Hepatitis B virus vaccine in chronic kidney disease: Improved immunogenicity by adjuvants? A meta-analysis of randomized trials

Fabrizio Fabrizi a,∗, Vivek Dixit b, Piergiorgio Messa a, Paul Martin b

a Division of Nephrology, Maggiore Hospital, IRCCS Foundation, Milano, Italy
b Division of Hepatology, School of Medicine, University of Miami, FL, USA

A R T I C L E   I N F O

Article history:
Received 3 November 2011
Accepted 19 January 2012
Available online 26 January 2012

Keywords:
Hepatitis B virus
Vaccine
Adjuvants
Dialysis
Chronic kidney disease
Meta-analysis

A B S T R A C T

Background: Patients with chronic kidney disease typically show an impaired immune response to hepatitis B virus vaccine compared with healthy individuals. A variety of inherited or acquired factors have been implicated in this diminished response. Some authors suggested a benefit with adjuvantation to improve the immunogenicity of existing HBV vaccines.

Aim: To evaluate the efficacy and safety of adjuvantation for hepatitis B virus vaccine in patients with chronic kidney disease.

Methods: Only prospective, randomized clinical trials (RCTs) were included. We used the random effects model of DerSimonian and Laird with heterogeneity and subgroups analyses. The primary end-point of interest was the seroprotection rate after HBV vaccination with recombinant vaccine plus adjuvants (study group) versus recombinant vaccine alone (control group).

Results: We identified ten studies involving 1228 unique patients with chronic kidney disease. Pooling of study results did not show a significant increase in seroprotection rate among study (HBV recombinant vaccine plus adjuvants) versus control (HBV recombinant alone) patients; the pooled odds ratio of seroprotection rate was 1.47 (95% CI: 0.88; 2.46, NS). The pooled OR for seroresponse rate after HBV vaccine (adjuvanted recombinant vaccine versus recombinant vaccine alone) did not change in the subgroup of studies based on novel adjuvant systems (i.e., HBV-AS02 or HBV-AS02), the pooled OR was 2.22 (95% CI, 0.72; 6.78), NS. Q-test for heterogeneity being 10.819 (P=0.004).

Conclusions: Our meta-analysis showed that adjuvanted hepatitis B vaccine did not significantly improve the seroprotection rate in patients with renal insufficiency. These results do not support adjuvantation as an approach to increase the immunogenicity of existing recombinant vaccines towards HBV in this high-risk population.

© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

The frequency of hepatitis B virus (HBV) infection, as detected by persistent positivity for hepatitis B surface antigen in serum, is low but not negligible among patients with chronic kidney disease (CKD) on maintenance dialysis in the industrialized world [1]. In 2002, the Centers for Disease Control and Prevention (CDC, Atlanta, US) has reported that the prevalence of HBsAg seropositivity among dialysis patients was 0.9% in the U.S. [2]. Also, outbreaks of HBV infection in haemodialysis (HD) units continue to occur [3]. Prevalence and incidence rates of HBV infection remain much higher within dialysis units in less-developed countries [4,5]. It is well known that patients undergoing long-term dialysis have a lower response to HBV vaccine compared with the non-uraemic population: the number of patients who develop protective antibody (anti-HBs) against HBV surface antigen (HBsAg) is lower, the antibody titres of those who mount an antibody response are reduced and decline logarithmically with time [6].

Various attempts have been made in order to improve the response rate to hepatitis B vaccine in chronic kidney disease patients including increased vaccine doses [7], additional vaccine shots [7], or intradermal vaccine route [8]. Also, hepatitis B vaccine in chronic kidney disease patients not yet requiring dialysis has been given [9]. One approach to improve the immunogenicity of recombinant HBV vaccines is adjuvantation. Schedules including the administration of adjuvants such as thymopentin [10], granulocyte macrophage colony stimulating factor [11], or interferon [6] have been reported. Recently, adjuvanted vaccines towards HBV consisting of recombinant hepatitis B surface antigen formulated with novel adjuvant systems (i.e., aluminium phosphate and/or...
lipids) have been developed to optimize vaccine-induced immune response [12]. The approach of adjuvantage to improve the immunogenicity of recombinant HBV vaccines has not been fully evaluated and preliminary conflicting results have been given. The goal of this study was to investigate the available evidence on the efficacy and safety of adjuvanted recombinant vaccines towards HBV in chronic kidney disease population by performing a systematic review of the literature with a meta-analysis of randomized, clinical trials (RCTs).

