Intradermal versus intramuscular hepatitis B re-vaccination in non-responsive chronic dialysis patients: a prospective randomized study with cost-effectiveness evaluation

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Abstract

Background. It has been calculated that 30% of chronic uraemic patients fail to produce antibodies to HBsAg antigen after hepatitis B (HB) vaccination. Low-dose intradermal (i.d.) inoculations and supplementary intramuscular (i.m.) injections have been reported to improve the response rate in previous non-responder chronic uraemic patients, but no cost-effectiveness evaluations have been made about this issue.

Methods. We re-vaccinated 50 chronic dialysis patients, who did not have any detectable anti-HBs antibody after a reinforced protocol of hepatitis B vaccine given by i.m. route, with hepatitis B recombinant DNA yeast vaccine (80 μg) by intradermal (25 patients) or intramuscular (25 patients) administration (randomly allocated). We used the same amount of HBsAg in order to exclude the confounding effect of the dose level administered on the immune response of uraemic patients. We studied, over a 20-month follow-up, the persistence of anti-HBs antibodies in our responder vaccinees. We made a comparison between the costs of our re-vaccination protocol and the other re-vaccination strategies that have been recently suggested.

Results. One month after completion of re-vaccination protocol, seroconversion rates (100% vs 48%, P = 0.008) and proportion of patients who elicited protective anti-HBs titres (96% vs 40%, P = 0.0001) were significantly higher in i.d. compared to i.m. patients. The levels of anti-HBs, expressed as geometric mean titres and 95% confidence intervals (GMT (95% CI)), were significantly increased in i.d. than in i.m. groups, 100 (44–187) vs 26 (14–52) mUI/ml (P = 0.018). At month 12, the seroconversion rates were 57 vs 14% in i.d. and i.m. groups respectively (P = 0.158); the seroprotection rate was higher in i.d. individuals in comparison with i.m. patients, 50 vs 0%, P = 0.072. At month 20, the seroconversion rates were 54 and 0% among i.d. and i.m. patients respectively (P = 0.055); the seroprotection rate was higher in i.d. than in i.m. group (30 vs 0%, P = 0.2). At month 20, the median anti-HBs titres in i.d. patients were 21 mUI/ml, and GMT (95% CI) were 20.9 (2–54) mUI/ml. No important general or local side-effects were observed. The cost of our schedule was $92 US whereas the costs of other re-vaccination protocols ranged between 138 and $807 US.

Conclusions. Our results show that the unresponsiveness to recombinant yeast-derived vaccine may be mostly reversed by repeated low-dose i.d. injections of the same agent. In spite of an equal amount of HBsAg received, i.d. hepatitis B re-vaccination shows higher immunogenicity compared to i.m. administration over a 20-month observation period. Cost-effectiveness analysis demonstrated that the intradermal administration of HB vaccine is the most clinically effective re-vaccination strategy; it is also the most unexpensive one. We strongly recommend low-dose intradermal inoculations in order to re-vaccinate chronic dialysis patients who fail to respond to hepatitis B vaccination.

Key words: intradermal re-vaccination; chronic dialysis patients; non-responsiveness to HB vaccine; cost analysis

Introduction

Since 1960 HBV liver disease has been considered an important problem in dialysis units in both Europe and north America. For this reason, the Centers for Disease Control and Prevention (CDC) has conducted surveillance of haemodialysis-associated hepatitis since 1970s [1]. Between 1976 and 1993, the incidence of HBV infection decreased from 3.0 to 0.1% and the prevalence of HBsAg positivity declined from 7.8 to 1.2% among haemodialysis patients in the United States [2]. These results are probably attributable to use of CDC guidelines, screening of blood donors for HBsAg and anti-HBc, and the decline in blood transfusion requirement because of the use of erythropoietin.
Although not statistically significant, reporting of HBV infection was higher from centres where ≤50% of patients received hepatitis B vaccine [2]. Therefore there is the need of very careful surveillance for full application of measures to prevent HBV spread, i.e. the combined use of vaccine with infection control strategies. Indeed, HBV infection remains an important problem in developing countries [3] and dialysis units of western countries may sometimes experience episodes of HBV infection because of inadequate infection control procedures or to breaks in technique.

