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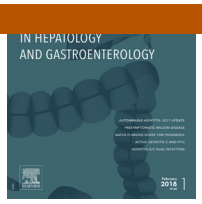

ORIGINAL ARTICLE

HBV vaccination with Fendrix is effective and safe in pre-dialysis CKD population

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KEYWORDS
Adjuvant;
Hepatitis B vaccine;
Chronic kidney disease;
Immunogenicity;
Safety

Summary
Background: Patients with chronic kidney disease have a poor response to hepatitis B vaccine due to the immunodeficiency conferred from chronic uremia. A recombinant HB vaccine containing an improved adjuvant system AS04 (HBV-AS04) has been manufactured but scarce evidence exists on HBV-AS04 use among patients with CKD.
Aim: To assess efficacy and safety of an adjuvanted recombinant vaccine (HBV-AS04) in a large cohort of CKD patients at pre-dialysis stage (with susceptibility to HBV infection).
Methods: Patients were prospectively enrolled to receive four 20-mcg doses of HBV-AS04 by intramuscular route (deltoid muscle) at months 1, 2, 3, and 4. Anti-HBs surface antibody concentrations were tested at intervals of 1, 2, 3, 4, and 12 months. Multivariate analyses were performed to assess the parameters, which predicted immunologic response to HBV-AS04 vaccine.
Results: One hundred and seven patients were included and 102 completed the study. At completion of vaccine schedule, the frequency of responders (anti-HBs titers $\geq$ 10 mIU/mL) was 95% (97/102) (mean anti-HBs antibody titers, 688.9 $\pm$ 385 mIU/mL), according to per-protocol analysis. Serum haemoglobin levels were greater in responder than non- or low-responder patients to HBV-AS04 ($P = 0.04$) and this was confirmed by multivariate analysis. The seroprotection rate at month 50 was 88% (30/34) with lower anti-HBs antibody titers (218.5 $\pm$ 269.6 mIU/mL, $P = 0.001$). No major side effects were observed.
Conclusions: Our prospective study performed in a real-world setting showed a high immunogenicity and safety of HBV-AS04 vaccine in patients with CKD not yet on maintenance dialysis. Studies provided with longer follow-ups are under way to assess the durability of seroprotection in responders.

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Abbreviations

AEs	adverse events
CAPD	continuous ambulatory peritoneal dialysis
CDC	centers for disease control and prevention
CI	confidence intervals
CKD	chronic kidney disease
CKD EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HD	haemodialysis
IFN	interferon
PD	peritoneal dialysis
RT	renal transplant
STROBE	Strengthening the Reporting of Observational studies in Epidemiology

Introduction

Viral hepatitis B is a major health challenge worldwide and it has been recently estimated that around 257 million people are living with hepatitis B virus infection (defined as hepatitis B surface antigen positive). Hepatitis B virus is a double DNA stranded virus leading to chronic hepatitis, cirrhosis, hepatocellular carcinoma and liver failure. Patients on dialysis have high risk for HBV infection due to skin breaching, exposure to blood products, and sharing of dialysis machines and ancillary instrumentation within dialysis rooms [1]. The immune deficiency conferred from chronic uremia is another factor, which supports the transmission of HBV between patients on dialysis.

The incidence of HBV in the dialysis population of the developed world has been consistently reduced due to the screening of blood derived products and the implementation of several infection control procedures including universal precautions, separate rooms and machines for HBsAg positive patients [2,3]. However, transmission of hepatitis B virus between patients on dialysis continues to occur in both developed [4] and developing [5,6] countries.

Hepatitis B virus vaccination is another means of preventing the spread of HBV in dialysis units and a recombinant HBV vaccine has been made available since the early eighties. It is well known, however, that CKD patients have a poor immunologic response to HBV vaccine compared to those with intact kidneys [2,3]. The immunization rate is reduced, and responder patients show lower anti-HBs titers, which fall logarithmically after completion of the vaccination schedule. Numerous approaches have been adopted to improve the immunogenicity of recombinant HBV vaccine in patients with CKD including reinforced HB vaccine schedule [7], concomitant use of immuno-modulatory agents [8,9], vaccination by ID route [10], and administration of vaccine at pre-dialysis stage [11], among others. A recombinant HB vaccine containing an improved adjuvant system (AS04) has been introduced in the market specifically for patients with CKD [12—17]; it contains as active substance 20 mcg recombinant hepatitis B surface antigen which is adjuvanted by AS04C (containing 3-0-desacyl-4′-monophosphoryl lipid A, MPL), adsorbed on aluminium phosphate and produced in *Saccharomyces cerevisiae* by recombinant DNA technology. MPL is a powerful stimulant of the immune system and acts through binding on the Toll-like receptor 4 on antigen-presenting cells. MPL-stimulated antigen-presenting cells express increased levels of co-stimulatory molecules (including CD86 molecules) and cytokines inducing strong humoral and cellular responses.