2. Material and methods

2.1. Search strategy and data extraction

Electronic searches of the National Library of Medicine’s MEDLINE database, Current Contents, and manual searches of selected specialty journals to identify all pertinent literature were performed to identify all pertinent literature. It has previously demonstrated that an electronic search alone may not sensitive enough [13]. We searched MEDLINE (PubMed and Ovid technologies), EMBASE (Ovid Technologies), Current Contents (Institute for Scientific Information), and the Cochrane Library (Update Software). The key words ‘hepatitis B’; ‘vaccine’; ‘adjuvants’; ‘seroprotection’; and ‘reactogenicity’ were used. Reference lists from qualitative topic reviews and published clinical trials were also searched. Our search was limited to human studies that involved individuals aged >18 years published in the English literature. All articles were identified by a search from 2000 to November 2011. Data extraction was conducted independently by two investigators (F.F. and V.D.) and consensus was achieved for all data. Studies were compared to eliminate duplicate reports for the same patients; which included contact with investigators when necessary. Eligibility and exclusion criteria were prespecified.

2.2. Criteria for inclusion

To be included in this systematic review, a clinical trial had to fulfill a set of criteria. It had to be published as a peer-reviewed paper; we included only prospective, randomized clinical trials (RCTs) comparing the sero-protection rate after vaccination with adjuvanted recombinant vaccine versus recombinant vaccine alone in patients with chronic kidney disease (patients on maintenance dialysis or at pre-dialysis stage). The decision as to inclusion or exclusion of clinical trials was not related to results.

2.3. Ineligible studies

Studies were excluded if they reported inadequate data on measures of response. Trials that were published in abstract form, or as interim reports were excluded; review articles were not considered for this analysis.

2.4. Definitions

Outcomes were analyzed on an intention-to-treat basis, i.e., all patients included in these studies were considered for the calculation of the response rate, while patients without the endpoint were considered as failures. When not given in the publication, the outcome according to the intention-to-treat method was calculated by the data abstractors (F.F. and V.D.).

In all trials, recombinant vaccine towards HB was administered as an intramuscular injection into the deltoid region of the arm without or least likely to be used for the arteriovenous fistula in hemodialysis and pre-dialysis patients or the non-dominant arm in peritoneal dialysis patients. Primary outcome measure in this systematic review was seroprotection rate. It was defined as the frequency of patients developing protective titres (patients with anti-HBs titres >10 mIU/mL). Seroprotection rate was calculated at completion of vaccination schedule and over follow-up. These definitions were consistent with standards published in the scientific literature.

2.5. End-points of interest

The primary end-point (as a measure of efficacy) was the comparison of the seroprotection rate at completion of vaccination course in dialysis patients vaccinated with recombinant hepatitis B vaccine plus adjuvants compared to those receiving recombinant vaccine alone. Additional end-points include the adverse effects of hepatitis B vaccine (local injection site, systemic reactions, liver-related morbidity and mortality).

2.6. Statistical methods

The odds ratios (OR) were generated using the random effects model. The random effects approach was taken according to DerSimonian and Laird [14]. The Cochrane's Q-test was used for quantifying the heterogeneity; a value <0.10 was considered indicative of a statistically significant difference [15]. In addition, the consistency of effects across studies was evaluated by I² index [16]. Sensitivity analysis using a fixed-effects model was also performed to assess the consistency of results. In addition, the Galbraith plot was used to assess the heterogeneity and precision of single studies [17]. The publication bias assessment (PBA; number of void or negative trials necessary to render the meta-analysis meaningless) was calculated according to the Klein formula [18]. The publication bias was also measured by the test for funnel plot asymmetry. Every estimate was given with 95% Confidence Intervals (CI). The 5% significance level was used for alpha risk. All the statistical analyses were performed using the Stata 8.0 software (Stata Corporation, College Station, TX, US).

3. Results

3.1. Literature review

Our electronic and manual searches identified 162 manuscripts, of which 133 were considered potentially relevant and were selected for full text review. A complete list of the 133 reports reviewed is available from the authors on request. A total of nine reports giving information on ten RCTs were included in our meta-analysis [19–27]. There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies reviewed based on the predefined inclusion and exclusion criteria.

3.2. Study design of clinical trials

All studies reported prospective, randomized-controlled trials (RCTs) published in the English language from 1990 to 2011. Only two RCTs were double-blinded [21,22]. Generation of allocation sequence was described in five [21,22,25–27], and allocation concealment was reported in two [21,22].

