Kidney International, Vol. 68 (2005), pp. 2298–2303

Immunogenicity and safety of an adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients

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Immunogenicity and safety of an adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients.

Background. Due to their impaired immune system, patients with renal insufficiency have a suboptimal response to hepatitis B (HB) vaccination and frequent boosters are needed to maintain protection. GlaxoSmithKline Biologicals has developed a HB vaccine containing a new adjuvant system AS04 for use in this immunocompromised patient population.

Methods. In an open, randomized clinical trial conducted in pre-hemodialysis (documented creatinine clearance ≤30 mL/min) and hemodialysis patients, over 15 years of age and naïve for HB, the immunogenicity and safety of single doses of HB-AS04 (Fendrix™, GlaxoSmithKline Biologicals) were compared to double doses of commercially available HB vaccine (Engerix™, GlaxoSmithKline Biologicals) administered at 0, 1, 2, and 6 months, and followed-up for 36 months.

Results. The HB-AS04 vaccine elicited a more rapid onset of protection than the currently licensed vaccine for this particular population, with 74% versus 52% of subjects seroprotected at month 3. After the vaccination course, seroprotection rates increased to 91% versus 84% in the HB-AS04 and standard vaccine groups, respectively. Differences persisted up to 36 months post-vaccination (73% vs. 52%, respectively). Antibody concentrations were higher following the HB-AS04 vaccine at all post-vaccination time points. During the follow-up, significantly fewer subjects primed with the HB-AS04 vaccine needed a booster dose as a consequence of anti-HBs loss below seroprotective levels (11/62 subjects in the HB-AS04 group vs. 22/57 subjects in the standard vaccine group, respectively, $P = 0.014$). The HB-AS04 was more locally reactogenic than the standard immunization regimen, with pain at the injection site occurring with 41% of HB-AS04 doses versus 19% of standard vaccine doses. The occurrence of grade 3 pain was less than 1% in both groups and all events resolved within the 4-day follow-up period.

Conclusion. The improved immunogenicity profile and clinically acceptable reactogenicity of HB-AS04 vaccine are of key importance to provide a more rapid, enhanced, and longer seroprotection to these immunocompromised patients at risk for HB infection.

Key words: hepatitis B, HB-AS04 vaccine, adjuvant, hemodialysis, immunogenicity, reactogenicity, immunization.

Received for publication March 1, 2005
and in revised form May 10, 2005
Accepted for publication June 20, 2005

Currently available hepatitis B (HB) vaccines have an excellent safety and immunogenicity profile, conferring seroprotection in more than 95% of the vaccinated population [1]. Nevertheless, certain population subgroups, such as some healthy people and immunocompromised subjects, do not respond adequately to vaccination. Among these groups, end-stage renal disease (ESRD) patients, comprising pre- and hemodialysis patients, are considered at high risk for HB infection due to cross-contamination to patients via environmental surfaces, disposables, or equipment during the process of hemodialysis [2–5]. Once infected, about 60% of hemodialysis patients will become chronic carriers of the HB surface antigen (HBsAg), increasing the risk of contamination for other hemodialysis patients, medical personnel, and family members [6], and leading to significant logistic and practical difficulties, including provision for separate medical devices and staff.

Attempts to overcome the impaired immune response in hemodialysis patients have produced mixed results. An increased dose strategy with additional injections was found to be necessary to improve the response rate in these subjects. Currently a 0-, 1-, 2-, and 6-month schedule with double doses hepatitis B surface antigen (2×20 μg HBsAg) of commercially available HB vaccine is recommended in hemodialysis patients, with regular monitoring of antibody levels to ensure that antibody concentrations remain above the protective level of 10 mIU/mL [7].

In order to improve the immunogenicity of existing HB vaccines, GlaxoSmithKline Biologicals (Rixensart, Belgium) has developed several adjuvant systems

containing immunostimulants. One of them was shown to significantly increase the immune response to the HBsAg and has been used in the formulation of an improved HB vaccine. The new adjuvant system, AS04, is composed of aluminium salt and 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL®, Corixa, Seattle, WA, USA). In the case of pre-hemodialysis and hemodialysis patients, the impaired immune response observed in this group, including a diminished activation of helper T-cells, can in part be explained by a suboptimal costimulation by antigen presenting-cells due to a deficit of CD86. The hypothesis, therefore, is that, in these patients, the adjuvant system AS04 could stimulate cellular and humoral responses via an increased antigen-presenting capacity through up-regulation of the CD86 molecule and/or via an increased production of cytokines.

