria, fatigue and abdominal upper pain) and one as probably related (injection-site haematoma). For two events the relationship was assessed as certain, which were both described as mild haematoma at the injection site. At the end of the study, 117 events were resolved, two were in the process of resolving, 11 were not resolved and five were of unknown outcome. A total of 19 serious adverse

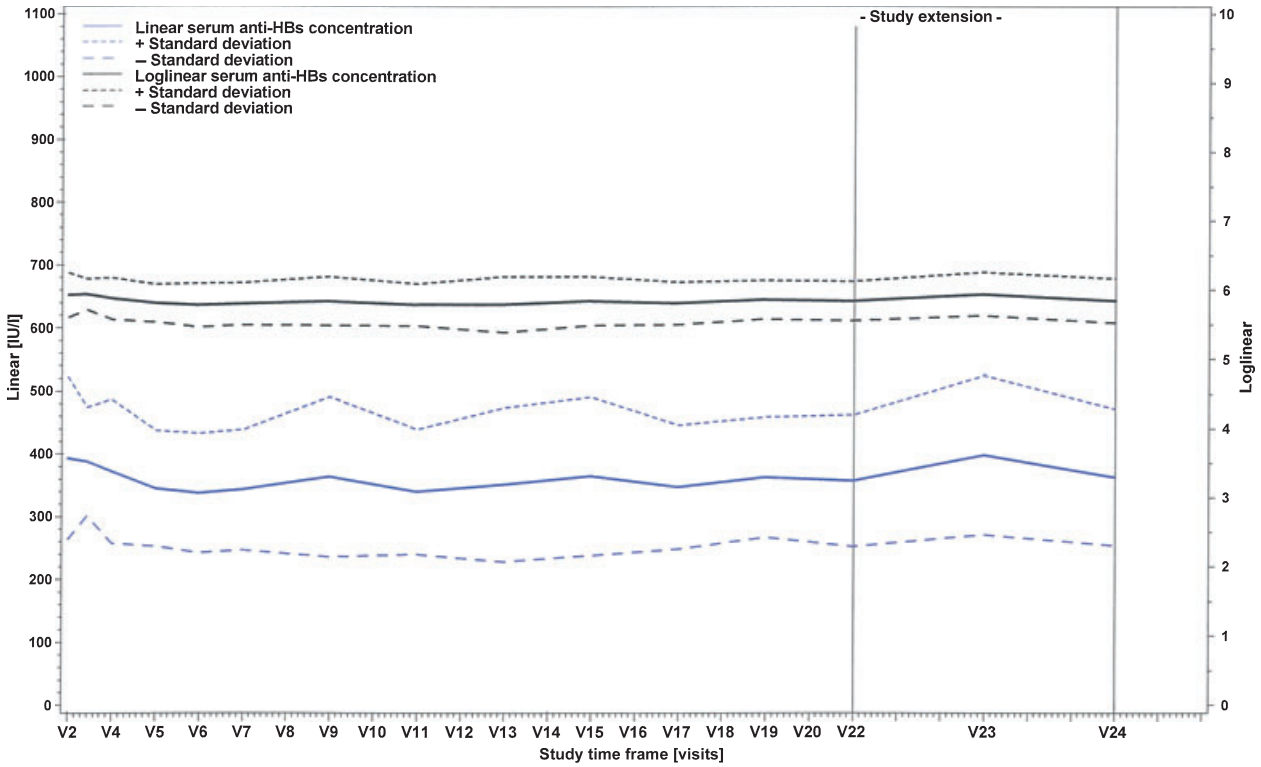

Figure 2 Mean course of serum anti-HBs concentration over time. Demonstration of the course of mean serum anti-HBs levels of patients of the ITT set (n = 23) during the study period of 18 or optionally 24 weeks. A stable maintenance of anti HBs levels of around 350–400 IU/l was recorded.