3.3. Patient characteristics

Some salient demographic and clinical characteristics of subjects enrolled in the RCTs of the current meta-analysis are shown in Tables 1–3. There were six reports from Europe. Mean age of subject cohorts ranged from 43 ± 2 to 66 ± 12 years, and gender distribution ranged from 45% to 82% male. A minority of patients had chronic renal insufficiency at pre-dialysis stage [20,23,24,27].
Table 1  
Baseline characteristics of studies included in the analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Patients, n</th>
<th>Publication year</th>
<th>Reference year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiroga et al.</td>
<td>Spain</td>
<td>41/40</td>
<td>1990</td>
<td>19</td>
</tr>
<tr>
<td>Jungers et al.</td>
<td>France</td>
<td>25/27</td>
<td>1994</td>
<td>20</td>
</tr>
<tr>
<td>Evans et al.</td>
<td>US</td>
<td>11/19</td>
<td>2000</td>
<td>21</td>
</tr>
<tr>
<td>Perez-Garcia et al.</td>
<td>Spain</td>
<td>132/137</td>
<td>2002</td>
<td>22</td>
</tr>
<tr>
<td>Singh et al.</td>
<td>India</td>
<td>35/36</td>
<td>2003</td>
<td>23</td>
</tr>
<tr>
<td>Tong et al.</td>
<td>Malaysia, Spain, Czech Republic</td>
<td>83/82</td>
<td>2005</td>
<td>24</td>
</tr>
<tr>
<td>Salih et al.</td>
<td>Iran</td>
<td>32/38</td>
<td>2008</td>
<td>25</td>
</tr>
<tr>
<td>Miquilena-Colina et al.</td>
<td>Spain, Italy</td>
<td>34/30</td>
<td>2009</td>
<td>26</td>
</tr>
<tr>
<td>Tielemans et al.</td>
<td>Belgium, Hungary</td>
<td>126/125</td>
<td>2011</td>
<td>27</td>
</tr>
</tbody>
</table>

Data are given for controls/study patients wherever appropriate.

Table 2  
Baseline characteristics of studies included in the analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age, years</th>
<th>Male (%)</th>
<th>Pre-dialysis stage, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiroga et al.</td>
<td>19–65</td>
<td>46 (57%)</td>
<td>0</td>
</tr>
<tr>
<td>Jungers et al.</td>
<td>60 ± 12/57 ± 15</td>
<td>35 (67%)</td>
<td>28 (54%)</td>
</tr>
<tr>
<td>Evans et al.</td>
<td>52/47</td>
<td>5 (45%)/13 (68%)</td>
<td>0</td>
</tr>
<tr>
<td>Perez-Garcia et al.</td>
<td>60 ± 15/60 ± 15</td>
<td>67 (51%)/93 (68%)</td>
<td>0</td>
</tr>
<tr>
<td>Singh et al.</td>
<td>45 ± 11/45 ± 15</td>
<td>19 (54%)/21 (58%)</td>
<td>18 (51%)/21 (58%)</td>
</tr>
<tr>
<td>Tong et al.</td>
<td>58 ± 15/58 ± 5</td>
<td>48 (58%)/46 (56%)</td>
<td>42 (51%)/38 (46%)</td>
</tr>
<tr>
<td>Salih et al.</td>
<td>43 ± 2/47 ± 2</td>
<td>21 (66%)/20 (53%)</td>
<td>0</td>
</tr>
<tr>
<td>Miquilena-Colina et al.</td>
<td>58 ± 13/60 ± 10</td>
<td>28 (82%)/23 (77%)</td>
<td>0</td>
</tr>
<tr>
<td>Tielemans et al.</td>
<td>65 ± 11/66 ± 12</td>
<td>67 (53%)/71 (57%)</td>
<td>15 (12%)/16 (13%)</td>
</tr>
<tr>
<td></td>
<td>64 ± 12/65 ± 13</td>
<td>48 (53%)/47 (52%)</td>
<td>7 (8%)/9 (98%)</td>
</tr>
</tbody>
</table>

Data are given for controls/study patients wherever appropriate.