Several studies in which 3500 subjects received 8670 doses of different formulations of the candidate vaccine were performed and have shown that the HB-AS04 vaccine is safe and immunogenic in different populations [8–11].

To further characterize the immune response induced by the HB-AS04 vaccine, cell-mediated immunity (CMI) data were collected as exploratory measurements in several studies performed in healthy subjects. These data included measurement of lymphoproliferation (expressed as stimulation index) and lymphokines (IFNγ and IL-5) secretion in subgroups of subjects enrolled in these studies. The results indicated that when similar schedules were compared, the HB-AS04 vaccine tended to improve the cellular response and to increase IFNγ secretion, suggesting that part of the immune response follows a Th-1 pathway.

In this open, randomized clinical trial conducted in pre-hemodialysis and hemodialysis patients over 15 years of age, the immunogenicity and safety of HB-AS04 were compared to the currently recommended immunization regimen for these patients.

METHODS

Study population and design

In 1999, 165 ESRD patients were enrolled into this multinational study conducted at 6 study centers in Spain, Czech Republic, and Malaysia, respectively. The study was approved by the respective institutional ethics review boards, and was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines effective at study initiation. Written informed consent in the local language was obtained from the subjects or parents or guardians prior to entry into the trial.

Subjects were excluded if they had hepatomegaly, elevated serum liver enzymes, history of allergic disease likely to be stimulated by any vaccine component, a family history of congenital or hereditary immunodeficiency, received simultaneous vaccination or immunoglobulins and/or any blood products (with the exception of recombinant erythropoietin), or were receiving immunosuppressive therapy. Eligible pre-hemodialysis and hemodialysis (documented creatinine clearance $\leq$30 mL/min) subjects over 15 years of age and naive for HB were randomized to 1 of 2 groups to receive either single doses of HB-AS04 vaccine or the current standard of care [i.e., double doses (2×20 μg HBsAg) of commercial HB vaccine at 0, 1, 2, and 6 months] and followed-up for 36 months.

Materials. Both vaccines are commercially available and manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium. One dose (0.5 mL) of HB-AS04 (Fendrix™) contained 20 μg of recombinant HBsAg, 50 μg of MPL®, and 0.5 mg of aluminium as salt. One dose (1.0 mL) of the commercial HB vaccine (Engerix™-B) was composed of 20 μg recombinant HBsAg and 0.5 mg aluminium as salt; two 1.0 mL monodose vials of the vaccine were mixed and given as a single injection. In accordance with current standard of care for hemodialysis patients, both vaccines were administered at 0, 1, 2, and 6 months as an intramuscular injection in the deltoid region of the arm without the hemodialysis arteriovenous fistula.

Methods. Prevaccination blood samples obtained at screening and postvaccination blood samples obtained at months 1, 2, 3, 6, 7, and at months 12, 24, 30, 36 for persistence data, were assayed for the presence of antibodies against HBsAg (anti-HBs) using a commercial enzyme-immunoassay (EIA) produced by Abbott Laboratories (AUSAB, Abbott Laboratories, Abbott Park, IL, USA). The assay cut-off was 3.3 mIU/mL; antibody concentrations $\geq$ this cut-off were designated as seropositive. Seroprotection was defined as anti-HBs concentration $\geq$10 mIU/mL.

Local injection site symptoms (pain, redness, swelling) and general symptoms (headache, fatigue, gastrointestinal symptoms, fever) were solicited on the day of vaccination and for 3 subsequent days. The size of redness and swelling was obtained by measuring the largest diameter; a grade 3 event was defined as a diameter over 50 mm. Grade 3 injection site pain was defined as "spontaneously painful." Subjects were asked to record axillary temperature daily and any other findings on diary cards and to contact the investigator immediately if they felt any symptom was serious. Fever was defined as axillary temperature above 37.4°C; grade 3 fever was axillary temperature above 39°C. Any signs and symptoms that prevented normal daily activities were designated grade 3 in intensity. Serious adverse events, defined according to Good Clinical Practice guidelines, that occurred at any time throughout the study period up to at least 30 days after receiving the last vaccine dose were reported and described in detail.