Several authors [4,5] observed that chronic uraemic patients, whether dialysed or not, have an impaired immune response to hepatitis B vaccine. Indeed, patients with end-stage renal disease show lower seroconversion rates compared to healthy subjects. Moreover, after completion of the vaccination schedule anti-HBs titres of responder dialysis patients are low and fall rapidly. We have previously reported [6] that 33% of chronic haemodialysis (HD) patients at our centre did not show seroprotection after completion of a reinforced protocol with hepatitis B recombinant DNA yeast vaccine given by i.m. route. Different approaches have been used to overcome the non-responsiveness of chronic uraemic patients—the intramuscular administration of multiple doses [7] or double doses [6,8], the co-administration of zinc [9,10] or immune modulators such as gamma interferon [11], thymopentine [12], interleukin-2 [13,14], and the intradermal administration of HBV vaccine [15–20]. Inclusion in the vaccine of a more extended portion of the HBV genome containing the pre-S2 protein might increase the response rate [21,22]. Alternatively it has been recommended to start vaccination in the early stages of a renal disease, when one could anticipate that the primary immune response is still sufficient [23]. Among these vaccination schedules, the repeated administration of low doses of recombinant B vaccine by i.d. route seemed to be effective in reversing non-responsiveness to HBsAg in chronic dialysis patients. High seroprotection rates also have been reported by using supplementary i.m. inoculations of HB vaccine [8]; however, large amounts of HB vaccine were used, with high costs.

On the other hand, the relative low response to HB vaccine of HD patients and the low incidence rates of HBV infection in many countries point out questions about cost effectiveness of vaccination and re-vaccination strategies in dialysis patients. Thus we have made an evaluation of costs regarding different re-vaccination schedules.

The aim of this prospective randomized trial was to compare safety and immunogenicity of i.d. vs i.m. re-vaccination in a large cohort of chronic dialysis individuals non-responsive to a reinforced i.m. vaccination protocol. Moreover, we analysed the costs for intradermal HB administration and other re-vaccination schemes that have been recently suggested.

Subjects and methods

Study protocol

Effective January 1991, we started our vaccination dialysis programme at the Nephrology and Dialysis Unit in Lecco, northern Italy. To date, 193 chronic dialysis patients have completed a full course of HBV vaccination with a reinforced schedule (40 μg × 3) of recombinant HB vaccine by intramuscular route. One hundred and twenty-seven patients developed anti-HBs levels more than 10 UI/ml (a level felt to provide protection), after completion of vaccination schedule. Sixty-six patients did not show anti-HBs antibody after vaccination and were classified as non-responders, 50 of them were randomly included in the present study—a prospective randomized clinical trial.

After obtaining informed consent, the patients were randomly assigned to either intradermal or intramuscular hepatitis B vaccine administration. Patients were allocated into the two groups using a table of random numbers. Twenty-five patients received Engerix-B by intradermal route (i.d. group), and 25 patients were given Engerix-B by intramuscular administration (i.m. group). The vaccine used in this study was a new genetically engineered HB vaccine Engerix-B (Smith Kline & Beecham). Patients of i.d. group received (Figure 1) 16 doses of 5 μg (0.25 ml) of formalin-free HBs antigen every week. To this aim, each low-dose was obtained from a standard 20 μg vial stored in sterile conditions at 5–8°C in a refrigerator. Engerix-B was administered intradermally on the volar surface of the forearm contralateral to the side of vascular access or in the non-dominant forearm (CAPD patients) using a standard disposable 1-ml tuberculin syringe with a 25-gauge needle by one individual experienced in the technique of inoculation. A visible cutaneous bleb was regarded as evidence of i.d. inoculation. Patients of the i.m. group received (Figure 1) two doses of 40 μg (2 ml) of vaccine at monthly intervals in the deltoid region of the non-dominant arm, in 2 consecutive months.

