ANNALS of Hepatology

ORIGINAL ARTICLE

April-June, Vol. 9 No.2, 2010: 166-171

Efficacy of maintenance subcutaneous hepatitis B immune globulin (HBIG) post-transplant for prophylaxis against hepatitis B recurrence†

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ABSTRACT

Background. Patients who receive liver transplantation for chronic hepatitis B infection require long-term combination therapy with hepatitis B immunoglobulin (HBIG) and oral antiviral medication to prophylax against graft re-infection. This study examines the efficacy and patient preference of subcutaneous (SC) administration of HBIG in maintaining anti HBs titres > 100 IU/L. **Materials and methods.** 12 patients who were stable while receiving our standard IM HBIG protocol received an alternate formulation by SC injection, consisting of 10 mL (3120 IU) HBIG as 4 x 2.5 mL SC injections. SC injection were repeated as soon as titres reached 100-150 IU/mL during the 3 month study period. A questionnaire was administered upon study entry and exit to subjectively assess patient preference. **Results.** Anti- HBs Cmax after first injection was 441.6 IU/L ± 81.5, and Tmax was 7.1 ± 3.2 days. SC injections were required every 56 days, which compared well to the frequency of required IM injections prior to study enrollment of 45 days. The patients mean ratings of pain on a 0-10 scale were 5 for the IM route and 1.6 for the SC route. All patients preferred the SC injections to the IM. **Conclusion.** SC administration of HBIG can effectively maintain anti HBs levels above the requisite 100 IU/L while substantially decreasing patient discomfort and improving patient satisfaction, and therefore becomes a very attractive alternative to IM HBIG injections. Further studies and wider use of SC HBIG based on this study may alter the standard practice of transplantation centers

Key words. Hepatitis B. Immune globulin. Liver transplantation. Subcutaneus. Prophylaxis. HBIG.

INTRODUCTION

For much of its history, liver transplantation has not been feasible for patients with end-stage disease secondary to hepatitis B virus (HBV) because of post-transplant viral graft re-infection rates as high as 70-100%.[1-3] Chronic hepatitis B ceased being a contraindication to liver transplantation when the use of post-operative passive immunization via Hepatitis B immunoglobulin (HBIG) reduced the re-infection rate to 20-40%.[1-4] Subsequent use of antiviral agents like lamivudine in combination with HBIG has further reduced the re-infection rate to 0-10%, and is now considered the standard of care.[5,6] Traditionally, HBIG was administered in high doses via an intravenous (IV) route, but later studies showed that low dose intramuscular (IM) administration is of equal efficacy and more cost effective when compared with the IV route (3,4). Thus a long-term or indefinite course of low dose IM HBIG, in concert with lamivudine or another comparable antiviral medication, to maintain anti- HBs titres greater than 100 IU, is the post liver transplantation strategy currently used by transplant centers to prevent graft reinfection.[2,3]

IM administration of HBIG is not ideal in all situations however, and many patients experience significant pain associated with IM injections. Furthermore, IM injections are contraindicated in patients with coagulopathies, as well as patients who are pharmaceutically anticoagulated secondary to other comorbidities such as thromboembolism or atrial fibrillation, as IM injections in these patients are associated with an increased risk of intramuscular hematomas. We recently reported a case of a liver transplant patient who developed recurrent

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Manuscript received: April 18, 2010.
Manuscript accepted: April 23, 2010.

portal vein thrombosis post-operatively such that he required anticoagulation, and thus IM injections were contraindicated. Therefore subcutaneous (SC) HBIG was successfully used instead to maintain anti-HBs titres above the required range to stave off graft re-infection.[7] This case report posed the question as to whether SC HBIG can be used as a potentially safer and less painful alternative to IM HBIG to prevent viral graft re-infection in liver transplant patients, which we attempted to answer in this pilot study.

METHODS

Study design and patients

In this single centre, prospective observational study, consecutive patients were enrolled during their regularly scheduled clinic visits. Patients enrolled were orthotopic liver transplantation recipients for hepatitis B infection at the Vancouver General Hospital at least one year prior to enrollment, who had stable graft function (ALT, AST, ALP, GGT, total and direct bilirubin), and were on our centre's standard IM HBIG protocol (Table 1). Patients were excluded if they had an episode of acute rejection within the past 6 months, were non-compliant with bloodwork or injections, changes had been made to their antiviral (lamivudine or alternate agent) or immunosuppressive medication in the previous 6 months. This study was approved by our institution's ethics review board and all patients provided written informed consent prior to study entry.