There is limited information in the medical literature on HBV-AS04 vaccine in the CKD population [12—17]. We have undertaken a prospective, real-world study was to assess immunogenicity and safety of HBV-AS04 in a large cohort of CKD patients not yet requiring dialysis and who are susceptible to HBV infection.

Patients and methods

Setting and study subjects

This was a prospective, cohort study in outpatients on regular follow-up at a metropolitan hospital (Milano city). There was a program-wide screening for hepatitis B virus infection susceptibility and immunization since early nineties at the unit. Hepatitis B virus susceptible patients with CKD were given an opportunity to participating in the study.

Inclusion criteria were receiving periodic follow-up at a inner city nephrology center, 18 years or older, serum HBsAg/anti-HBs negative at baseline, and able and willing informed consent. Exclusion criteria were treatment with intravenous immune globulin within the last 6 months, previous allergic reactions including hypersensitivity to components of vaccine, contraindication to intramuscular injections, elevated liver enzymes, serious systemic illness, and concomitant immunosuppressive therapy. Patients with previous administration of a vaccine containing monophosphoryl lipid A were excluded.

The study was considered exempt by the institutional review board at Maggiore Hospital and IRCCS Foundation, Milano, Italy. It was conducted in accordance with the ethical principles reported in the 1996 version of the Declaration of Helsinki and Good Clinical Practice guidelines. All participants gave informed and written consent before they were enrolled. The study was reported according to the STROBE initiative [18]; the checklist of 22 items that it is considered essential for good reporting of cohort observational studies can be found in the Additional file n.1.

Study design

Patients were given four doses of recombinant vaccine formulated with an improved adjuvant system (HBV-AS04, Fendrix) and manufactured by GlaxoSmithKline Biologicals. HBV-AS04 vaccine was administered as a 0.5 mL intramuscular injection (deltoid muscle) according to a 0-, 1-, 2-, 3-month schedule. In the case of patients who had been equipped with arteriovenous dialysis fistula, HB vaccine was administered to the contralateral arm. One dose of HBV-AS04 contained 20 mcg of recombinant HBsAg, 50 mcg of

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MPL (3-0-desacyl-4′-monophosphoryl lipid A) and 0.5 mcg of aluminium salt.

The primary outcome of interest in this study was the seroprotection rate in the According to Protocol (ATP) cohort, as a measure of efficacy. The ATP cohort included all patients who had complied with primary vaccination protocol. The secondary end-point was the frequency of side effects associated with vaccine administration.

Serum studies

Upon entry into the study, a baseline serum sample was obtained. Samples for anti-HBs antibodies were taken from all study patients at intervals of 1, 2, 3, 4, and 12 months. HBV, HCV, and HIV markers were tested in all patients at baseline. Hepatitis B surface antigen (HBsAg), antibodies to hepatitis B surface antigen (HBsAb) and hepatitis core antigen (HBcAb) were measured in plasma samples by enzyme immunoassays (Abbott Laboratories, USA). Serum aminotransferase levels were tested with spectrophotometric methods. Screening for antibody to hepatitis C virus was performed by a third generation ELISA test. Antibodies to the human immunodeficiency virus were measured by commercially test kits (Abbott Diagnostics).

A large number of demographic, clinical and biochemical parameters were collected at baseline for each patient. Serum creatinine was measured at the beginning of the study and used to calculate the baseline estimated GFR through the CKD EPI equation. Study subjects were classified into 5 groups (CKD stage 1—5) according to the baseline eGFR [19].

Safety and reactogenicity

The patients were observed closely for at least 15 minutes after each vaccine dose. The safety and reactogenicity were evaluated by the patients recording solicited local (pain, redness, swelling) and general (fatigue, fever, headache, and GI symptoms) AEs. All local symptoms were considered as related to vaccination. Unsolicited adverse events occurring within 30 days after each vaccination regardless of attribution were also recorded as well as any serious AE that occurred during the whole study period up to 30 days after the last vaccination.