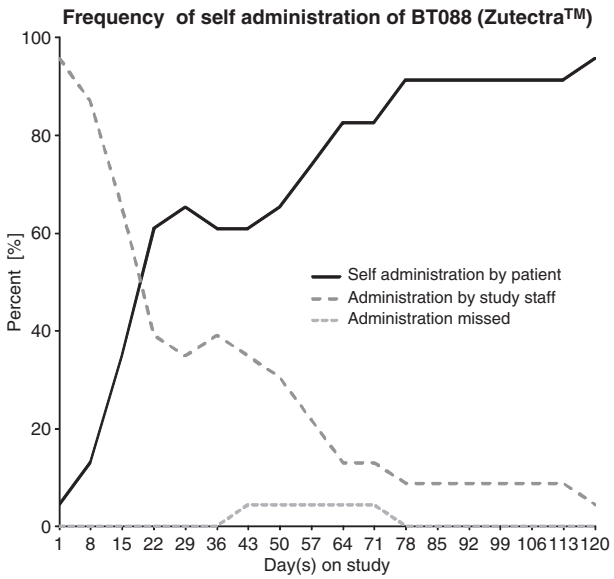

Figure 3 Frequency of self-administration of BT088. Illustration of the development of self-administrations in the ITT set (n = 23). A total of 409 administrations were performed. A steadily increase of self-administration during the study period was recorded.

events were reported in 9/30 (30%) patients, 16 of which were treatment-emergent. Ten of those latter serious adverse events were assessed as unlikely related, six as not related, none were considered possibly, probably or certainly related. At the end of the study, 15 events were resolved; one was in the process of resolving. No clinically relevant changes in safety laboratory parameters, vital signs and physical condition were observed.

Feasibility results

A total of 409 administrations to patients of the ITT were administrated with an average of 287 (70.2%) self-administrations and an average of 122 (29.8%) were administrations by study site staff. Five administrations were missed by one patient who did not appear to four consecutive visits (9–12) and did not receive BT088 at visit 13 but IV anti-HBV IgG (Fig. 3). The number of patients with self-administration of BT088 increased steadily during the study, from one patient (4.4%) on day 1 to 14 patients (60.9%) on day 22 and to 22 patients (95.7%) on day 120. One remaining patient preferred injections by study

staff. The mean time to first self-administration by the patients was 32.8 ± 30.5 days and the mean time to complete self-administration was 47.4 ± 39.1 days.

Discussion

The study was initially planned as a randomized comparative trial assessing trough levels of patients administered with HBIg either via IM or SC routes. However, after enrolling seven patients, the trial was suspended and amended to continue as a single-arm, non-randomized, observational trial using only the SC route of administration. After enrolment of the first patients and collection of data from up to five doses of BT088, it was determined that the dose should be increased to 1000 IU/week for patients with a body weight of ≥75 kg or higher antibody consumption. Patients with a higher body mass index may have a greater amount of SC tissue and an extended SC space that could lead to slower absorption from SC space and/or lower bioavailability. In the study, the dosage was adapted individually, according to the serum anti-HBs concentrations, up to 1500 IU/week in patients with higher body weight or higher antibody consumption to ensure sufficient anti-HBs concentrations (≥100 IU/l). IM HBIg maintenance prophylaxis in place of IV has become standard care at many centres. However, the IM route of administration was sometimes painful, and local side effects seemed to affect some patients' QoL. Moreover, there are some contraindications for IM injections, e.g. in patients suffering from coagulopathies or on oral anticoagulation medication. Maintenance HBIg prophylaxis is a life-long endeavour for OLT recipients at risk. SC administration, which can be carried out at home by patients, simplifies treatment for patients, who typically have to travel to receive IV or IM therapy or must set aside time to get treatment at home from a visiting nurse (8,15,16). As the IM administration of 2 ml BT088 into the deltoid muscle could impair the patient's well-being and consecutively the compliance, the IM study arm was cancelled and only the SC study arm retained in our study. For many patients, SC injections improve QoL by offering greater independence and better control of the therapy situation and daily life. Studies on QoL during immunoglobulin replacement therapy in primary immunodeficiency syndromes compared hospital iv therapy versus SC home self-administration. Moreover, home self-administration may contribute to decrease costs by avoiding the need for an appointment with a doctor/a nurse in a hospital. The switch to SC treatment at home resulted in a gain of QoL, including improvements in the scales for vitality, mental health and social functioning. Treatment satisfaction increased and 73% of the adults preferred SC over iv treatment (17). The high number of BT088 self-administrations (287 vs. 122 by study site staff) of patients of the ITT set demonstrates the general feasibility of self-administration in our study. The number of patients with self-administration of BT088 increased steadily during the study up to overall 22 patients (95.7%) on day 120. The mean time to first self-administration by the patients was 32.8 ± 30.5 days. Treatment compliance was good, the once weekly dosing also facilitates compliance, as the patient does not have to count weeks between doses. Regular SC dosing (generally weekly) at a level high enough to provide sufficient protection (and minimal injection volume) constitutes standard care in the related indication of normal immunoglobulin replacement therapy for patients who have a primary immunodeficiency and require life-long protection. Home care has been successfully implemented in this setting (18,19), although injection volumes are larger in this indication (10–20 ml) than for HBIg prophylaxis (1–2 ml). The small injection volumes in our study (a single ml for 500 IU dose) were very well tolerated. The need for intermittent dose increase in one patient indicates interindividual differences in the pharmacokinetic profile of BT088 leading to the necessity of regular antibody measurement. In total, 2/30 patients experienced two episodes in injection-site bruising, and these patients completed the study with no missed doses. All 23 patients achieved the primary endpoint of maintaining serum HBs antibody concentrations ≥100 IU/l. A minimum level of serum anti-HBs antibodies of ≥100 IU/l is state of the art in clinical practice and commonly accepted as protective level in HBV re-infection prophylaxis (20,21). With the weekly administration of BT088 HBIG all patients trough levels of >100 IU/l serum anti-HBs were maintained (safety population, $n = 30$) at all time points. Mean anti-HBs levels were more or less constant and within the range of 350–400 IU/l during the 18- to 24-week study period. This steady level of exposure with lower peak levels and higher trough levels compared with iv administration is considered to be advantageous. The lower peak levels reduce the risk of severe headache and other systemic adverse events, whereas the higher trough levels provide more protection against breakthrough infections (19,22,23). Overall the adverse event data indicate that treatment with BT088 is well tolerated and safe after SC administration. Furthermore, no relevant changes in safety laboratory parameters, vital signs and physical condition occurred, confirming safety of BT088 in male and female liver-transplanted patients and suggesting no complement activation or other immunological adverse effects. Additionally, no patient showed a hepatitis B-related infection which confirms that effective protection against HBV re-infection was provided by SC administration of BT088. One possible limitation to our study