Statistical methods

In accordance with sample size calculations performed for the primary study, assuming that the seroprotection rate would be equal to 71% in the Engerix™-B group and 91% in the HB-AS04 group, 57 evaluable subjects in each group were needed to reject the null hypothesis that HB-AS04 vaccine was not better than Engerix™-B with at least 80% power, using a one-sided ($\alpha = 5\%$) Fisher exact test. Allowing for 20% of subjects not to be evaluable for analysis, 72 subjects per treatment group (a total of 144 subjects) were planned to be enrolled, and an over-randomization was prepared for 196 subjects. However, for the analysis, it was decided to apply two-sided test calculations.

For each blood sampling time point, the percentage of subjects with anti-HBs concentrations ≥10 and ≥100 mIU/mL, and geometric mean concentrations (GMC) of anti-HBs were calculated with 95% CI. Anti-HBs seroprotection rates were compared between groups using two-sided Fisher exact test. Wilcoxon's test was used to compare GMCs, which were calculated using log transformation of positive concentrations and taking the antilog of the mean of the transformed values. A P value < 0.05 was considered statistically significant. The percentage of doses followed by any solicited/unsolicited symptoms was calculated with exact 95% CI following each vaccination and overall.

RESULTS

The demographic profile of the 2 study groups was similar in terms of mean age, body mass index, male:female ratio, and smoking habit (Table 1). The mean hemodialysis duration was longer in the comparator group (22.5 months) than in the HB-AS04 group (15.1 months) due to the influence on the mean by a very long hemodialysis period in 2 subjects (132 months and 239 months). Without these 2 outliers, the mean hemodialysis duration of the comparator group becomes 14.1 months, similar to that of the HB-AS04 group.

Table 1. Demographic characteristics (total cohort)

	Fendrix™ ($N = 82$)	Engerix™-B ($N = 83$)
Age *years*	58.7 ± 15.50[a]	58.6 ± 15.46[a]
Body mass index	25.0 ± 5.04[a]	25.0 ± 4.78[a]
Male:female	1:0.78	1:0.73
Smoking habit	4.9%	8.4%[b]
Pre-hemodialysis	46%	51%
Hemodialysis	54%	49%
Months on hemodialysis	15.1 ± 17.5[a,c]	22.5 ± 42.1[a]
Frequency of hemodialysis *times/week*	2.9 ± 0.46[a]	2.8 ± 0.50[a]

[a]Mean ± standard deviation.
[b]$P = 0.5346$, 2-sided Fisher exact test.
[c]There was no significant difference between study groups after exclusion of 2 subjects with very long hemodialysis periods.

Immunogenicity of the vaccine

As can be seen in Table 2, a significantly faster onset of protection (antibody concentration ≥10 mIU/mL) was observed in the HB-AS04 group from month 1 to month 6. At month 3, essentially three fourths (74.4%) of the subjects in the HB-AS04 group were seroprotected against HB as compared to one half (52.4%) of subjects in the comparator group. Despite a statistically significant difference between the groups at earlier time points and an observed increase in the seroprotection rate at month 7 (HB-AS04: 90.9% vs. comparator: 84.4%), a statistically significant difference was not seen at month 7. The percentage of subjects with antibody concentrations ≥100 mIU/mL was greater at all time points in the HB-AS04 group, which was statistically significant from month 3 to month 7. Significantly higher GMCs ($P \leq 0.05$) were obtained in the HB-AS04 group than the comparator group at all time points from month 3 to month 7. At month 7, GMCs were more than threefold higher in the HB-AS04 group than in the comparator group (3559 mIU/mL vs. 933 mIU/mL).

As shown in Table 3, the persistence of protective antibody levels was higher in the HB-AS04 group than in the comparator group at all time points (months 12, 24, 30, 36). The difference in seroprotection rates between groups was statistically significant at month 36 ($P = 0.03$). At month 36, a seroprotection rate of 72.9% was still observed in the HB-AS04 group versus 52.0% in the comparator group. A higher percentage of subjects also retained anti-HBs concentrations above 100 mIU/mL in the HB-AS04 group (54.2%) versus comparator group (36.0%).