Patients

The study was performed in 20 females and 30 males, the mean age was 65.3 years (range, 25–87), the median duration of dialysis treatment was 25 months (range, 9–228). The distribution of underlying nephropathies was as follows: polycystic kidney disease (n = 8), chronic glomerulonephritis (n = 6), diabetic nephropathy (n = 13), nephroangiosclerosis (n = 10), chronic interstitial nephritis (n = 5), autoimmune diseases (n = 1), and others (n = 7). Forty-five patients were on chronic haemodialysis (HD) treatment and five patients on continuous ambulatory dialysis treatment (CAPD). Bicarbonate haemodialysis was performed for 3–4 hours three times a week using 1–1.3 m² capillary flow cuprophane dialyser at a blood and a dialysate flow rate of 300 and 500 ml/min respectively, in order to satisfy the criteria of adequacy based upon urea kinetic analysis [24].

Serum studies

Upon entry into the study, a baseline serum sample was obtained—the patients were with normal aminotransferase levels, seronegative for HBsAg, anti-HBc, and anti-HBs antibodies. All patients of the i.d. and i.m. groups were tested every 2 months for HBsAg, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities, and at the beginning and at the end of the
Fig. 1. Re-vaccination schemes and GMT titers during the follow-up.

observation period (months 0 and 20) for IgM anti-HBc antibody, in order to assess the efficacy of recombinant vaccine in preventing HBV-related events. A patient was considered to have a clinically important (type I) HBV infection if he showed positivity for HBsAg or the AST or ALT levels were more than twice the upper limit of normal. Participants who remained positive for HBsAg for 6 or more months were considered to be HBsAg carriers.

Infections characterized by development of anti-HBc only, or slight increase of aminotransferase values or symptoms were considered clinically unimportant (type II). One, 3, 6, 12 and 20 months after completion of the vaccination protocol, titres of IgG HBs antibody were determined. Anti-HBs levels of 10 mIU/ml or more were regarded as seroprotective. An anti-HBs titre of 1 mIU/ml or more defined seroconversion. The upper normal limits in the AST and ALT assays were 46 and 40 U/l respectively. Hepatitis B surface antigen (HBsAg); antibodies to hepatitis B surface (HBsAb) and hepatitis core antigen (HbcAb) were measured in plasma samples by enzyme immunoassays (Abbott Laboratories, USA). Serum aminotransferase levels were tested with spectrophotometric method. The patients were not under immunosuppresant drugs either during the vaccination or the follow-up period and with no serious systemic illness or previous allergic reactions. Screening for antibody to hepatitis C virus (HCV) was performed by a second-generation ELISA test (Ortho HCV 2.0 ELISA test system) and positive samples were confirmed by a second-generation confirmatory assay (RIBA® HCV 2.0 Strip Immunoblot Assay (SIA), Chiron Corporation). Reactive samples were interpreted according to the instructions of the manufacturers [25]. Antibodies to the human immunodeficiency virus (HIVAb) were measured by commercially available kits from Abbott Diagnostics. No patients had detectable human immunodeficiency virus antibodies in our dialysis unit in spite of the fact that some had received several blood transfusions. The history of blood transfusion requirement for each patient was evaluated. No patient admitted a history of intravenous drug abuse.

Vaccine side-effects

The presence of side-effects after vaccination was monitored in all patients. After every vaccine shot, the patients were asked to report the presence of unusual symptoms or signs during the following 3 days.

Analysis of costs

We calculated the costs of our re-vaccination schedule and those of other re-vaccination protocols that have been recently suggested. The costs of vaccine and adjuvants were based on the prices paid by the medical centre for the products. These prices reflect the actual cost of the products to the hospital. No labour cost was included in our evaluation, since dialysis patients receive intense care and undergo regular follow-up from physicians and staff of dialysis units. We have made several assumptions to facilitate the analysis: (1) a cost of $23 US for a 20 μg dose of recombinant vaccine; (2) a cost of $784 US for low-dose (2.52 × 10^5 UI) human recombinant interleukin-2; (3) a cost of $140 US for recombinant interferon-gamma (2 MUI); (4) a cost of $73 US for each dose of thymopentin.
We made a descriptive analysis reporting the frequency (with 95% confidence intervals (CI)) of the patients who showed seroconversion or seroconversion after completion of the re-vaccination protocol. The percentile distributions (25, 50 and 75 percentiles) and the geometric mean titres (with 95% confidence intervals) of anti-HBsAg antibody values were assessed in the i.m. and i.d. groups respectively. Comparisons between median values of anti-HBs titres were performed by using the Mann-Whitney test. Comparisons between frequencies were performed by using chi-square test (with Yates’ correction). Comparisons between geometric mean titres were made by Student t test (after logarithmic transformation of data). The ratio of kurtosis and skewness with their course, there was a significant difference between the two groups with regard to the number of blood transfusions received before the start of the re-vaccination program, 76 vs 37%, P = 0.03. No patient received blood transfusions during the re-vaccination programme. There was no significant difference between the i.d. and i.m. groups concerning the type of dialysis treatment. There were 22 patients on HD treatment in the i.d. group (22/25 = 88%) and 23 (23/25 = 92%) in the i.m. group, NS.