Our centre's standard regimen in the stable post liver transplant patients with hepatitis B consists of 10 mL (2170 IU) HyperHEP B® (Talecris Biotherapeutics Inc, Research Triangle Park NC) by IM injection as 2 x 5 mL injections into each gluteal muscle. The dosing frequency is approximately once a month, based on maintaining anti-HBs titres > 100 IU/L according to a standard protocol.[8] (Table 1).

Table 1. Standard protocol to determine frequency of IM HBIG injections based on Anti HBs titres.

Anti HBs Titre (IU/L)	Action
> 300	Recheck level in 2 weeks
200-300	Injection in 3 weeks
150-200	Injection in 2 week
100-150	Injection in 1 week
< 100	Injection now

Intervention

Patients meeting the inclusion and exclusion criteria were switched to the study SC injection protocol on their next scheduled IM injection date. Each SC dose consisted of 10 ml (3120 IU) HBIG (HepaGam B®, Cangene Corp, Winnipg MB, Canada) as 4 x 2.5 mL injections, administered as 2 injections into each arm. As SC administration decreases absorption by 20%, it was deemed appropriate to use a higher total dose of HBIG for this initial study. The use of 4 x 2.5 mL injections was required as the maximum SC injection volume according to our institute's patient care manual is 2.5 mL. Anti-HBs titres were measured at twice weekly intervals on Mondays and Thursdays after the first sc injection was given for a study period of 12 weeks. Subsequent injections were given to maintain anti- HBs titres greater than 100 IU/L, and once titres were 100-150 IU/L the next SC injection was given on the next scheduled bloodwork day. All patients were continued on their baseline antiviral therapy for hepatitis B virus (100 mg of lamivudine orally) as per our center's standard practice. No changes were made to the antiviral therapy or immunosuppressive therapy during the study period.

For safety purposes, in addition to anti- HBs titres at study entry and then twice weekly, assessment of graft function (via AST, ALT. ALP, GGT, direct and total bilirubin) was also done. Routine monthly bloodwork including complete blood cell count, electrolytes, creatinine, and immunosuppressive medication trough levels (tacrolimus or cyclosporine) continued as part of our centre's standard of care.

A questionnaire was given at the beginning and at the end of the study period to assess the pain intensity (from a scale of 0-10, 0 being no pain and 10 being very painful) of each mode of administration (IM versus SC), and which mode the patients subjectively preferred. The questionnaire further determined whether they experienced any local or systemic side effects from either or both medications in order to subjectively compare side effect profiles.

Efficacy was objectively evaluated by recording the frequency of IM injections the patients required to maintain anti- HBs levels greater than 100 IU/L prior to study enrollment, the frequency of SC injections the patients required within the 12 week observation period, as well as serial anti- HBS titres, and liver function during the study period. Patient satisfaction and adverse effects were subjectively measured via the aforementioned surveys. All statistical analysis was descriptive.

RESULTS

Seventeen patients were initially enrolled in the study. Three patients subsequently withdrew consent secondary to the personal inconvenience of increased frequency of phleobotomy required for the study, and two more patients were excluded due to non-adherence with the required bloodwork during the study period. Therefore 12 patients were included in the data analysis (Table 2). Of these patients 11 were male and 1 was female, and the average age was 57. All of the patients were adequately immunosuppressed on 1 or 2 immunosuppressive medications, and all patients had concomitant antiviral therapy with lamivudine 100 mg once daily.

Table 2. Demographics, antiviral therapy and immunosuppressive regimens of study patients.

Characteristic	Variable	Patients (%)
Gender	Male	11 (91.7)
	Female	1(8.3)
Age (years)	Mean (SD)	56.7 (9.38)
	Range	30-66
Antiviral Therapy	Lamivudine	12 (100%)
Immunosuppressive Therapy	TAC	3 (25)
	MMF	1 (8.3)
	TAC + CSA	1 (8.3)
	TAC + AZA	2 (16.7)
	CSA + AZA	4 (33.3)
	TAC + MMF	1 (8.3)

TAC: Tacrolimus. **MMF:** Mycophenolate mofetil. **CSA:** Cyclosporine. **AZA:** Azathioprine.