Anti-HBs GMCs in HB-AS04 recipients were higher than in subjects administered comparator at month 36 (173.4 mIU/mL vs. 99.6 mIU/mL). However, the difference between groups was not statistically significant.

During the follow-up, significantly fewer subjects primed with the HB-AS04 vaccine needed a booster dose as a consequence of anti-HBs loss below seroprotective levels (11/62 subjects in the HB-AS04 group vs. 22/57 subjects in the standard vaccine group, respectively, $P = 0.014$).

Safety and reactogenicity of the vaccine

The overall incidence of local symptoms (solicited or unsolicited) was higher in the HB-AS04 group than that observed in the comparator group (Table 4), resulting from the higher incidence of pain at the injection site (40.5% vs. 14.7% of doses in the HB-AS04 and comparator groups, respectively). However the incidence of

Table 2. Seroprotection rates (SP) and GMCs for anti-HBs antibodies (total cohort)

		Fendrix™ ($N = 82$)		Engerix™-B ($N = 83$)		
	Timing	%	95% CI	%	95% CI	*P* value
SP *concentration ≥10 mIU/mL*	PI(M1)	17.5	9.9; 27.6	4.8	1.3; 11.9	0.0120
	PII(M2)	48.7	37.2; 60.3	21.7	13.4; 32.1	<0.001
	PIII(M3)	74.4	63.2; 83.6	52.4	41.1; 63.6	0.0053
	PIII(M6)	81.8	71.4; 89.7	66.2	54.6; 76.6	0.0425
	PIV(M7)	90.9	82.2; 96.3	84.4	74.4; 91.7	NS
SP *concentration ≥100 mIU/mL*	PI(M1)	5.0	1.4; 12.3	2.4	0.3; 8.4	NS
	PII(M2)	16.7	9.2; 26.8	7.2	2.7; 15.1	NS
	PIII(M3)	41.0	30.0; 52.7	15.9	8.7; 25.6	<0.001
	PIII(M6)	61.0	49.2; 72.0	35.1	24.5; 46.8	0.0021
	PIV(M7)	83.1	72.9; 90.7	67.5	55.9; 77.8	0.0389
GMC *mIU/mL*	PI(M1)	36.1	13.7; 95.0	28.7	4.0; 206.1	NS
	PII(M2)	74.5	41.8; 132.8	55.8	25.1; 124.1	NS
	PIII(M3)	223.0	129.3; 384.6	50.1	30.8; 81.5	<0.001
	PIII(M6)	247.9	154.1; 398.9	89.5	57.0; 140.6	0.0028
	PIV(M7)	3559.2	2130.3; 5946.5	933.0	515.8; 1687.8	0.0005

Abbreviations are : SP, seroprotection rate; NS: not significant; PI(M1), etc., postdose 1 (month 1), etc.; 95% CI, lower and upper limits of 95% CI.

Table 3. Persistence data for seroprotection rates (SP) and GMCs for anti-HBs antibodies (total cohort)

		Fendrix™			Engerix™-B			
	Timing	*N*	%	95% CI	*N*	%	95% CI	*P* value
SP *concentration ≥10 mIU/mL*	PIV(M7)	77	90.9	82.2; 96.3	77	84.4	74.4; 91.7	NS
	PIV(M12)	71	85.9	75.6; 93.0	70	77.1	65.6; 86.3	NS
	PIV(M24)	62	80.6	68.6; 89.6	57	70.2	56.6; 81.6	NS
	PIV(M30)	60	76.7	64.0; 86.6	53	60.4	46.0; 73.5	NS
	PIV(M36)	59	72.9	59.7; 83.6	50	52.0	37.4; 66.3	0.0293
SP *concentration ≥100 mIU/mL*	PIV(M7)	77	83.1	72.9; 90.7	77	67.5	55.9; 77.8	0.0389
	PIV(M12)	71	73.2	61.4; 83.1	70	54.3	41.9; 66.3	0.0231
	PIV(M24)	62	61.3	48.1; 73.4	57	47.4	34.0; 61.0	NS
	PIV(M30)	60	58.3	44.9; 70.9	53	37.7	24.8; 52.1	0.0381
	PIV(M36)	59	54.2	40.8; 67.3	50	36.0	22.9; 50.8	NS
GMC *mIU/mL*	PIV(M7)	77	3559.2	2130.3; 5946.5	77	933.0	515.8; 1687.8	0.0005
	PIV(M12)	71	907.6	579.1; 1422.3	70	320.8	186.4; 552.2	0.0037
	PIV(M24)	62	334.3	202.1; 553.0	57	253.8	137.4; 468.9	NS
	PIV(M30)	60	205.7	122.3; 345.9	53	111.9	57.4; 218.1	NS
	PIV(M36)	59	173.4	100.1; 300.6	50	99.6	49.5; 200.4	NS