Statistical analysis

Descriptive analyses are expressed in terms of mean ± standard deviation for continuous variables and percentages for categorical variables. Skewed variables were log transformed. We performed multivariate analysis by nominal logistic regression model: demographic, clinical and biochemical characteristics were adopted as independent variables, and anti-HBs titers were assumed a dependent parameter. Statistical analysis was carried out using the program JPM (SAS Institute, USA, 1996).

Definitions

Successful vaccine response (seroprotection) was defined as anti-HBs concentration ≥ 10 IU/L. Seroconversion was an anti-HBs value of 1 mIU/mL or more. We defined responder and non-responder patients according to level of anti-HBs one month after the final injection (non-responders, HBsAb < 10 IU/L). Low-responders were those responders who had detectable anti-HBs antibody ranging between 10—100 IU/L one month after the end of vaccine course.

Table 1 Baseline characteristics of study patients.

	Patients, *n*	(%)
Gender		
Males	74	72.5
Age, years		
Mean (SD)	66.26 ± 14	
Ethnicity		
Caucasians	94	92.2
Underlying nephropathy		
Polycystic kidneys	9	
Diabetic nephropathy	11	
Glomerulonephritis	19	
Nephrosclerosis	25	
Unknown cause	20	
Others	18	
CKD stage		
CKD stage 1	0	
CKD stage 2	1	
CKD stage 3	12	
CKD stage 4	52	
CKD stage 5	37	
Experienced patients, *n*	3	2.9
Serum creatinine, mg/dL		
Mean (SD)	3.4 ± 1.23	
Azotemia, mg/dL		
Mean (SD)	107.7 ± 32.3	
eGFR, mL/min/1.73 m^2		
Mean (SD)	19.6 ± 9.9	
Diabetes mellitus, *n*	32	31.3
Arterial hypertension, *n*	86	84.1
Anti-HCV positive patients, *n*	2	1.9
Anti-HBc positive patients, *n*	4	3.9
Haemoglobin, g/dL		
Mean (SD)	12.05 ± 1.4	
Transferrin, mg/dL		
Mean (SD)	229 ± 41.03	
Parathyroid hormone, pg/mL		
Mean (SD)	108.0 ± 64.8	
25 (OH) vitamin D, ng/mL		
Mean (SD)	23.8 ± 13	

eGFR: estimated glomerular filtration rate; HCV: hepatitis C virus; HBc: hepatitis core.

Results

Patient characteristics

We originally enrolled 107 patients, 102 of them completed the study, for which per-protocol analysis was done. Five patients did not complete the vaccine course — three patients were lost to follow-up, and two patients died or withdrew from the study on a voluntary basis, respectively.

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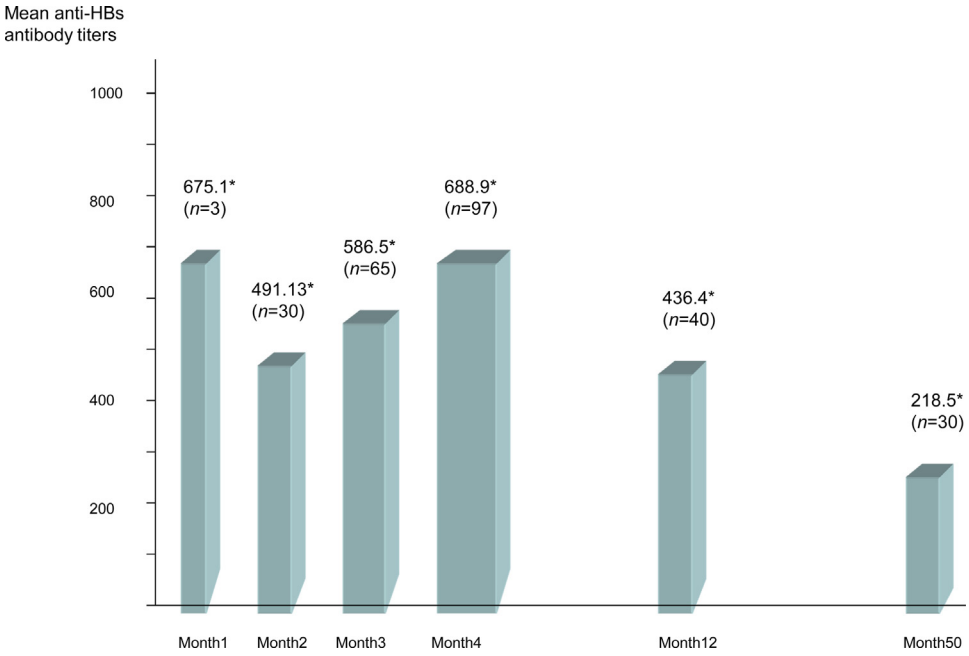

Figure 1 Persistence of anti-hepatitis B (HBs) antibody seroprotection rates.