is the absence of HBV-DNA measurements after the study period. However, low levels of HBV-DNA in serum or liver specimen are described by several authors in patients on combined HBV-prophylaxis without HBV-recurrence (24,25). In general SC application is favourable because of the maintenance of stable trough levels well above the minimum required, increased patient autonomy (flexibility in every day life), the lack of a requirement for vascular access, and decreased systemic adverse effects.

Conclusions

The results of this study showed that trough levels of serum anti-HBs ≥100 IU/l were achieved during SC weekly treatment with BT088 (Zutectra®) in liver-transplanted patients previously suffering from HBV-related liver disease. No HBV re-infection was observed during the study. Self-administration at home and in the hospital setting was well accepted by the majority of patients and efficacious. As maintenance HBIg prophylaxis is commonly a life-long endeavour for OLT recipients at risk, SC administration, which can be performed at home by patients, is an important factor in improving patients' flexibility in his daily life, and in reducing the severity and frequency of adverse events attributable to high-peak and low-trough serum anti-HBs levels. SC treatment with BT088 was well tolerated and safe.

Authorship

AY: conducted the trial, collected the data, processed the data, wrote the manuscript and responsible for proof reading of manuscript. SB: conducted the trial, collected the data and processed the data. VC, CK and AP: conducted the trial and collected the data. AP: conducted the trial, wrote the manuscript and responsible for proof reading of manuscript. RN: conducted the trial and responsible for proof reading of manuscript.