Abbreviations are: SP, seroprotection rate; NS: not significant; PIV(M7), etc., postdose 4 (month 7), etc.; 95% CI, lower and upper limits of 95% CI.

grade 3 pain remained low and comparable in the 2 groups (0.6% in both groups). There was no increase in the incidence of pain with subsequent doses, and all pain symptoms resolved during the 4-day follow-up period.

For the 4 solicited general symptoms, a similar incidence was observed in the 2 groups, with fatigue reported most frequently (Table 4). Few solicited general symptoms were scored as grade 3 (i.e., 3.2% vs. 1.5% of doses in the HB-AS04 and comparator groups, respectively).

Over the active phase of the study, 63 unsolicited symptoms were reported in the HB-AS04 group and 44 unsolicited symptoms in the comparator group. Unsolicited symptoms of grade 3 intensity were reported after 19 doses of HB-AS04 and 18 doses of comparator. Three unsolicited symptoms were considered to have a 'probable/suspected' relationship to study medication in the HB-AS04 group compared to 7 in the comparator group; none of these events were of intensity grade 3.

A total of 39 serious adverse events were reported during the active phase of the study (21 in the HB-AS04 group and 18 in the comparator group), 6 of which were fatal events (2 vs. 4 in the HB-AS04 and comparator groups, respectively). All of these events were determined by the investigator to be unrelated to vaccination.

DISCUSSION

Due to their impaired immune system, patients with renal insufficiency have a suboptimal response to hepatitis B (HB) vaccination, and frequent boosters are needed to maintain protection [12–16]. In the target population of pre-hemodialysis and hemodialysis patients, the HB-AS04 vaccine induced a more rapid onset of protection than the comparator vaccine, which has a licensed schedule for this particular population. Indeed, 3 months after the first vaccine dose, 74.4% of the HB-AS04 recipients were seroprotected, compared to 52.4% of the comparator recipients. Fast onset of protection is of particular importance for this population at increased risk for HB infection. As previously mentioned, the risk to contract

Table 4. Percentage of doses leading to reported symptom (total cohort)

		Fendrix™ ($N = 317$)			Engerix™-B ($N = 327$)		
		N	%	95% CI	*N*	%	95% CI
Any symptom (solicited/unsolicited)	Total	168	53.0	47.3; 58.6	132	40.4	35.0; 45.9
	Grade 3	13	4.1	2.2; 6.9	6	1.8	0.7; 4.0
Solicited injection site symptoms							
Pain	Total	128	40.5	35.0; 46.1	48	14.7	11.0; 19.0
	Grade 3[a]	2	0.6	0.1; 2.3	2	0.6	0.1; 2.2
Redness	Total	23	7.3	4.7; 10.7	22	6.7	4.3; 10.0
	Grade 3[a]	0	0.0	0.0; 1.2	0	0.0	0.0; 1.1
Swelling	Total	20	6.3	3.9; 9.6	12	3.7	1.9; 6.3
	Grade 3[a]	2	0.6	0.1; 2.3	0	0.0	0.0; 1.1
Solicited general symptoms							
Fatigue	Total	50	15.8	12.0; 20.3	57	17.4	13.5; 22.0
	Grade 3[b]	6	1.9	0.7; 4.1	3	0.9	0.2; 2.7
Gastrointestinal symptoms	Total	14	4.4	2.4; 7.3	22	6.7	4.3; 10.0
	Grade 3[b]	0	0.0	0.0; 1.2	0	0.0	0.0; 1.1
Headache	Total	37	11.7	8.4; 15.8	45	13.8	10.2; 18.0
	Grade 3[b]	2	0.6	0.1; 2.3	1	0.3	0.0; 1.7
Fever	Total	30	9.5	6.5; 13.3	32	9.8	6.8; 13.5
	Grade 3[b]	0	0.0	0.0; 1.2	0	0.0	0.0; 1.1