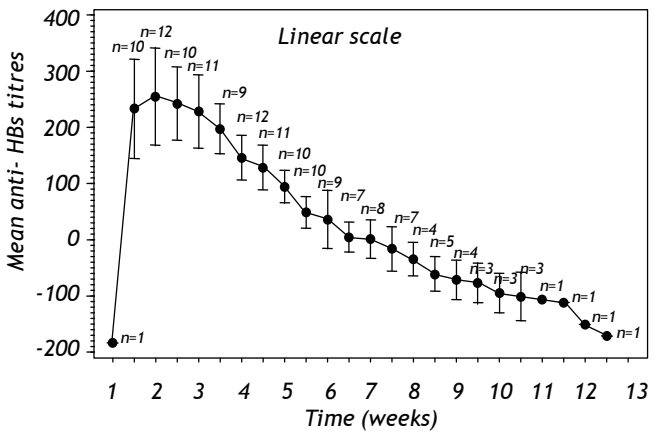

***Figure 1**. Mean anti- HBs titres post first injection over time. The number of patients at each time value changes based on patient compliance with bloodwork each week, and with those that need to be removed from this figure as they required a repeat injection, such that n values are shown at each week.*

The maximum anti HBs titre post first injection (Cmax) was 465.8 ± 94.2 (range 304.8-631.1) The mean time to measured (Tmax) was 12 ± 4.8 days, (range 7-21). Figure 1 outlines the mean anti-HBs titres over time following the first injection until the next dose was administered. Individual patient anti HBs titres over the entire 12 week study period is depicted in Figure 2. Only one patient deviated from protocol and fell below an anti HBs titre of 100 IU/L during the study period due to injection scheduling problems. As the IM injections were administered according to the standard protocol with anti HBs titres measured at 4 weeks post injection, and SC injections were administered whenever the measured anti HBs titre was less than 150 IU/L, it was determined a priori that direct comparison between the two medications could not be made in this study. Injections were required on average every 48.4 days while the patients were receiving HBIG intramuscularly, and every 56.5 days when receiving the drug subcutaneously.

All except one patient had normal liver biochemical levels for the 6 month period prior to study enrollment, while maintained on IM HBIG for anti-reinfection prophylaxis. These values remained stable throughout the study period. The one patient who did have elevated liver enzymes prior to enrollment had a long standing history of idiopathic post-transplant hepatitis and steatosis, with multiple biopsies since 2005 suggestive of this. A liver biopsy performed on this patient during the study period suggested histopathological improvement when compared with previous biopsies, and liver biochemistry was at its lowest level in the past 4 years and did not change during the study period. Although routine HBV DNA levels were not done on these patients, there was no clinical or bloodwork abnormalities that raised suspicion of graft re-infection.

Pre and Post study questionnaires were completed by 9 of 12 patients. The patients mean rating of pain associated with the injections, based on the previously mentioned pain scale of 0-10, was 5 for the IM route and 1.6 for the SC route. Based on subjective responses to the question "have you experienced any adverse reaction at the site of the intramuscular (into the muscle) injection", 6 of 9 (66%) patients specifically reported significant pain that lasted for over a day after the IM injections. 7 patients (78%) described the SC injections as "much less painful", 5 patients described less bruising, and all nine patients reported less burning/stinging with the SC injections as compared to IM. All 9 patients did not find the 4 SC injections as a disadvantage when compared to

