Efficacy of a pre-S containing vaccine in patients receiving lamivudine prophylaxis after liver transplantation for chronic hepatitis B

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Abstract

Lamivudine monoprophylaxis against hepatitis B virus (HBV) reinfection after liver transplantation is associated with recurrence due to escape mutants and second generation recombinant HBV vaccine is not effective. We studied the efficacy of 2 courses each of 3 double-doses (20 ug) of third generation recombinant pre-S containing vaccine (Sci-B-Vac[TM]) in 20 patients on lamivudine prophylaxis at a median of 637 days (range, 390-2,666 days) after transplantation. At enrolment, all patients were seronegative for HBsAg, anti-HBs and HBVDNA (by qPCR). Lamivudine (100 mg/day) was continued throughout the study. Five patients (25%) responded to the first course and 5 additional patients responded after the second course (overall response rate 50%). The response rate was 88% in patients younger than 50 years old and 25% in older patients (p=0.02). The median peak anti-HBs titer was 153 mIU/mL with 6 responders having a titer > 100 mIU/mL and 7 sustained > 6 months. Among 7 previous non-responders to second generation recombinant vaccine, 3 (44%) responded. At the end of the study, all patients remained seronegative for HBsAg. In conclusion, Sci-B-Vac[TM] is effective in about 50% of patients receiving lamividine prophylaxis and may prevent recurrence due to escape mutants.

Keywords: **Active immunization; Immunity; Recurrence; Antibody against hepatitis B surface antigen**

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1. Introduction

The results of liver transplantation for hepatitis B virus (HBV)-related liver disease has dramatically improved over the last decade. Passive immunoprophylaxis with hepatitis B immunoglobulin (HBIG) (1,2) and anti-viral agents such as lamivudine (3,4,5) are both effective in preventing HBV reinfection after liver transplantation. The graft survival with lamivudine monoprophylaxis is comparable to that of long-term HBIG prophylaxis (4) but reinfection due to emergence of escape mutant with prolonged therapy is the major concern. Combining HBIG with lamivudine prophylaxis has proved to be extremely effective in reducing HBV reinfection to less than 10% (6-12) and this combination has been regarded by many as the preferred prophylactic strategy (13). Nonetheless, the potential drawbacks of long-term HBIG continues to be an issue and the optimal dosage and duration of HBIG therapy remain unknown. Hence, attempts to develop less costly and more definitive means of prophylaxis against HBV reinfection continue.

Vaccination to confer active immunity for endogenous production of anti-HBs is theoretically a simpler, safer and cheaper prophylactic strategy than passive immunization using HBIG. We have previously proposed a strategy of combining active immunization with antiviral prophylaxis, and attempted HBV vaccination as an additional prophylactic measure to reduce the risk of emergence of escape mutants in patients receiving lamivudine prophylaxis after liver transplantation (14). Unfortunately, 2 courses of an accelerated schedule of double-dose second-generation recombinant HBV vaccine had limited efficacy in this setting. In this study, we continue to explore this strategy and evaluated the efficacy of a more immunogenic third-generation recombinant HBV vaccine containing S, pre-S1 and pre-S2 antigens.

2. Patients and methods

Patients

Twenty liver transplant recipients who had undergone liver transplantation for chronic hepatitis B-related liver disease and had no evidence of HBV recurrence nor immunity at more than 12 months after transplantation were recruited at the outpatient clinic into the current study. The baseline demographic, clinical and virologic characteristics of these patients are shown in Table 1. There were 15 men and 5 women with a mean age of 50.8 years (median, 52 years; range, 35-60 years). The disease indication for transplantation was decompensated cirrhosis in 18 patients and cirrhosis with acute flare in 2 patients. Serum HBV DNA was positive by a branched-chain DNA (bDNA) assay (Quantiplex; Chiron Diagnostics, Emeryville, CA; lowest detection limit, 700,000 copies/mL) in 6 patients on listing and in 4 patients at transplantation. None had coinfection with hepatitis delta virus or hepatitis C virus. Two patients had received lamivudine therapy (100 mg daily) for more than 12 months before transplantation and 8 for 1 month to 12 months. The remaining 10 patients had pretransplant lamivudine for less than 1 month. Lamivudine therapy was continued indefinitely after transplantation according to a protocol as described previously (5) and HBIG was not used at any stage.

