Response to Active Hepatitis B Vaccination in Incident Dialysis Patients and All-Cause Mortality

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INTRODUCTION

Current guidelines suggest that all patients with advanced chronic kidney disease (CKD) or on renal replacement therapy should receive active immunisation against hepatitis B virus. Malnutrition as well as chronic inflammation, which are present in many CKD patients, contribute to impaired immune function in general and to a diminished response to hepatitis B vaccination in particular. This may explain why only 50% to 60% of dialysis patients develop an anti-HBs antibody titer ≥10 IU/l, which is defined as seroconversion (SC), whereas the response rate in healthy individuals is greater than 90%. Even fewer dialysis patients develop anti-HBs antibody titers of ≥100 IU/l, defined as seroprotection (SP). We reasoned that the response to active hepatitis B vaccination, which depends on an intact immune response and is influenced by the inflammatory and nutritional status of an individual allows a more integrated interpretation of these systems and therefore might be an additional predictor of mortality. The aim of this study was to investigate whether failure or attenuated success in mounting an immune response to hepatitis B vaccination was associated with all-cause, cardiovascular or infection-associated mortality in incident dialysis patients.

PATIENTS AND METHODS

- All incident dialysis patients starting chronic dialysis treatment between January 1st 2001 and December 31st 2008 and had undergone active hepatitis B vaccination entered the retrospective analysis.
- Baseline parameters: age, gender, renal disease, presence of diabetes, cardiovascular disease, chronic heart failure, body mass index, date of first dialysis treatment, dialysis modality, C-reactive protein, serum albumin, 25(OH) vitamin D_3, hemoglobin, phosphorous, calcium and PTH.
- Vaccination protocol, the cumulative dose of vaccine, the time point of vaccination and the maximal anti-HBs antibody titer one to two months after the last immunisation were determined. A recombinant hepatitis B surface antigen vaccine (Engerix B, GlaxoSmithKline Pharma, Vienna, Austria) was used.
- Anti-HBs antibody assays: chemiluminescence immunoassay (Anti-HBs ARCHITECT® Abbott, IL, USA) or microparticle EIA (Anti-HBs AXSYM® Abbott, IL, USA).
- Vaccination response was defined as follows: an absent antibody titer or a titer <10 IU/L was classified as non-response; SC was defined as a titer ≥10 IU/L; and SP as a titer ≥100 IU/L. By definition the SC group also includes all patients with SP, whereas the SP group contains only patients with an antibody titer ≥100 IU/L.
- Patient mortality, date and cause of death were retrieved from the Austrian Dialysis and Transplant Registry. Follow-up ended on December 31st, 2011.

RESULTS

Tab. 1. Clinical characteristics of patients at baseline and during follow-up stratified by immune response.