Table 3  
Baseline characteristics of studies included in the analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Diabetics, n</th>
<th>Time on dialysis, months</th>
<th>Caucasian race, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiroga et al.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Jungers et al.</td>
<td>NA</td>
<td>NA</td>
<td>24 (96%)/24 (89%)</td>
</tr>
<tr>
<td>Evans et al.</td>
<td>NA</td>
<td>73.2/65.4</td>
<td>6 (54%)/8 (42%)</td>
</tr>
<tr>
<td>Perez-Garcia et al.</td>
<td>20 (15.0%)/29 (22%)</td>
<td>38.4 ± 41/35.3 ± 38.9</td>
<td>128 (96.9%)/133 (97.1%)</td>
</tr>
<tr>
<td>Singh et al.</td>
<td>8 (23%)/9 (25%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tong et al.</td>
<td>NA</td>
<td>22 ± 42/15 ± 17</td>
<td>NA</td>
</tr>
<tr>
<td>Salih et al.</td>
<td>NA</td>
<td>17 ± 3/13 ± 3</td>
<td>NA</td>
</tr>
<tr>
<td>Miquilena-Colina et al.</td>
<td>13 (38%)/11 (37%)</td>
<td>23 ± 50/14.2 ± 14</td>
<td>31 (91%)/28 (93%)</td>
</tr>
<tr>
<td>Tielemans et al.</td>
<td>40 (39%)/60 (48%)</td>
<td>40 (44%)/48 (53%)</td>
<td>124 (99%)/124 (98%)</td>
</tr>
</tbody>
</table>

Data are given for controls/study patients wherever appropriate, NA = not available.

and patients on peritoneal dialysis were included only in two studies [27]. The frequency of PD patients being 8% and 7% [27]. Data on vaccine schedule in the RTCs included in this meta-analysis are shown in Table 4.

3.4. Summary estimates of outcome

As shown in Fig. 1, the pooled OR (random effects model) for seroprotection rate after adjuvanted HB vaccine was 1.473; 95% CI, 0.880; 2.466, P = NS. The test for heterogeneity was significant, Q-test = 29.9, P(Q) = 0.0001, I² = 73.3%. The publication bias assessment (PBA), according to the Klein formula, was 31. The test of funnel plot asymmetry was not significant a = −1.78; 95% CI, −4.88; 1.32, P(z) = 0.26. The Galbraith plot (Fig. 2) highlighted the great precision of every single study, and the absence of heterogeneity in the analysis.

Subgroup analyses were undertaken to explain the heterogeneity across trials. As listed in Table 5, the pooled OR for seroresponse

Table 4  
Vaccine schedules of studies included in the analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Vaccine, schedule (Controls/Study)</th>
<th>Adjuvant, type</th>
<th>Prior vaccine schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiroga et al.</td>
<td>40 mcg × 3/40 mcg × 3</td>
<td>Interferon</td>
<td>No</td>
</tr>
<tr>
<td>Jungers et al.</td>
<td>20 mcg × 1/20 mcg × 1</td>
<td>Interleukin-2</td>
<td>Yes</td>
</tr>
<tr>
<td>Evans et al.</td>
<td>40 mcg × 1/40 mcg × 1</td>
<td>Granulocyte-macrophage CSF</td>
<td>Yes</td>
</tr>
<tr>
<td>Perez-Garcia et al.</td>
<td>40 mcg × 4/40 mcg × 4</td>
<td>Immunoferon</td>
<td>Yes</td>
</tr>
<tr>
<td>Singh et al.</td>
<td>40 mcg × 4/40 mcg × 4</td>
<td>Granulocyte-macrophage CSF</td>
<td>No</td>
</tr>
<tr>
<td>Tong et al.</td>
<td>40 mcg × 4/20 mcg × 4</td>
<td>HBV-AS04</td>
<td>No</td>
</tr>
<tr>
<td>Salih et al.</td>
<td>40 mcg × 3/40 mcg × 3</td>
<td>Levamisole</td>
<td>Yes</td>
</tr>
<tr>
<td>Miquilena-Colina et al.</td>
<td>40 mcg × 4/40 mcg × 4</td>
<td>Interferon</td>
<td>No</td>
</tr>
<tr>
<td>Tielemans et al.</td>
<td>40 mcg × 2/20 mcg × 2</td>
<td>HBV-AS02</td>
<td>No</td>
</tr>
</tbody>
</table>

Data are given for controls/study patients wherever appropriate, NA = not available.
The pooled OR for the rate of adverse effects after HBV vaccine (adjuvanted recombinant vaccine versus recombinant vaccine alone) was 3.267 (95% CI, 1.693, 6.60), P = 0.001. The test for heterogeneity was significant (Q-test = 40.7; P = 0.0001); I² = 85.3. The test for funnel plot asymmetry was not significant (z = 1.63; 95% CI, −1.28; 4.54, P = 0.27). The most frequent local and general symptoms were pain at the injection site and fatigue or mild fever, respectively. These were light side-effects and were not found to be unacceptable by any of the participants. No liver-related side-effects were recorded.