We excluded patients who had received the transplant for less than 12 months, who had received other prophylaxis such as passive immunoprophylaxis with HBIG or add-on adefovir dipivoxil therapy, who were HBsAg-positive with or without viral breakthrough, or who remained positive for anti-HBs after transplantation. The median interval from transplantation to enrolment was 637 days (range, 390 to 2666 days). Thirteen (65%) patients had received liver transplant for 1-3 years and 7 (35 %) had the transplant more than 3 years ago. Eight patients had previously been enrolled in a study on vaccination using two courses of a double-dose reinforced schedule of second generation recombinant HBV vaccine (14). Seven did not respond and only one developed a peak anti-HBs titer of 27 mIU/mL that disappeared rapidly. The last dose of

vaccination was administered no less than 18 months before entry into the current study and the serum anti-HBs had remained negative for at least 6 months. At the time of enrolment into the current study, all 20 patients had negative serology for HBsAg, anti-HBs, and HBV DNA by qPCR assay (Cobas Amplicor qPCR, Roche Molecular Diagnostics, Branchburg, NJ; lowest detection limit 300 copies/mL). Graft functions were normal and there were no significant posttransplant complications. Immunosuppressive medications consisted of tacrolimus alone in 16 patients, tacrolimus with steroid and mycophenolate mofetil in 2 patients, tacrolimus with mycophenolate, and steroid alone in one patient each.

Vaccination protocol

Patients enrolled in the study received a third generation recombinant hepatitis B vaccine (Sci-B-Vac[TM], Bio-Technology General Ltd., Rehovot, Israel) produced in HBV transfected Chinese hamster ovary cells which secretes all 3 epitopes of the envelope proteins, namely S, pre-S1 and pre-S2. The schedule consisted of 2 courses each of 3 double-doses (20 μg) of vaccine administered by intramuscular injection into deltoid muscle at months 0, 1, and 2 and then months 6, 7, and 8 after enrolment.

Follow-up and response

The patients were followed at least monthly at the clinic and the anti-HBs titer was measured using a microparticle enzyme immunoassay (IMx AUSAB, Abbott Laboratories, Chicago, IL) before each dose of vaccine, and monthly for at least 6 months after the last dose of vaccine. The primary outcome was the development of anti-HBs, and a titer greater than 10 mIU/ml was considered a positive response. A positive response that persisted at 6 months after the last dose of vaccine was considered a sustained response. Patients who responded after the first course of vaccine were regarded as early responders. Hematological and biochemical

parameters were tested at each study visit. Recurrent disease was monitored by hepatitis B serologies including serum HBsAg (Auszyme Monoclonal EIA; Abbott Laboratories, Chicago, IL), HBeAg (Axsym HBe 2 MEIA; Abbott Laboratories), and HBV DNA (Cobas Amplicor qPCR) at 3 monthly intervals throughout the study period and when clinically indicated. The study protocol was approved by the institutional review board and informed consent was obtained from each patient.

3. Results

Response to vaccination

Upon completion of the first course of vaccination, 5 patients had positive response (median anti-HBs titer, 34 mIU/mL; range 14 to 66 mIU/mL) giving an early response rate of 25%. The only patient who had previously responded to second generation recombinant vaccine had an early response after the first course (peak anti-HBs titer of 66 mIU/mL) but he did not comply with the schedule of the second course. Hence, 19 patients received the second course of vaccination and 5 additional patients developed anti-HBs afterward. Hence, the overall response rate in these 20 patients was 50%. The median peak anti-HBs titer was 153 mIU/mL (range, 13 to >1000 mIU/mL) with 7 of the responders (70%) having a maximum titer > 100 mIU/mL, including 2 (20%) > 1,000 mIU/mL.

The demographic, clinical and virologic data of the responders and non-responders were compared in Table 2. Response to HBV vaccine was not related to the pretransplant HBV serology, duration of lamivudine treatment, donor anti-HBs status, use of living donor graft, interval since transplantation or previous HBV vaccination but was associated with a younger age. A positive response was found in 7 of 8 patients (88%) younger than 50 years of age as compared to 3 of 12 (25%) older patients (p=0.02). Among the 7 patients who had previously not responded to second-generation recombinant HBV vaccine, 3 (44%) responded to the vaccine in

the current study. The only patient who had previously responded to the second generation recombinant vaccine responded again in this study.