N, total number of documented doses; *N* and%, number and percentage of doses followed by specified symptom; 95% CI, lower and upper limits of 95% CI.
[a]Spontaneously painful or greatest surface diameter of redness/swelling >50 mm
[b]Prevented normal daily activities or axillary temperature >39°C

HB infection exists for these patients from the start of hemodialysis treatment due to potentially contaminated blood products or medical devices. Moreover, for patients who will undergo renal transplantation, protection before transplantation is important in order to avoid de novo HB acquired during or after transplantation and non- or poor responsiveness to vaccination linked to immunosuppressive drugs.

Although statistical comparison failed to show superiority of the HB-AS04 vaccine in terms of seroprotection (anti-HBs antibody concentrations ≥10 mIU/mL) at month 7, it is important to note that the seroprotection rate observed in the HB-AS04 group at this time point was 90.9%, which is higher than expected in this population of immune-deficient patients.

In the normal healthy population, long-term protection relies on immune memory in subjects reaching anti-HBs concentrations ≥10 mIU/mL postvaccination. However, in immunocompromised subjects, protection against hepatitis B infection does not rely on immune memory, but on circulating antibodies. Prospective studies in hemodialysis patients have shown that many individuals with anti-HBs levels between 10 and 100 mIU/mL do not retain protective antibody levels 1 year postvaccination. It has been suggested that an acceptable response to hepatitis B vaccination in hemodialysis patients corresponds to anti-HBs concentrations ≥100 mIU/mL, allowing protection to last for 1 year postvaccination [17, 18]. According to European vaccination advisory bodies [19, 20], a cut-off at 100 mIU/mL is considered to be necessary for maintaining protection in immunocompromised patients. The percentage of subjects with anti-HBs antibody concentrations ≥100 mIU/mL was significantly higher in the HB-AS04 group than in the comparator group at all time points from month 3 to month 12.

Based on the higher GMCs after vaccination, a longer persistence of circulating anti-HBs antibodies would be expected with HB-AS04 as compared with the current standard of care. While the actual rate of antibody decline is independent of the initial post-vaccination antibody concentration, vaccinees with higher concentrations have been shown to retain antibody for a longer period of time [21]. Indeed, the data on the persistence of HB-AS04 at month 36 confirm the hypothesis that, by inducing higher anti-HBs concentrations, a better persistence of seroprotection is reached after vaccination of hemodialysis patients with HB-AS04.

As a consequence of better persistence of anti-HBs antibodies observed in the HB-AS04 group, and importantly from a medical point of view, fewer subjects in this group required booster doses, as compared to subjects in the standard vaccine group.

The reactogenicity profile of HB-AS04 in a total of 82 pre-hemodialysis and hemodialysis patients was generally comparable to that seen in healthy subjects [11]. The overall reactogenicity of the HB-AS04 vaccine was higher than the comparator vaccine due to an increase in local reactogenicity. On the contrary, incidences of general symptoms (any grade) were similar in the 2 groups and grade 3 general symptoms remained infrequent (≤3% of doses). The higher local reactogenicity was mainly due to a higher incidence of pain (40.5% with HB-AS04 vs. 14.7% with the comparator). However, occurrence of grade 3 pain was very low and similar in both groups. As a consequence, the higher incidence of mild or moderate transient local symptoms remained clinically acceptable

and was compensated by an improved immunogenicity, which is of key importance for these immunocompromised patients who are at high risk for HB infection.

CONCLUSION

The improved immunogenicity profile and acceptable reactogenicity of HB-AS04 vaccine are key factors to providing a more rapid, enhanced, and longer seroprotection to immunocompromised hemodialysis patients at risk for HB infection.

ACKNOWLEDGMENTS

The authors wish to thank all the Deans and Directors of the Medical Faculties involved, as well as all other contributors to this study funded by GlaxoSmithKline Biologicals.