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References

1. Samuel D, Muller R, Alexander G, *et al.* Liver transplantation in European patients with the hepatitis B surface antigen. *New Engl J Med* 1993; **329**: 1842.
2. Seehofer D, Berg T. Prevention of hepatitis B recurrence after liver transplantation. *Transplantation* 2005; **80**: 120.
3. Angus P, McCaughan G, Gane E, *et al.* Combination low-dose hepatitis B immune globulin and lamivudine therapy provides effective prophylaxis against posttransplantation hepatitis B. *Liver Transpl* 2000; **6**: 429.
4. Gane E, Angus P, Strasser S, *et al.* Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. *Gastroenterology* 2007; **132**: 931.
5. Weber NK, Forman LM, Trotter JF. HBIg discontinuation with maintenance of oral anti-viral therapy and HBV vaccination in liver transplant recipients. *Dig Dis Sci* 2010; **55**: 505.
6. Wong SN, Chu J, Wai CT, *et al.* Low risk of hepatitis B virus recurrence after withdrawal of long-term hepatitis B immunoglobulin in patients receiving maintenance nucleos(t)ide analogue therapy. *Liver Transpl* 2007; **13**: 374.
7. Jiang L, Jiang LS, Cheng NS, *et al.* Current prophlactic strategies against hepatits B virus recurrence after transplantation. *World J Gastroenterol* 2009; **15**: 2489.
8. Gardulf A, Andersen V, Björkander J, *et al.* Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. *Lancet* 1995; **345**: 365.
9. Shibata Y, Baba M, Kuniyuki M. Studies on the retention of passively transferred antibodies in man. II. Antibody activity in the blood after intravenous or intramuscular administration of anti-HBs human immunoglobulin. *Vox Sang* 1983; **45**: 77.
10. Burbach GJ, Bienzle U, Neuhaus R, *et al.* Intravenous or intramuscular anti HB-s immunoglobulin for the prevention of hepatitis B re-infection after orthotopic liver transplantation. *Transplantation* 1997; **63**: 478.
11. Faust D, Rabenau HF, Allwinn R, *et al.* Cost-effective and safe ambulatory long-term immunoprophylaxis with intramuscular instead of intravenous hepatitis B immunoglobulin to prevent re-infection after orthotopic liver transplantation. *Clin Transplat* 2003; **17**: 254.
12. Thürmann PA, Szymasnki J, Haffner ST, *et al.* Pharmacokinetics and safety of a novel anti- HBs-enriched immunoglobulin in healthy volunteers after subcutaneous and intramuscular administration. *Eur J Clin Pharmacol* 2006; **62**: 511.
13. Thürmann PA, Sonnenburg-Chatzopoulos C, Lissner R. Pharmacokinetic characteristics and tolerability of a novel intravenous immunoglobulin preparation. *Eur J Clin Pharmacol* 1995; **49**: 237.
14. Thürmann PA, Sonnenburg C, Valentova K, *et al.* Pharmacokinetics of viral antibodies after administration of intravenous immunoglobulin in patients with chronic lymphocytic leukaemia or multiple myeloma. *Eur J Clin Pharmacol* 2001; **57**: 235.
15. Abrahamsen TG, Sandersen H, Bustnes A. Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. *Pediatrics* 1996; **98**: 1127.
16. Zampelli AR. improving quality of life at home for pediatric patients and families with primary immune deficiencies

using subcutaneous immune globulin infusions. *Home Health Care Manag Pract* 2007; **19**: 431.
17. Berger M. Subcutaneous administration of IgG. *Immunol Allergy Clin North Am* 2008; **28**: 779.
18. Gustafson R, Gardulf A, Hansen S, *et al.* Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. *Clin Exp Immunol* 2008; **152**: 274.
19. Helbert M, Farragher A. Subcutaneous immunoglobulin for patients with antibody deficiency. *EJJP Pract* 2007; **13**: 83.
20. Beckebaum S, Sotiropoulos G, Gerken G, Cicinnati VR. (2008). Hepatitis B and liver transplantation: 2008 update. *Rev Med Virol* 2009; **19**: 7. DOI: 10.1002/rmv.595.
21. Cornberg M, Protzer U, Dollinger MM, *et al.* Prophylaxis, diagnosis and therapy of hepatitis B virus (HBV) infection: the German guidelines for the management of HBV infection. *Z Gastroenterol* 2007; **45**: 1281.
22. Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol* 2004; **112**: 1.
23. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci* 2004; **93**: 2645.
24. Roche B, Feray C, Gigou M, *et al.* HBV DNA persistence 10 years after liver transplantation despite successful anti-HBS passive immunoprophylaxis. *Hepatology* 2003; **38**: 86.
25. Terrault NA, Zhou S, Combs C, *et al.* Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatits B immunoglubulin. *Hepatology* 1996; **24**: 1327.