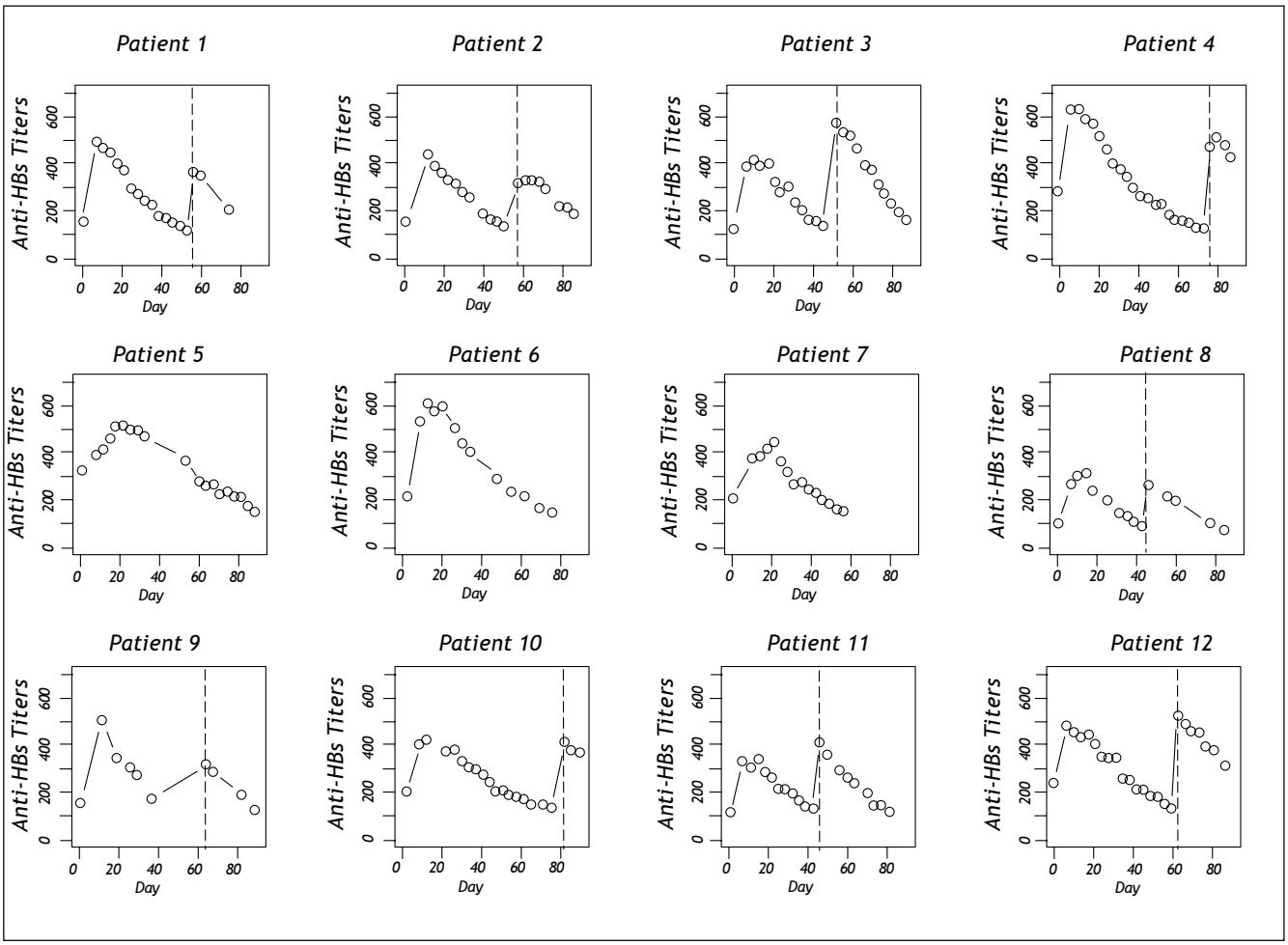

***Figure 2**. Anti- HBs titres for each patient over time throughout the study period.*

the 2 IM injections, and over half found the 4 injections easier. All 9 patients preferred the SC injections to the IM. No local or systemic adverse effects were reported with either injection method.

DISCUSSION

Patients with end stage liver disease secondary to HBV infection represent 10-20% of all recipients of orthotopic liver transplants in America, and this number is higher in regions such as China where the prevalence of HBV is higher.[8] These patients are at significant risk of graft re-infection if appropriate prophylaxis is not employed.[8-10] HBV re-infection leads to graft dysfunction and may lead to chronic hepatitis, cholestatic fibrosing hepatitis and progressive cirrhosis.[9,10] The risk of graft re-infection has been shown to be associated with pre-transplant viral replicavity, represented by the presence of Hepatitis B e antigen (HBeAg) in the serum, and with a detectable HBV DNA load.[11] Additionally, the presence of an extra-hepatic reservoir of latent HBV in sites such as blood, mononuclear cells and the spleen provide an ongoing source of infection even after liver transplantation.[1,2,12]

Passive immunization with HBIG has been used since the 1980's to prophylax against post-transplant re-infection, and recurrence rates dropped to 20-40%.[1-4,11] HBIG works by binding to and neutralizing circulating HBV and hepatitis B surface antigen (HBsAg), and by entering hepatocytes via endocytosis and interacting with and decreasing release of HBsAg.[1,3,13] HBIG effectively prophylaxes against re-infection when used in doses sufficient to maintain anti HBs titres greater than 100 IU/L. It is believed that passive immunization alone cannot reduce re-infection rates further because of the development of a mutation in the S region of the genome, which encodes the HBsAg.[1] Moreover, passive immunization does not affect the presence of HBe-