One month after completion of the re-vaccination schedule, there was a significant difference between i.d. and i.m. patients concerning the frequency of individuals who developed seroconversion, 100% (25/25) vs 48% (12/25) P = 0.008 and the proportion of patients who showed seroconversion, 96% (24/25) vs 40% (10/25) P = 0.001 (Table 2). The median values of anti-HBs titres in responder patients re-vaccinated with low-dose i.d. inoculations were significantly higher compared to i.m. patients, 60 (range 10–1000) vs 16 (range 10–213) mUI/ml (P = 0.04). Geometric mean titres (GMT) and 95% confidence intervals (CI) in the i.d. and i.m. groups were 100 (44–187) and 26.4 (14–52) mUI/ml respectively (Figure 1), the difference was significant (P = 0.018).

Three months after completion of the vaccination course, the seroconversion rate was increased in i.d. patients in comparison with i.m. individuals 94% (17/18) vs 67% (6/9), the statistical difference was not significant (NS). The seroconversion rate was 83% (15/18) among i.d. patients and 44% (4/9) in the i.m. group, there was no significant difference (NS). The median levels of anti-HBsAb titres in responder patients of i.d. group were significantly higher than those of the i.m. group, 123 (range 13–927) vs 178.3 (14–52) mUI/ml. GMT (95% CI) in the i.d. and i.m. groups were 55.9 (3–117) and 11.5 (4–32) mUI/ml (Figure 1) respectively (P = 0.027).

Six months after the last vaccination shot, there was no significant difference between i.d. and i.m. patients.

Table 2. Titres of anti-HBs (expressed as GMT and percentiles) of the patients who showed seroconversion, seroconversion and the whole group respectively, 1 month after completion of the re-vaccination schedule

<table>
<thead>
<tr>
<th></th>
<th>Intradermal (n = 25)</th>
<th>Intramuscular (n = 25)</th>
<th>P</th>
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<tbody>
<tr>
<td>Seroconversion rate</td>
<td>100%</td>
<td>48% (28%; 68%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>79 (38; 167)</td>
<td>20 (11; 40)</td>
<td>0.01</td>
</tr>
<tr>
<td>(25%; median; 75%)</td>
<td>15; 60</td>
<td>10; 13</td>
<td></td>
</tr>
<tr>
<td>Seroconversion rate</td>
<td>96% (88%; 100%)</td>
<td>40% (21%; 59%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>100 (44; 187)</td>
<td>26 (14; 52)</td>
<td>0.018</td>
</tr>
<tr>
<td>(25%; median; 75%)</td>
<td>18; 60</td>
<td>11; 16</td>
<td></td>
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<tr>
<td>Whole group GMT</td>
<td>83 (40; 171)</td>
<td>4 (2; 9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>(25%; median; 75%)</td>
<td>15; 60</td>
<td>0; 13</td>
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Table 1. Demographic characteristics of the chronic dialysis patients enrolled in the study
with regard to the seroconversion rate, 11/16 (69%) vs 3/7 (43%), NS. There was a significant difference between the i.d. and i.m. groups with regard to the seroprotection rate, 69% (11/16) vs 14% (1/7) respectively (P = 0.048). GMT (95% CI) were significantly increased in the i.d. compared to i.m. groups, 26.5 (15–48) vs 6.3 (5–9) mUI/ml (Figure 1) respectively (P = 0.0001).