Follow-up

None of the patients reported any side effects related to the vaccination. The serial changes in the anti-HBs titers of the 10 responders are shown in the figure. Sustained response beyond 6 months after the completion of the second course of vaccination was found in 7 of the 9 responders (one early responder did not receive the second course). All 4 early responders responded to the second course with a rapid rise in anti-HBs titer to > 100 mIU/mL (median peak titer 317 mIU/mL; range 100 to >1000 mIU/mL) and all had sustained response. Five of 15 early non-responders developed a response to the second course of vaccine (median peak titer 20 mIU/mL; range 13 to >1000 mIU/mL) with an anti-HBs titer > 100 mIU/mL in 2 patients and only 3 had sustained response. All the study patients continued to receive lamivudine 100 mg daily. As on the date of the latest follow up (median, 55 months; range, 47-111 months after transplantation), none of the 20 patients developed recurrence and all were negative for HBsAg, HBeAg, and HBV DNA (by qPCR). Four patients remained positive for anti-HBs with a median titre of 55 mIU/mL (range 42 to 135 mIU/mL) at 33 months after vaccination.

4. Discussion

Recurrence due to emergence of escape mutant is common with long-term lamivudine prophylaxis after liver transplantation (3,4) and additional prophylactic measure such as passive immunoprophylaxis has been recommended. On the other hand, lamivudine-resistant HBV mutant can now be effectively controlled with other anti-viral agents such as adefovir dipivoxil (15,16). As a result of the prohibitive cost of HBIG, we have adopted a strategy of anti viral prophylaxis using primary lamivudine with adefovir rescue with fairly good results in terms of graft and patient survival (16). A recent study indicated that the cost-effectiveness of combination of lamivudine and HBIG is highly sensitive to the cost of HBIG (17) and when compared to a strategy of lamivudine with adefovir rescue, the incremental cost-effectiveness ratio of lamivudine with HBIG exceeds the threshold for cost-effectiveness even when a regimen of very low dose intramuscular HBIG was considered. Antiviral prophylaxis using lamivudine with adefovir rescue was found to be the more cost-effective option, though at a possible price of higher recurrence rate.

The current study shows that a strategy of combining active immunization to reduce the recurrence rate with anti-viral prophylaxis is feasible in a proportion of patients after liver transplantation for chronic hepatitis B. About half of post-transplant patients receiving lamivudine prophylaxis responded to 2 courses of a more immunogenic third-generation pre-S containing HBV vaccine, Sci-B-Vac[TM]. In a significant proportion of the responders, the ani-HBs titer was higher than 100 mIU/mL and the response was sustained for more than 6 months. All early responders who responded to the first course had intense and sustained antibody response after the second course suggesting that a second course of vaccination is necessary and should be given even in the early responders. Whether additional courses of vaccine or boosters would enhance or prolong the humoral immune response remains to be defined by

further studies. Admittedly, the follow up period of the current study is relatively short and we assessed immunogenicity of the vaccine instead of its efficacy to prevent recurrence. Nonetheless, this is the first report of the successful induction of active humoral immune response in a sizable proportion of patients on lamivudine prophylaxis after transplantation. Anti-HBs response is protective against HBV infection and is likely to offer protection against the emergence of lamivudine-resistant mutant which is the major drawback of long term anti-viral monoprophylaxis. The ultimate objective of this strategy, however, is to provide definitive protection against HBV reinfection. Before lamivudine prophylaxis can be discontinued, more studies are needed to provide proof on the complete clearance of HBV and the durability of the HBV immune response.

The results of the present study contrasted with our previous report in which 2 courses of a second-generation recombinant vaccine failed to induce active immunity in a similar setting (14). In fact, 44% of previous non-responders in the last study responded to Sci-B-Vac[TM], hence, confirming the enhanced immunogenicity of the third-generation vaccine. The vaccine contains glycosylated and nonglycosylated forms of all 3 epitopes of the envelope proteins absorbed to alum and has been shown to have an immunogenic advantage by eliciting a faster and more intense antibody response (18,19) as well as a superior response rate in non-responders of second-generation yeast-derived vaccine (20).