The demographic, clinical and biochemical parameters of the patients at baseline are reported in Table 1. The majority of patients had Caucasian origin, none had detectable human immunodeficiency virus antibodies or admitted current or previous intravenous drug use. The majority of patients had advanced CKD, as reported in Table 1.

Immunogenicity of vaccine

After the first vaccine dose, the seroprotection rate was 12% (3/25) (Fig. 1). The seroprotection rate after the second and third dose was 58% (30/52) and 89% (65/73), respectively. The frequency of responders (anti-HBs titers $\geq$ 10 mIU/mL) one month after completing vaccine course was 95% (97/102). The sero-response rate over follow-up was 82% (40/49) and 88% (30/34) at month 12 and 50, respectively (Fig. 1).

According to univariate analysis (Table 2), there was no difference between responders (HBsAb > 100 IU/L) and non- ($n = 5$) or low- ($n = 8$) responders with regard to various demographic, clinical, and biochemical characteristics. Haemoglobin and serum transferrin were greater among responder patients (HBsAb > 100 IU/L) and this was confirmed by multivariate analysis (Table 3).

After the end of the vaccination cycle, 29 and 9 patients initiated long-term haemodialysis and peritoneal dialysis, respectively. Four patients died and 7 underwent kidney transplant from deceased donor. Nineteen patients were lost to follow-up and 34 are still in pre-dialysis CKD stage and in charge at the nephrology division. Nine patients are in the active list for renal transplant.

There was significant difference with regard to the mean titers at 1, 2, 3, 4, 12 and 50 months — anti-HBs antibody levels at month 50 were lower than that observed at month 12 or 4 ($P = 0.016$ and $P = 0.009$), respectively (Fig. 2).

Safety of vaccine

Table 4 reports that many patients (51/102 = 50%) experienced AEs. The great majority of the side effects were injection-site AEs; the most common being pain (42/102 = 41%). The most common vaccine-related systemic AEs were headache and asthenia (13/102 = 13%). Two deaths were reported and none was considered to be linked with the administration of HBV-AS04 vaccine by the investigators.

Discussion

The evidence in the literature regarding the use of recombinant adjuvanted (HBV-AS04) vaccines in patients with CKD is extremely limited. In this prospective, cohort study aimed to assess immunogenicity and safety of HBV-AS04 in a large group of CKD patients not yet requiring dialysis we found a high immunization rate (97/102 = 95%); of note, this study concerns a real-life practice. As listed above, the study group presented several co-morbidities at baseline (such as arterial hypertension, diabetes mellitus, and others), which are typical of CKD populations. The most important paper on this issue has been carried out by Tong et al. [12] who conducted an open, randomized clinical trial. It is well known that an important shortcoming of the RCTs is their external validity as they address selected populations which are closely monitored over time. In addition, the work by Tong et al. regarded mostly patients on long-term dialysis.

The data in the medical literature regarding efficacy and safety of HBV-AS04 are scarce and preliminary in nature (Table 5). Evidence exists in some patient groups including HIV-positive patients [20], renal transplant recipients [17] and non-responder patients with intact kidneys [21]. Fendrix™ has always shown a high level of immunogenicity.

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Table 2 Baseline characteristics of responder and non-responder patients: univariate analysis.