4. Discussion

The importance of HBV vaccination in patients requiring dialysis is well recognized in most industrialized countries and the CDC recommends that all dialysis patients should be vaccinated against HBV [7]. Chronic kidney disease patients who are candidates for kidney transplantation should also be vaccinated against HBV before transplantation [28]. However, patients with CKD and renal insufficiency have an impaired immune response to conventional recombinant HBV vaccines when compared with healthy individuals. Numerous in vivo and in vitro experiments have shown specific and varied deficiencies in the immune response of patients with chronic kidney disease, such as decreased immunoglobulin production, diminished interleukin-2 secretion by T lymphocytes, and impaired macrophage function [29,30]. In addition, the impaired efficacy of HBV vaccine in dialysis population has been attributed to numerous clinical factors including older age [31], male gender [32], nutritional status [33], serological positivity for hepatitis C virus (HCV) [34] or human immunodeficiency virus (HIV) [35] infection, diabetes mellitus [36], blood transfusion history [37], and possession of the major histocompatibility complex phenotype HLA-B [38] among others. Finally, the failure to complete a full course of HBV vaccination may cause a poor active immunization [39].

Efforts to overcome the impaired response rate to hepatitis B vaccine among patients with chronic kidney disease have given mixed results. Available options include alternative [40,41] or adjuvanted preparations [42] of recombinant vaccine. We have evaluated the efficacy and safety of adjuvanted recombinant vaccine towards HBV in patients with chronic kidney disease with a meta-analysis of RCTs. We observed that the immune response to recombinant HBV vaccine continues to be unsatisfactory despite adjuvants; in fact, recombinant vaccine plus adjuvants is not associated with a higher likelihood of seroprotection compared to controls, OR, 1.47 (95% CI: 0.88; 2.46, NS). Our primary analysis showed significant heterogeneity, Q-test = 29.9, P = 0.0001, I² = 73.3%. Stratified analysis in various subgroups yielded only minimal changes on the effect size showing the robustness of our results.

As with all systematic reviews, this study has several limitations, an examination of which may inform the design and conduct of future studies on this topic. First, despite stringent inclusion criteria, the methodological quality of the studies was on average not ideal, though varied considerably in individual studies. Among the 10 studies included in this analysis, some did not describe methods of randomization and double-blinding was uncommon; it is
possible that some so-called ‘randomized controlled trials’ were not real randomized controlled trials owing to a lack of rigorous clinical trial design [43]. It has been already emphasized that trials with low methodology quality can increase the estimates of intervention efficacy reported in meta-analysis [44]. However, pooling the subgroup of trials provided with more rigorous clinical trial design did not significantly change our findings (data not shown). Secondly, individual data (e.g., “patient-level” data) from each study were not available; thus, it was impossible to perform our own adjustments. Thirdly, this study has the potential limitation of publication bias; negative trials are less likely to be published. To limit the possible effects of publication bias, we adopted various strategies to identify published and unpublished trials. Inclusion criteria, established a priori, were chosen to increase the likelihood that high-quality studies would be included. Finally, the limited number of studies included in this meta-analysis clearly precludes more definitive conclusions.

An additional limitation of this study concerns the use of anti-HBs titer as a surrogate marker of protection against HBV infection. The protective effect of recombinant vaccine against acquisition of HBV infection among patients on long-term dialysis has been already reported by the CDC [45]. The efficacy of adjuvanted recombinant vaccine versus recombinant vaccine alone against HBV should be evaluated in terms of reduced incidence of HBV infection in CKD populations. The very low incidence of HBV infection among patients on maintenance dialysis in developed world clearly makes difficult the implementation of such clinical trials.

The Centers for Disease Control (CDC) [7] currently recommend that dialysis patients receive by intramuscular route double doses (20 mcg × 2) of licensed conventional recombinant HBV vaccine at 0, 1, 2, and 6 months. Regular monitoring of antibody levels to ensure that antibody concentrations remain above the protective level of 10 mIU/mL and booster vaccination whenever the levels of antibody against hepatitis B surface antigen (anti-HBs titers) fall below 10 mIU/mL have been recommended.

In summary, this meta-analysis of prospective RCTs has not shown significant benefit of adjuvantation in order to increase the immunogenicity of existing recombinant vaccines towards HBV in patients with CKD. The impaired immunologic response to HB vaccine in uremic individuals remains a challenge to clinicians involved in the management of patients with chronic kidney disease.

Acknowledgements

Declaration of personal interests: None of the authors has any conflict of interest to declare. Declaration of funding interests: The authors’ work is supported in part by the grant ‘Project Glomerulonephritis’ in memory of Pippo Neglia.

References


