Early introduction of subcutaneous (s.c.) hepatitis B immunoglobulin (HBIg) provides effective prophylaxis for hepatitis B virus (HBV) reinfection after liver transplantation

Didier Samuel[1], Paolo De Simone* [2], Mauro Salizoni[3], Antonio D. Pinna[4], Umberto Cillo[5], Fausto Zamboni[6] and David Mutimer[7] on behalf of the ZEUS Study Group

[1]AP-HP Hôpital Paul Brousse Centre Hepato-Biliaire, Villejuif, France, [2]General Surgery & Liver Transplantation, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [3]Liver Transplantation Centre, University Hospital Molinette, Torino, Italy, [4]School of Medicine and Surgery, University Hospital, Policlinico S. Orsola-Malpighi, Bologna, Italy, [5]Unità Operativa di Chirurgia Epatobiliare e Trapianto Epatico, Azienda Ospedaliera Universitaria di Padova, Padova, Italy, [6]Centro Trapianti di Fegato e Pancreas, Azienda Ospedaliera "G. Brotzu" di Cagliari, Cagliari, Italy, [7]NIHR Liver BRU, QE Hospital and Birmingham University, Birmingham, United Kingdom

Background

- Hepatitis B immunoglobulin (HBIg) therapy has dramatically reduced hepatitis B virus (HBV) recurrence after liver transplantation[1,2]
- HBIg with nucleos(t)ide antiviral therapy is considered standard of care. However, the cost and inconvenience of intravenous (i.v.) HBIg has prompted alternative strategies including subcutaneous (s.c.) HBIg
- S.c. HBIg maintains serum anti-HBs concentration above 100 IU/l in maintenance liver transplant patients[3-5], a threshold regarded as the minimum for effective prevention of HBV reinfection[6,7], with few adverse events[8]
- Data are limited regarding the efficacy and safety of early switch from i.v. to s.c. HBIg after liver transplantation[9]

Study objective

- To assess prevention of HBV reinfection in HBV-DNA negative liver transplant patients following initiation of s.c. HBIg by week 3 post-transplant

Methods

- This was a prospective, open-label, single-arm, Phase III, 6-month study undertaken at 17 centers in Italy, Spain, UK and France

Patient population

- Patients receiving a liver transplant due to HBV infection were switched from i.v. to s.c. HBIg at 8–18 days post-transplant

Key inclusion criteria:

- 18–75 years
- HBV-DNA negative at time of transplant
- HBsAg negative with serum anti-HBs trough level ≥400 IU/l on day 7–10 or day 14–17 post-transplant i.e. the time of switch to s.c. HBIg

Key exclusion criteria:

- Retransplantation due to viral recurrence, HIV or hepatitis C positivity, HBsAg-positive donor

- Patients positive for hepatitis D virus could be enrolled, as could patients transplanted for hepatocellular carcinoma due to HBV infection

Study treatment

- Patients were converted from i.v. HBIg to s.c. HBIg (Zutectra®) at approximately day 8–11 or 15–18 post-transplant, according to their individual dosing schedule
  - S.c. HBIg was given once a week or once every two weeks
  - Maximum dose was 1000 IU other than in exceptional cases
  - If serum anti-HBs trough levels were <100 IU/l, s.c. HBIg treatment was discontinued
- After week 4 post-transplant, s.c. HBIg could be administered by the patient or a caregiver following training, if serum anti-HBs trough level was >100 IU/l
- Concomitant antiviral therapy with a nucleos(t)ide analogue could be administered according to local practice

Primary endpoint

- Failure rate by month 6, defined as serum anti-HBs ≤100 IU/l during the active treatment phase or HBV reinfection (defined as HBsAg-positivity and clinical symptoms) with serum anti-HBs >100 IU/l

Results

Patients

- 49 patients were treated. Baseline characteristics are shown in Table 1
- 1 patient was lost to follow-up and 1 patient discontinued the study due to graft rejection
- All 48 patients tested were HBV-DNA negative at time of transplant (assessment was missing for 1 patient), and all patients were HBsAg negative when s.c. HBIg was started. All donors were HBsAg negative

Table 1. Baseline characteristics (n=49)

Age (years), mean (SD)	52.2 (9.2)
Male gender, n (%)	41 (83.7)
Caucasian, n (%)	45 (91.8)
Indication for liver transplantation, n (%)[a]	
HBV-induced cirrhosis	45 (91.8)
Hepatocellular carcinoma	24 (49.0)
Acute liver failure	1 (2.0)
Retransplantation	3 (6.1)
Other	4 (8.2)
Co-infection with hepatitis D virus, n (%)	21 (42.9)
Clinical signs of HBV infection, n (%)	21 (42.9)
Anti-HBV or antiviral treatment pre-transplant, n (%)	40 (81.6)
HBV-DNA negative pre-transplant, n (%)	49 (100.0)

[a] More than one reason could be selected HBV, hepatitis B virus

HBIg therapy and concomitant medication

- S.c. HBIg was started during days 8–11 post-transplant in 37 patients and during days 15–18 in 12 patients. At study entry, a weekly treatment interval was documented for 20 patients, with fortnightly or longer treatment intervals in 29 patients (Table 2)