The question remains open why some patients respond to Sci-B-Vac[TM] while others do not. The response to vaccination was not related to the donor's HBV immunity status and was unlikely to be a secondary response of the adoptively transferred immunity from an HBV immune donor (21). The relatively small number of study subjects limited the power of the current study but age was found to be a predictor of response and this is compatible with

previous findings on the effect of age on response to HBV vaccination in non-transplant

setting (22,23). The favorable response rate of 88% in patients younger than 50 years of age

in the current study indicates that these patients are likely to benefit from the vaccination and

should receive at least 2 courses of the vaccine. For patients who were older, the response

rate was low (25%) and an early non-response to the first course of vaccination would be

predictive of a failure of active immunization.

Reported trials of active immunization to replace HBIG in patients receiving passive

immunoprophylaxis included only patients who were at low risk for HBV reinfection based

on a pretransplant non-replicative HBV status and a prolonged post-transplant recurrence-

free period (24-27). On the other hand, the value of prevention depends on the risk of an

event and the cost-effectiveness of any prophylactic measure against HBV refection increases

with the risk of recurrence. Hence, in order to investigate the value of vaccination as an

additional measure to prevent the emergence of lamivudine-resistant mutant, we did not

exclude high-risk patients with active HBV replication before transplant who were most

likely to benefit from the additional protection. All patients in the current study suffered from

chronic HBV-related cirrhosis and none had fulminant hepatitis B or coinfection with

hepatitis delta virus. Active HBV replication as indicated by a positive serum HBV DNA by

bDNA assay (lowest detection limit 0.7×10^6 copies/ml) was present in 6 patients on listing

and in 4 patients before transplantation. Since the risk of recurrence increases rapidly with

prolonged therapy, the vaccination should ideally be initiated as early as possible just before

the surge of escape mutants. Nonetheless, in contrast to most patients receiving HBIG who

have no detectable HBsAg in serum within a few days after transplantation, serum HBsAg

may remain positive initially in many patients receiving lamivudine monoprophylaxis,

progressively declining over a period of several months to become undetectable. Furthermore,

we have previously observed that about 40% of our patients on lamivudine prophylaxis developed anti-HBs spontaneously after transplantation which lasted for a median of about 7 months (21). As a result of such distinct post-transplant serologic profile, the optimal time for active immunization for these patients would probably be at one year after transplant. It would be necessary to conduct a prospective study in which active immunization is included as part of the protocol for prophylaxis for all patients who are at risk.

In conclusion, 2 courses of double-dose third-generation recombinant pre-S containing HBV vaccine induce humural immune response in selected patients receiving lamivudine prophylaxis after liver transplantation. The additional protection may prevent the emergence of escape mutants and improve further the outcome of the strategy of lamivudine prophylaxis with adefovir rescue. More studies should be performed to identify the patients who would benefit most from active immunization and to increase the response rate by defining the optimal schedule and timing of vaccination.

Acknowledgements

Figure legend

Serial changes in anti-HBs titers after vaccination in 10 responders.

References

1. Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, et al. Liver transplantation in European patients with the hepatitis B surface antigen. New Engl J Med 1993;329:1842-1847.

2. Shouval D, Samuel D. Hepatitis B immune globulin to prevent hepatitis B virus graft reinfection following liver transplantation: a concise review. Hepatology 2000;32:1189-1195.

3. Mutimer D, Dusheiko G, Barrett C, Grellier L, Ahmed M, Anschuetz G, et al. Lamivudine without HBIg for prevention of graft reinfection by hepatitis B: long-term follow-up. Transplantation 2000;70:809-815.

4. Perrillo RP, Wright T, Rakela J, Levy G, Schiff E, Gish R, et al. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. Hepatology 2001;33:424-432.

5. Lo CM, Cheung ST, Lai CL, Liu CL, Ng IO, Yuen MF, et al. Liver transplantation in Asian patients with chronic hepatitis B using lamivudine prophylaxis. Ann Surg 2001;233:276-281.

6. Markowitz JS, Martin P, Conrad AJ, Markmann JF, Seu P, Yersiz H, et al. Prophylaxis against hepatitis B recurrence following liver transplantation using combination lamivudine and hepatitis B immune globulin. Hepatology 1998;28:585-589.

7. Angus PW, McCaughan GW, Gane EJ, Crawford DH, Harley H. Combination low-dose hepatitis B immune globulin and lamivudine therapy provides effective prophylaxis against posttrasnplantation hepatitis B. Liver Transpl 2000;6:429-433.