	All patients (n=426)	Non-Responders (titer<1:10, n=217)	Seroconversion (titer≥1:10, n=209)	Seroprotection (titer≥1:100, n=118)	P
Sex					0.27[a], 0.13[b]
Male, n (%)	263 (61.7)	128 (59)	135 (64.6)	80 (67.8)	
Female, n (%)	163 (38.3)	89 (41)	74 (35.4)	38 (32.2)	
Age (years)	63.4 ± 14.2	66.5 ± 12.5	60.2 ± 15.1	58.9 ± 15.7	<0.001[a]
Body Mass Index (kg/m²)	25.2 ± 5.1	25.0 ± 5.5	25.4 ± 4.8	25.4 ± 4.7	0.47[a], 0.52[b]
Start of dialysis with					0.006[a], 0.009[b]
Hemodialysis, n (%)	376 (88.3)	201 (92.6)	175 (83.7)	98 (83.1)	
Peritoneal dialysis, n (%)	50 (11.7)	16 (7.4)	34 (16.3)	20 (16.9)	
Comorbidities at baseline					
Diabetes mellitus, n (%)	167 (39.2)	96 (44.2)	71 (34)	39 (33.1)	0.04[a], 0.04[b]
Hypertension, n (%)	351 (82.4)	177 (81.6)	174 (83.3)	93 (78.8)	0.70[a], 0.57[b]
Coronary artery disease, n (%)	181 (42.5)	101 (46.5)	80 (38.3)	44 (37.3)	0.09[a], 0.11[b]
Heart failure, n (%)	147 (34.5)	88 (40.6)	59 (28.2)	29 (24.6)	0.008[a], 0.004[b]
Vascular disease*, n (%)	221 (51.9)	126 (58.1)	95 (45.5)	51 (43.2)	0.01[a,b]
COPD, n (%)	72 (16.9)	41 (18.9)	31 (14.8)	18 (15.3)	0.24[a], 0.37[b]
Laboratory parameters at baseline					
C-reactive protein (mg/dL)	3.4 ± 5.6 [0.5; 1.1; 3.6]	3.9 ± 6.1 [0.6; 1.6; 4.0]	2.9 ± 5.1 [0.4; 1.0; 3.2]	2.7 ± 3.9 [0.4; 1.0; 3.3]	0.17[a], 0.12[b]
Albumin (g/dL)	3.5 ± 0.7 [3.1; 3.6; 4.0]	3.5 ± 0.7 [3.0; 3.5; 4.0]	3.6 ± 0.6 [3.2; 3.7; 4.1]	3.7 ± 0.5 [3.3; 3.7; 4.1]	0.03[a], 0.006[b]
Hemoglobin (g/dL)	107.5 ± 19.0 [96.3; 108;119]	106.8 ± 18.3 [95; 106; 120]	108.2 ± 19.8 [98; 110; 119]	109.7 ± 20.6 [99.5; 112; 121.4]	0.49[a], 0.22[b]
Calcium (mmol/L)	2.15 ± 0.28 [2.00; 2.20; 2.33]	2.12 ± 0.29 [1.98; 2.16; 2.30]	2.19 ± 0.27 [2.04; 2.21; 2.37]	2.19 ± 0.26 [2.03; 2.22; 2.39]	0.03[a], 0.05[b]
Phosphorus (mmol/L)	1.93 ± 0.61 [1.52; 1.81; 2.22]	1.96 ± 0.67 [1.49; 1.88; 2.31]	1.91 ± 0.53 [1.56; 1.81; 2.15]	1.92 ± 0.54 [1.56; 1.79; 2.16]	0.53[a], 0.73[b]
iPTH (pg/mL)	299 ± 213 [148; 245; 379]	303 ± 210 [141; 252; 392]	295 ± 216 [148; 243; 369]	298 ± 227 [137; 262; 364]	0.79[a], 0.88[b]
25(OH)vitamin D_3 (ng/mL)	13.4 ± 7.9 [7.2; 10.4; 17.5]	11.5 ± 6.9 [6.7; 8.7; 14.4]	15.3 ± 8.6 [8.5; 14.1; 20.1]	16.9 ± 8.7 [9.7; 16.3; 22.1]	0.004[a], <0.001[b]
Vaccination data					
Immunisation regimen, n (%)					0.91[a], 0.13[b]
3 x 20 µg	173 (40.6)	91 (41.9)	82 (39.2)	48 (40.7)	
4 x 20 µg	154 (36.2)	83 (38.2)	71 (34.0)	31 (26.3)	
other	99 (23.2)	43 (19.8)	56 (26.8)	39 (33.1)	
Cumulative vaccine dose (µg)	76.5 ± 24.9 [60; 80; 80]	76.5 ± 24.9 [60; 80; 80]	76.5 ± 24.8 [60; 80; 80]	76.3 ± 27.6 [60; 60; 80]	0.99[a], 0.96[b]
Immunisation time point, n(%)					<0.001[a,b]
within 1 year prior to start of dialysis	175 (41.1)	63 (29)	112 (53.6)	70 (59.3)	
within 1 year after start of dialysis	251 (58.9)	154 (71)	97 (46.4)	48 (40.7)	
Follow-up					
Anti-HBs titer (IU/L)	356 ± 1667 [0; 10; 138]	1.3 ± 2.7 [0.0: 0.0; 1.0]	725 ± 2325 [43;139;557]	1252 ± 2995 [198; 409; 1001]	<0.001[a,b]
Transplantation, n (%)	96 (22.5)	32 (14.7)	64 (30.6)	39 (33.1)	<0.001[a,b]
All-cause mortality, n (%)	228 (53.5)	133 (61.3)	95 (45.5)	47 (39.8)	0.001[a,b]
CV mortality#, n (%)	105 (46.1)	63 (47.4)	42 (44.2)	20 (42.6)	0.03[a], 0.02[b]
Infection-related mortality#, n (%)	36 (15.8)	19 (14.3)	17 (17.9)	6 (12.8)	0.86[a], 0.28[b]
CV and infection-related mortality#, n (%)	141 (61.8)	82 (61.7)	59 (62.1)	26 (55.3)	0.03[a], 0.004[b]