	Responders ($n = 89$)	Non- or low-responders ($n = 13$)	P
Gender, males	65 (73%)	9 (69%)	NS
Age, years	66.01 ± 14.4	68.17 ± 13.2	NS
Ethnicity, Caucasians	81 (91%)	13 (100%)	NS
Experienced patients, *n*	3 (3.3%)	0	NS
Serum creatinine, mg/dL	3.4 ± 1.2	3.5 ± 0.7	NS
Underlying nephropathy			NS
Polycystic kidneys	8	1	
Diabetic nephropathy	9	2	
Glomerulonephritis	18	1	
Nephrosclerosis	24	1	
Unknown cause	15	5	
Others	15	3	
CKD stage			NS
CKD stage 1	0	0	
CKD stage 2	1	0	
CKD stage 3	11	1	
CKD stage 4	45	7	
CKD stage 5	31	6	
Azotemia, mg/dL	107.1 ± 34	111.7 ± 17.43	NS
eGFR, mL/min/1.73 m^2	20.1 ± 10.3	16.2 ± 6.2	NS
Diabetes mellitus, *n*	26 (29.2%)	6 (46%)	NS
Arterial hypertension, *n*	75 (84.3%)	11 (85%)	NS
Anti-HCV positive patients, *n*	2 (2.2%)	0	NS
Anti-HBc positive patients, *n*	4 (4.5%)	0	NS
Haemoglobin, g/dL	12 ± 1.47	11.6 ± 1.38	004
Transferrin, mg/dL	226.2 ± 39.3	247.9 ± 48.5	0.02
Parathyroid hormone, pg/mL	105.6 ± 66.7	135.8 ± 66.4	NS
25 (OH) vitamin D, ng/mL	23.1 ± 11.8	28.3 ± 18.9	NS

eGFR: estimated glomerular filtration rate; NS: non significant.

Table 3 Multivariate analysis: parameter estimates and effect test.

Effect test	NParm	DF	Wald Chi^2	P
Gender (M/F)	1	1	0.0155	0.90
Age, years	1	1	0.0488	0.82
Creatinine, mg/dL	1	1	0.0254	0.87
Azotemia, mg/dL	1	1	0.0048	0.94
eGFR, mL/min/1.73 m^2	1	1	0.0821	0.78
PTH (pg/mL)	1	1	0.023	0.87
25(OH) vit. D	1	1	0.182	0.67
Diabetes (y/n)	1	1	0.0014	0.96
Haemoglobin, g/dL	1	1	2.872	0.041
Hypertension (y/n)	1	1	0.359	0.545
Transferrin, mg/dL	1	1	5.1967	0.02
Albumin, g/dL	1	1	2.4278	0.07

M: male; F: female; eGFR: estimated glomerular filtration rate; y: yes; n: no.

On the other hand, further vaccines are being produced and offer promising results [22].

A major result of the current study was the assessment of predictive factors, which could play impact on the immune response to HBV-AS04. Greater HB levels were an independent predictor of immune response to HBV-AS04 in our CKD population. This is in keeping with that observed in patients on maintenance dialysis [23]. In contrast to what reported in prior studies [7,24,25], we observed no link between seroprotection rate and predictive factors such as CKD stage, age or nutritional status; this is likely due to the clinical characteristics of the patient group. Finally, we cannot exclude

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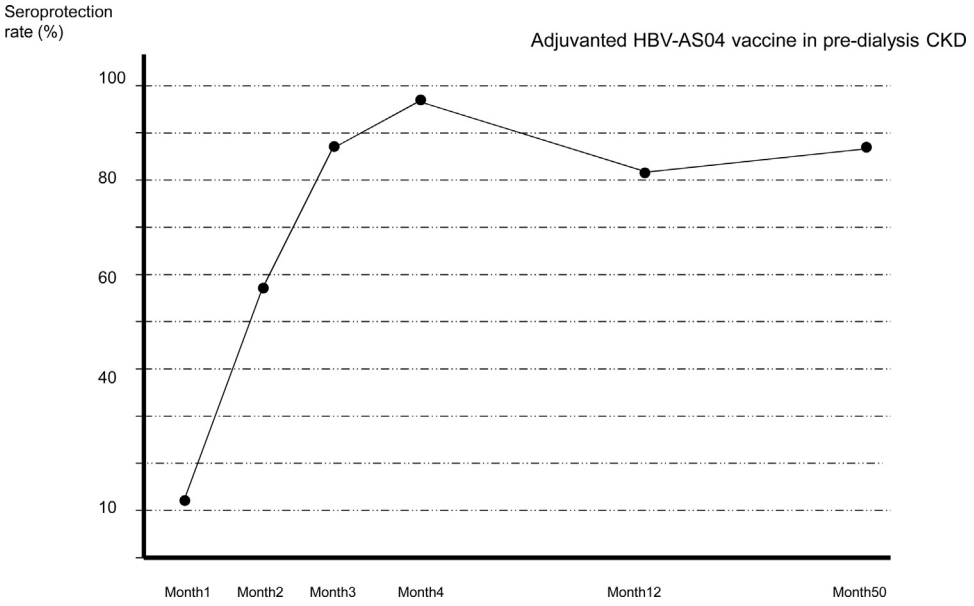

Figure 2 Mean anti-hepatitis B (HBs) antibody titers (*mIU/mL) at the end of vaccine course and over follow-up.