8. Han SH, Ofman J, Holt C, King K, Kunder G, Chen P, et al. An efficacy and cost-effectiveness analysis of combination hepatitis B immune globulin and lamivudine to prevent recurrent hepatitis B after orthotopic liver transplantation compared with hepatitis B immune globulin monotherapy. Liver Transpl 2000;6:741-748.

9. Han SH, Martin P, Edelstein M, Hu R, Kunder G, Holt C, et al. Conversion from intravenous to intramuscular hepatitis B immune globulin in combination with lamivudine is safe and cost-effective in patients receiving long-term prophylaxis to prevent hepatitis B recurrence after liver transplantation. Liver Transpl 2003;9:182-187.

10. Yao FY, Osorio RW, Roberts JP, Poordad FF, Briceno MN, Garcia-Kennedy R, et al. Intramuscular hepatitis B immune globulin combined with lamivudine for prophylaxis against hepatitis B recurrence after liver transplantation. Liver Transpl Surg 1999;5:491-496.

11. Rosenau J, Bahr MJ, Tillmann HL, Trautwein C, Klempnauer J, Manns MP, et al. Lamivudine and low-dose hepatitis B immune globulin for prophylaxis of hepatitis B reinfection after liver transplantation. Possible role of mutations in the YMDD motif prior to transplantation as a risk factor for reinfection. J Hepatol 2001;34:895-902.

12. Dumortier J, Chevallier P, Scoazec JY, Berger F, Boillot O. Combined lamivudine and hepatitis B immunoglobulin for the prevention of hepatitis B recurrence after liver transplantation: long-term results. Am J Transplant 2003;3:999-1002.

13. Anselmo DM, Ghobrial RM, Jung LC, Weaver M, Cao C, Saab S, et al. New era of liver transplantation for hepatitis B: a 17-year single-center experience. Ann Surg 2002;235:611-620.

14. Lo CM, Liu CL, Chan SC, Lau GK, Fan ST. Failure of hepatitis B vaccination in patients receiving lamivudine prophylaxis after liver transplantation for chronic hepatitis B. J Hepatol 2005;43:283-287.

15. Schiff ER, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Colombo M, et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. Hepatology 2003;38:1419-1927.

16. Lo CM, Fan ST, Liu CL, Lai CL, Wong J. Prophylaxis and treatment of recurrent hepatitis B after liver transplantation. Transplantation 2003;75:S41-44.

17. Dan YY, Wai CT, Yeoh KG, Lim SG. Prophylactic strategies for hepatitis B patients undergoing liver transplant: A cost-effectiveness analysis. Liver Transplantation 2006;12:736-746.

18. Shapira MY, Zeira E, Adler R, Shouval D. Rapid seroprotection against hepatitis B following the first dose of Pre-S1/Pre-S2/S vaccine. J Hepatol 2001;34:123-127.

19. Yap I, Guan R, Chan SH. Recombinant DNA hepatitis B vaccine containing Pre-S components of the HBV coat protein - a preliminary study on immunogenicity. Vaccine 1992;10:439-442.

20. Zucherman JN, Zucherman AJ, Symington I, Du W, Wiliams A, Dickson B, Young MD for The UK HEPACARE STUDY GROUP. Evaluation of a new hepatitis B triple-antigen vaccine in inadequate responders to current vaccines. Hepatology 2001;34:798-802.

21. Lo CM, Fung JT, Lau GK, Liu CL, Cheung ST, Lai CL, et al. Development of antibody to hepatitis B surface antigen after liver transplantation for chronic hepatitis B. Hepatology 2003;37:36-43.

22. Clements ML, Miskovsky E, Davidson M, Cupps T, Kumwenda N, Sandman LA, West D, et al. Effect of age on the immunogenicity of yeast recombinant hepatitis B vaccines containing surface antigen (S) or preS2 + S antigens. J Infect Dis 1994;170:510-516.

23. Havlichek, Jr. D, Rosenman K, Simms M, Guss P. Age-related hepatitis B seroconversion rates in health care workers. Am J Infect control 1997;25:418-420.

24. Sanchez-Fueyo A, Rimola A, Grande L, Costa J, Mas A, Navasa M, et al. Hepatitis B

immunoglobulin discontinuation followed by hepatitis B virus vaccination: A new strategy

in the prophylaxis of hepatitis B virus recurrence after liver transplantation. Hepatology

2000;31:496-501.