Mean SD [25th, 50th and 75th percentile for cases of non-normal distribution] or number (%).
[a]Non-Responders *vs* Seroconversion; [b]Non-Responders *vs* Seroprotection.
*Includes cerebrovascular disease (CVD) and peripheral arterial disease (PAD).
#% of all death causes.

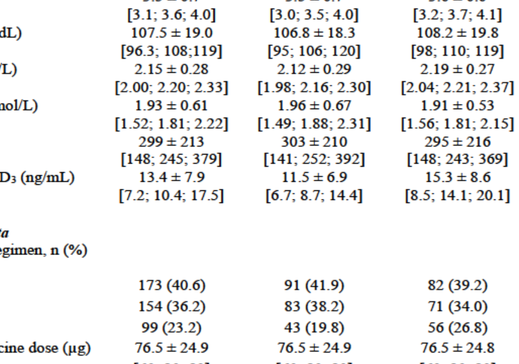

Fig. 1. Patient disposition flow chart

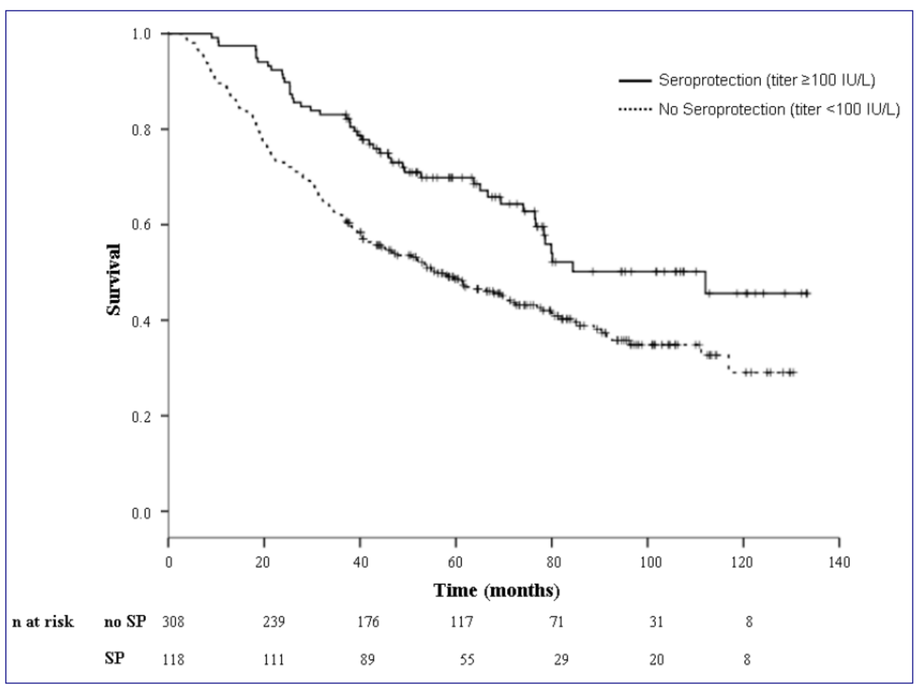

Fig. 2. Kaplan-Meier survival curves stratified for seroprotection after hepatitis B vaccination. The number of patients at risk in both groups is given for each 20 months of observation. P<0.001 (log-rank) for group difference.