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REFERENCES

1. Safary A, Andre F: Over a decade of experience with a yeast recombinant hepatitis B vaccine. *Vaccine* 18:57–67, 2000
2. Snydman DR, Bryan JA, Macon EJ, Gregg MB: Hemodialysis-associated hepatitis: Report of an epidemic with further evidence on mechanisms of transmission. *Am J Epidemiol* 104:563–570, 1976
3. Carl M, Francis DP, Maynard JE: A common-source outbreak of hepatitis B in a hemodialysis unit. *Dial Transplant* 12: 222–229, 1983
4. Alter MJ, Ahtone J, Maynard JE: Hepatitis B virus transmission associated with a multiple-dose vial in a hemodialysis unit. *Ann Intern Med* 99:330–333, 1983
5. Niu MT, Penberthy LT, Alter MJ, *et al*: Hemodialysis-associated hepatitis B: Report of an outbreak. *Dial Transplant* 18:542–546, 555, 1989
6. London WT, Drew JS, Lustbader ED, *et al*: Host response to hepatitis B infection in patients in a chronic haemodialysis unit. *Kidney Int* 12:51, 1977
7. Centers for Disease Control and Prevention: Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recommendations and Reports 50(RR05); 1–43, 2001
8. Thoelen S, De Clercq N, Tornieporth N: A prophylactic hepatitis B vaccine with a novel adjuvant system. *Vaccine* 19:2400–2403, 2001
9. Desombere I, Van der Wielen M, Van Damme P, *et al*: Immune response of HLA DQ2 positive subjects, vaccinated with HBsAg/AS04, a hepatitis B vaccine with a novel adjuvant. *Vaccine* 20:2597–2602, 2002
10. Jacques P, Moens G, Desombere I *et al*: The immunogenicity and reactogenicity profile of a candidate hepatitis B vaccine in an adult vaccine non-responder population. *Vaccine* 20:3644–3649, 2002
11. Boland G, Beran J, Lievens M, *et al*: Safety and immunogenicity profile of an experimental hepatitis-B vaccine adjuvanted with AS04. *Vaccine* 23:316–320, 2004
12. van Geelen JA, Schalm SW, de Visser EM, Heijtink RA: Immune response to hepatitis B vaccine in hemodialysis patients. *Nephron* 45:216–218, 1987
13. Bruguera M, Cremades M, Mayor A, *et al*: Immunogenicity of a recombinant hepatitis B vaccine in haemodialysis patients. *Postgrad Med J* 63(Suppl 2):155–158, 1987
14. Bruguera M, Rodicio JL, Alcazar JM, *et al*: Effects of different dose levels and vaccination schedules on immune response to a recombinant DNA hepatitis B vaccine in haemodialysis patients. *Vaccine* 8(Suppl 1):S47–S49, 1990
15. Waite NM, Thomson LG, Goldstein MB: Successful vaccination with intradermal hepatitis B vaccine in hemodialysis patients previously nonresponsive to intramuscular hepatitis B vaccine. *J Am Soc Nephrol* 5:1930–1934, 1995
16. Chang PC, Schrander-van der Meer AM, van Dorp WT, van Leer E: Intracutaneous versus intramuscular hepatitis B vaccination in primary non-responding haemodialysis patients. *Nephrol Dial Transplant* 11:191–193, 1996
17. Sezer S, Özdemir FN, Güz G, *et al*: Factors influencing response to hepatitis B virus vaccination in hemodialysis patients. *Transplant Proc* 32:607, 2000
18. Navarro JF, Teruel JL, Mateos ML, *et al*: Antibody level after hepatitis B vaccination in haemodialysis patients: Influence of hepatitis C virus infection. *Am J Nephrol* 16:95, 1996
19. Salisbury D, Begg N (editors): *Immunisation against Infectious Diseases*, London, Stationery Office, 1996, p 146
20. Anonymous: [Empfehlungen der Ständigen Impfkommission (STIKO) am Robert- Koch Institut]. *Epid Bull* 28:227–242, 2002
21. Watson B, West DJ, Chilkatowsky A, *et al*: Persistence of immunologic memory for 13 years in recipients of a recombinant hepatitis B vaccine. *Vaccine* 19:3164, 2001