25. Angelico M, Di Paolo D, Trinito MO, Petrolati A, Araco A, Zazza S, et al. Failure of a

reinforced triple course of hepatitis B vaccination in patients transplanted for HBV-related

cirrhosis. Hepatology 2002;35:176-181.

26. Sanchez-Furyo A, Martinez-Bauer E, Rimola A. Hepatitis B vaccination after liver

transplantation. Hepatology 2002;36:257-258.

27. Bienzle U, Gunther M, Neuhaus R, Vandepapeliere P, Vollmar J, Lun A, et al. Immunization

with an adjuvant hepatitis B vaccine after liver transplantation for hepatitis B –related

disease. Hepatology 2003;38:811-819.

Table 1 Demographic, clinical and virologic characteristics of study patients

Patient no.	Gender/Age	Disease indication	On listing		Pre-LTx		Pretransplant lamivudine (days)	Graft type	Donor anti-HBs	Response to previous HBV vaccine	Interval since LTx (days)	Immunosuppression at enrolment
			HBeAg	HBV DNA*	HBeAg	HBV DNA*						
1	M/60	Cirrhosis	-	-	-	-	245	Deceased	n/a	-	2302	Steroid
2	M/53	Cirrhosis	-	-	-	1.54	63	Live	+	Not done	498	Tac
3	F/57	Cirrhosis	+	-	+	-	2	Live	-	Not done	477	Tac
4	F/52	Cirrhosis	-	-	-	-	0	Live	-	Not done	522	Tac
5	M/60	Cirrhosis	-	2.436	-	-	197	Deceased	+	Not done	440	Steroid, Tac, MMF
6	M/55	Cirrhosis	-	-	-	-	193		+	Not done	562	Tac
7	M/46	Cirrhosis	-	-	-	-	1	Deceased	+	Not done	1757	Tac
8	F/53	Cirrhosis	-	-	-	-	46	Deceased	-	Not done	527	Tac
9	M55	Cirrhosis	-	1.652	-	-	560	Live	+	-	984	Tac
10	M56	Cirrhosis	-	-	-	-	45	Live	+	-	1166	Tac
11	M/45	Cirrhosis with acute flare	+	-	-	-	25	Live	+	-	1069	Tac
12	F/36	Cirrhosis with acute flare	-	-	-	-	6	Deceased	+	Not done	563	Tac
13	M/47	Cirrhosis	+	-	-	-	134	Deceased	-	Not done	390	Tac
14	M/48	Cirrhosis	-	-	-	-	45	Live	+	-	1617	Tac
15	F/60	Cirrhosis	+	2.8	+	2.8	0	Live	-	Not done	573	Tac
16	M/52	Cirrhosis	-	2.576	-	2.576	5	Live	+	Not done	443	Tac, MMF
17	M/50	Cirrhosis	-	-	-	-	20	Live	+	-	1143	Steroid, Tac, MMF
18	M/46	Cirrhosis	+	176.4	+	1.4	22	Live	-	-	1599	Tac
19	M/35	Cirrhosis	-	8.68	-	-	566	Deceased	+	Not done	701	Tac
20	M/49	Cirrhosis	+	-	-	-	4	Live	+	+	2666	Tac

LTx, liver transplantation; HBV, hepatitis B virus; -, negative; +, positive; n/a, not available; Tac, Tacrolimus; MMF, mycophanolate mofetil.

* by bDNA assay (x 10^6 copies/ml; lowest detection limit, 0.7 x 10^6 copies/ml).

Table 2 Comparison of demographic, clinical and virologic data of responders and non-responders

	Responder (n=10)	Non-responder (n=10)
Male gender	8	7
Age in years, median (range)	47.5 (36-57)	54(35-60)*
Age < 50 years	7	1#
HBeAg positive		
on listing	5	1
at transplantation	2	1
HBVDNA positive		
on listing	1	5
at transplantation	2	2
Disease indication		
Cirrhosis	8	10
Cirrhosis with acute flare	2	0
Duration of lamivudine pretransplant		
< 1 month	6	4
1 month – 1 year	4	4
> 1 year	0	2
Donor anti-HBs+	7	6
Living donor graft	7	6
Interval since transplantation		
1 – 3 years	6	7
> 3 years	4	3
Previous HBV vaccination	4	4

*P = 0.05
#P = 0.02