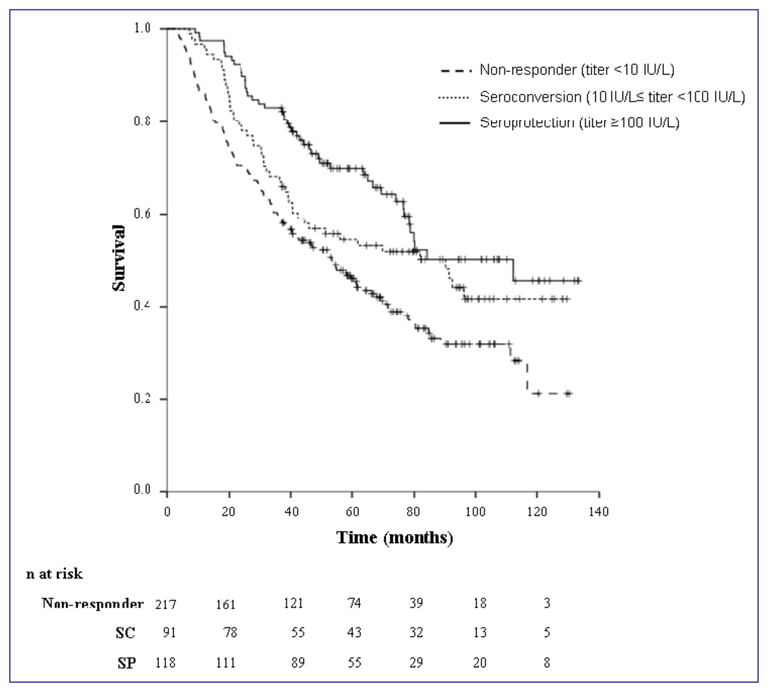

Fig. 3. Kaplan-Meier survival curves stratified for the immune response after hepatitis B vaccination. The number of patients at risk in all three groups is given for each 20 months of observation. P<0.001 (log-rank) for group differences.

	All-cause mortality			CV or infection mortality**		
	HR	(95% CI)	P	HR	(95% CI)	P
Age (years)	1.05	(1.04-1.07)	<0.001	1.05	(1.03-1.07)	<0.001
Sex						
Female	Ref.			Ref.		
Male	1.22	(0.92-1.60)	0.17	1.28	(0.89-1.82)	0.17
Type of dialysis						
Hemodialysis	Ref.			Ref.		
Peritoneal dialysis	0.57	(0.29-1.10)	0.09	0.74	(0.37-1.51)	0.37
Diabetes mellitus						
No	Ref.			Ref.		
Yes	1.40	(1.07-1.82)	0.01	1.52	(1.09-2.13)	0.01
Vaccination time point						
1st year after dialysis start	Ref.			Ref.		
Last year prior to dialysis start	0.73	(0.53-1.00)	0.05	0.92	(0.61-1.39)	0.53
Seroconversion						
No	Ref.			Ref.		
Yes	0.77	(0.58-1.02)	0.07	0.76	(0.54-1.06)	0.11
Seroprotection						
No	Ref.			Ref.		
Yes	0.71	(0.51-0.99)	0.04	0.62	(0.41-0.96)	0.03

* Adjusted for age, sex, diabetes mellitus, type of renal replacement therapy, vaccination time point.
** **Cardiovascular (CV) or infection-related mortality**: myocardial infarction (MI), heart failure, sudden death, ischemic stroke, hemorrhagic stroke, viral/bacterial/fungal infection, sepsis

Tab. 2. Association between immune response (seroconversion, seroprotection) and all-cause mortality and cardiovascular or infection-related mortality using multivariable adjusted Cox proportional hazards models*.

CONCLUSIONS

Achieving seroprotection, defined as an anti-HBs antibody titer ≥100 IU/L, after active hepatitis B immunisation is associated with significantly reduced all-cause and cardiovascular mortality in incident dialysis patients. This simple and readily available tool allows patient survival to be predicted independently of other well-known key parameters such as age, gender or the presence of diabetes.

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