Table 2. Subcutaneous HBIg administration (n=49)

Dosing interval, n (%)	
Once a week	20 (40.8)
Once every two weeks	29 (59.2)
Starting dose, IU, n (%)	
Once a week	
500	19 (38.8)
1000	1 (2.0)
Once every two weeks	
500	22 (44.9)
1000	5 (10.2)
1500	2 (4.1)
Final dose, IU, n (%)	
Once a week	
500	15 (30.6)
1000	5 (10.2)
Once every two weeks	
500	20 (40.8)
1000	8 (16.3)
1500	1 (2.0)

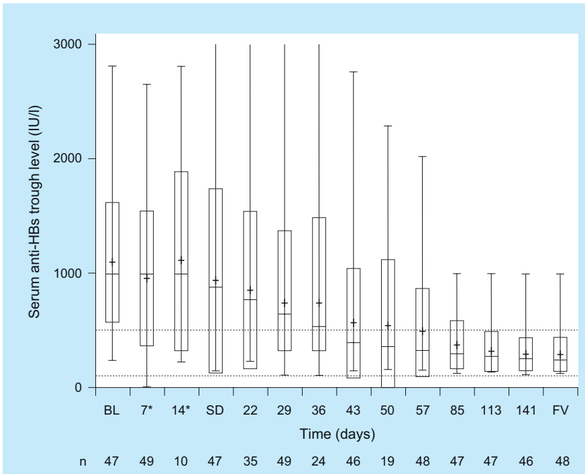
HBIg, hepatitis B immunoglobulin

- All patients achieved administration by a caregiver or self-injection by week 14, continuing until the end of the study (except for one patient on two visit days)
- All patients received concomitant antiviral therapy, comprising entecavir (n=27), lamivudine (n=12), tenofovir (n=10), valaciclovir (n=2) and adofovir (n=1)

Efficacy

- All patients maintained serum anti-HBs trough level >100 IU/l throughout the 6-month study and remained HBsAg-negative
- Accordingly, no treatment failures occurred (0.0 [95% CI 0.0; 0.0725])
- Mean anti-HBs peaked at the time of the second s.c. dose of HBIg (mean 1112 IU/l), then declined progressively to month 6, plateauing at approximately 290 IU/l (Figure 1)
- After the first s.c. dose of HBIg, the minimum serum anti-HBs trough level observed in any patient at any time point was 115 IU/l (Figure 1)

Figure 1. Serum anti-HBs trough level to month 6



* Pre-dose value

Vertical lines indicate maximum and minimum values, crosses indicate mean values, boxes indicate standard deviation values, and horizontal lines indicate median values.

BL, baseline; SD, second dose; FV, final visit

Safety and tolerability

- 45 patients reported ≥1 adverse event. One adverse event (graft rejection) led to study discontinuation
- No adverse event resulted in a change to the HBIg dose
- Only one adverse event, a mild injection site hematoma, was assessed as treatment-related, and HBIg administration was not altered as a consequence
- No serious drug-related adverse events occurred
- No re-infections with HBV were reported
- No patient showed clinically abnormal levels of IgG, IgA or IgM at the final study visit

- 44 patients completed an end-of-study questionnaire:
  - All respondents agreed that taking HBIg by s.c. injection was convenient
  - All respondents reported that s.c. application was easy to handle
  - All respondents confirmed that they were satisfied with the HBIg treatment

Discussion

- Early switch to s.c. HBIg after liver transplantation maintained serum anti-HBs at a level which effectively prevented HBV reinfection in all patients
  - No patient had an anti-HBs level below 100 IU/l after starting s.c. HBIg therapy
  - There were no cases of breakthrough viral replication
- The majority of patients were maintained on a s.c. dose of 500 IU once a week or once every two weeks
- S.c. HBIg was administered by the patient or caregiver in the majority of cases
- Treatment was well-tolerated with no requirement for dose adjustments in response to adverse events
- Patients universally reported that s.c. administration was convenient and that they were satisfied with s.c. HBIg

Conclusion

- Starting s.c. HBIg administration by week 3 after liver transplantation, combined with HBV virostatic therapy, is an effective and convenient strategy for preventing HBV reinfection in patients at risk for HBV recurrence

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The ZEUS study investigators

Umberto Cillo, Padova, Italy; Luciano De Carlis, Milano, Italy; Paulo De Simone, Pisa, Italy; Fabrizio Di Benedetto, Modena, Italy; Carmelo Loinaz, Madrid, Spain; Luigi Lupo, Bari, Italy; Antoni Mas, Barcelona, Spain; David Mutimer, Birmingham, UK; Antonio Daniele Pinna, Bologna, Italy; Martin Prieto, Valencia, Spain; Magdelena Salcedo, Madrid, Spain; Mauro Salizzoni, Torino, Italy; Didier Samuel, Villejuif, France; Abid Suddle, London, UK; Giuseppe Tisone, Roma, Italy; Fausto Zamboni, Cagliari, Italy; Fabien Zoulim, Lyon, France.