Ag, which as mentioned above is associated with re-infection. Therefore the addition of antiviral agents such as lamivudine was introduced to the regimen in the late 1990's, and re-infection rates were successfully reduced to 0-10%, such that these patients have a similar or better prognosis than those patients receiving a liver transplant for other reasons.[5,6,8,14,15] Effective protection against graft re-infection is sustained when the regimen of parenteral HBIG and oral antiviral agents are continued long-term, as HBV DNA becomes detectable again when HBIG is discontinued.[5,16,17] Although initially administered IV, low dose intramuscular HBIG has been shown to effectively prophylax against graft re-infection and be more cost effective.[4,15,18-21]

Ultimately, this means that patients who receive liver transplantation for HBV must be subjected to many years, if not a lifetime, of painful IM injections. As demonstrated by our pre-study questionnaires, patients do report substantial pain and discomfort from the IM injections, and would prefer an alternative route that would be more comfortable yet as efficacious in preventing graft re-infection. Given that IM administration is titrated to anti HBs levels greater than 100, and that maintenance of anti HBs above this level is thought to be adequate protection against re-infection, it stands to reason that another, less painful route to administer HBIG and maintain such therapeutic levels would be more attractive to the patients. Furthermore, IM injections are contraindicated in patients with coagulopathies or those pharmaceutically anticoagulated for other comorbidities. IM injections have also been associated with such complications as skin necrosis, nerve injury, nicolau syndrome (severe pain, skin discolouration, and tissue necrosis requiring amputation after IM injections) infection and sepsis.[23-25] Protecting patients from such complications by employing a safer route of administration is also an attractive strategy. This study, as well as our previously published case report, shows that SC HBIG adequately maintains anti HBs levels greater than 100 IU/L without significantly altering the frequency of injections required in stable liver transplant recipients maintained on an IM protocol. Throughout the 12-week study period, the liver enzymes did not change while the patients received the HBIG SC, nor was there any clinical changes that raised suspicion of graft re-infection, thus showing that the alternative route did not increase the risk of rejection, graft dysfunction or re-infection.

The main disadvantage to subcutaneous administration is the lower volume injection which requires increased needle pokes for each dose. Interestingly, the patients did not object to the 2 extra injections required for SC administration according to the survey results, and some even felt that the 4 total SC injections took less time than the 2 IM injections. This affords patients the safety and comfort of SC injections without making their clinic visits to receive the drug any more frequent or time consuming. It would be an appropriate next step to determine if a lower dosage of SC HBIG could mimic these effects and allow for a lower total volume and less injections while maximizing efficacy. Moreover, diabetic patients have for decades been self sufficient in administering their own subcutaneous insulin, and the advent of pre-filled insulin pens further increased patient safety and satisfaction.[27-29] Therefore the results of this study may result in a system by which patients do not need to attend clinic to receive their HBIG, but rather administer it themselves via vials or prefilled pens. The patients could have standard bloodwork measuring anti HBs levels, which can be monitored by transplant clinic staff, and the patient contacted when their next HBIG dose is required. This will provide the patient with substantial autonomy, and be very convenient to those patients residing in remote regions afar from tertiary transplantation centres. A further area of study may be for standard dosing frequency given that in the individual pharmacokinetic curves of SC HBIG for each patient in this study, the rate of decline of anti HBs between injections was also slow and predictable. This may allow for an initial individualization of dosing frequency and a reduction in the total bloodwork required for the regimen. Larger studies will be invaluable to determine pharmacokinetics of this medication which will allow evolution of new protocols for SC HBIG incorporating these proposed lower doses and self-administration.

Very striking in this study was the result that 100% of patients who returned the survey subjectively preferred SC HBIG when compared with IM, and reported less pain with the former. Furthermore, they also reported less bruising, burning and stinging, thus alleviating many of the patient concerns associated with IM injections. Such marked patient preference and satisfaction is difficult to ignore.

CONCLUSION

Patients who receive liver transplantation for end stage liver disease secondary to HBV infection require long-term prophyllaxis against graft re-infection with HBIG and antiviral therapy. This study

shows that SC administration of HBIG can effectively maintain anti HBs levels above the requisite 100 IU/L while substantially decreasing patient discomfort and improving patient satisfaction, and therefore becomes a very attractive alternative to IM HBIG injections. This study also shows that SC HBIG can be used as a safe alternative to IM HBIG when intramuscular injections are contraindicated. Further studies and wider use of SC HBIG based on this study may alter the standard practice of transplantation centres.

DISCLOSURE

This study was supported by an unrestricted research grant by Cangene Corporation.

ACKNOWLEDGEMENTS

The investigators sincerely thank the Solid Organ Transplant Clinic staff especially Ms. Irene Tse RN and Ms. Jo-Anne Harrigan RN.

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