Table 4 Adverse experience summary (days 1 to 30 following any vaccination visit).

	Patients, *n* (*n* = 102)
Patients with one or more AE	51 (50%)
Patients with injection-site AEs	45 (44.2%)
Erythema	1
Pain	42
Swelling	2
Patients with systemic AEs	13 (12.7%)
Headache	4
Fever	0
Asthenia	9
Gastrointestinal symptoms	0
Patients with serious AEs	0
Serious vaccine-related AEs	0
Patients who died	2
Patients who discontinued vaccine due to AEs	0
Maximum temperature (Days 1—5 post-vaccine dose)	
> 37.5	0
> 40	0

AEs: adverse events.

residual confounding as the role of additional factors including body mass index, smoking, quality of life, inflammatory status on the immune response after HBV-AS04 was not appropriately addressed. An additional shortcoming of this study was that the assessment of the decay rate of anti-HBs titers following initial vaccination with HBV-AS04 was done over a long follow-up in a minority of patients only ($n = 34$). Indeed, a high number of patients were lost to follow-up. It has already suggested that the protection against HBV in patients with immune compromise does not rely on immune memory (in the form of memory T and B lymphocytes) but on circulating anti-HBs antibody [26].

The achievement of protective anti-HBs titers can provide numerous benefits to CKD patients; first, evidence accumulated in the last decade suggests an independent role of chronic HBsAg carriage in increasing the incidence and the progression of CKD in the adult general population. The presence of sublinical atheromatosis induced by HBV at kidney level (atheromatous plaques in the renal arteries and arterioles) has been mentioned, irrespective of the glomerular manifestations induced by HBV [27,28]. Secondly, protective anti-HBs titers are crucial for RT candidates to be included in the waiting list from donors with evidence of HBV infection (hepatitis B surface antigen-negative/anti-hepatitis B core-positive). In fact, the increasing demand for available organ donors for RT and the continuing shortage of organs has led many transplant centers to expand their acceptance criteria by including deceased donors with special clinical situations (such as kidney donors with evidence of HBV infection) [29]. At last, we must consider that many of the patients with CKD in the pre-dialysis phase begin long-term haemodialysis; there is the opportunity for HBsAg negative patients with protective levels of anti-HBs antibody in serum to undergo HD even in shifts and machines dedicated to HBsAg positive patients. Isolation of HBsAg positive carriers by rooms, machines, and staff is still an important preventive measure against the spread of HBV within dialysis units, as recommended by the CDC [3].

We believe that the clinical benefits conferred from HBV vaccine need to be obtained in susceptible CKD patients as soon as possible; thus we have adopted an accelerated vaccine schedule (1, 2, 3, and 4 months) in comparison with the standard schedule (1, 2, 3 and 6 months) recommended by the manufacturers. In fact, the accelerated vaccine schedule allows the achievement of protective antibody levels more faster than the standard vaccine schedule.

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Table 5 Available data on the use of Fendrix in patients with CKD.

Authors	Ref	Patients, *n*	CKD status, *n*
Lindemann M et al., 2017	[17]	7/17 (41.2%)	RT
Fabrizi F et al., 2015	[16]	76/91 (84%)	HD
Surquin M et al., 2010	[14]	117/149 (78.6%)	HD (45%), PD (13.4%), pre-dialysis (41.6%)
Kong N et al., 2005	[13]	74/82 (90.9%)	HD (54%), pre-dialysis (46%)

CKD: chronic kidney disease; RT: renal transplant; HD: haemodialysis; PD: peritoneal dialysis.

Conclusion

Our prospective cohort study conducted in a 'real-life' setting suggests a great immunogenicity and safety of HBV-AS04 among patients with CKD not requiring maintenance dialysis. Studies are under way to assess the persistence of anti-HBs antibodies in patients with CKD who have been subjected to active immunization successfully.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinre.2019.06.010.

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