Twelve months after completion of the vaccination protocol, the seroconversion rates were 57% (8/14) vs 14% (1/7) in i.d. and i.m. groups respectively (P = 0.158). The seroprotection rate was higher in i.d. individuals in comparison with i.m. patients, 50% (7/14) vs 0% (0/7) P = 0.072. The median levels of anti-HBs antibodies were higher in the i.d. patients than in the i.m. group, but the difference was not significant, 25 (10–709) vs 0, P < 0.06. GMT and 95% CI in i.d. and i.m. patients were 33.2 (2–68) and 0.6 mUI/ml (Figure 1) respectively, P = 0.2.

At month 20 the seroconversion rate was 54% (7/13) vs 0% (0/7) in the i.d. and i.m. groups respectively (P = 0.055). The seroprotection rate was 30% (4/13) vs 0% (0/7), respectively (P = 0.2). In patients re-vaccinated by i.d. route, the median levels of anti-HBs antibodies were 21 (3–346) mUI/ml, and GMT (95% CI) were 20.9 (2–54) mUI/ml.

Five of 45 patients complained within the first 24 h of pain and erythema at the site of injections, two patients received intramuscularly hepatitis B vaccine and three patients belonged to the i.d. group. No patient reported body temperature above 37.5°C within the following week.

We did not detect episodes of HBV infection among our vaccinees during the 20-month study period.

As shown in Table 3, assuming a cost of $23 US for a 20 µg dose of recombinant B vaccine, the cost of our re-vaccination schedule by the i.d. or i.m. route is $92 US. The cost of a re-vaccination protocol with three or four 40 µg doses by the i.m. route is $138 US or $184 US respectively. The expected cost of a re-vaccination schedule with interleukin-2 as immunoadjuvant (low-dose (2.52 × 10^5 IU) human recombinant interleukin-2 plus one 20 µg dose of recombinant HB vaccine) is $807 US. We calculated a cost of a re-vaccination protocol based on the use of thymopentin as immunoadjuvant of $945 US, such a cost including 12 doses of thymopentin and three 20 µg doses of recombinant HB vaccine. The estimated cost a re-vaccination strategy with interferon-gamma as immunomodulator is $489 US (three 20 µg doses of recombinant HB vaccine and three doses of interferon-gamma).

**Table 3.** Cost of intradermal HB vaccine administration for each patient in comparison with costs of other re-vaccination schedules

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cost, US$</th>
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<tbody>
<tr>
<td>Low-dose i.d. re-vaccination</td>
<td>92</td>
</tr>
<tr>
<td>i.m. re-vaccination</td>
<td>138</td>
</tr>
<tr>
<td>i.m. re-vaccination with thymopentin</td>
<td>945</td>
</tr>
<tr>
<td>i.m. re-vaccination with gamma-interferon</td>
<td>489</td>
</tr>
<tr>
<td>i.m. re-vaccination with interleukin-2</td>
<td>807</td>
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</table>

**Discussion**

Hepatitis B surface antigen positive patients at a dialysis centre are a potential source of nosocomial transmission. In 1994 [26], five outbreaks of HBV infection among haemodialysis patients were reported from three states in US. In some instances, failure to perform routine screening for HBsAg and/or to routinely review screening results led to failure to recognize HBsAg-positive patients and isolate them. In other instances, HBsAg positive patients were isolated in separate rooms with separate machines, but shared staff members and other equipment with susceptible patients. Hepatitis B vaccination should reduce both community and nosocomial acquisition of HBV.

Moreover, a large portion of chronic dialysis patients shows an absent response to hepatitis B vaccine and i.d. administration of recombinant HB vaccine has been reported to reverse the unresponsiveness to HBsAg.

The i.d. route of anti-HB vaccination in healthy individuals has been previously suggested by several authors [27, 28]. They showed its safety, immunogenicity, and technical feasibility. Further, the i.d. route also has been used for immunization against rabies [29] and other infections.

The data regarding HB vaccination by i.d. route in chronic uraemic patients are very scanty. Some authors administered intradermally HB vaccine in uraemic patients who had not been previously vaccinated [15,19], in other studies HB vaccine by the i.d. route was given to dialysis patients who had showed unresponsiveness to intramuscular administration of HBsAg, but a partial seroprotection was observed [16], and the intradermal hepatitis B re-vaccination was not prospectively compared with i.m. administration [15–19]. Moreover, the number of patients evaluated was very small [15–20].

Our prospective randomized trial performed in a large cohort of non-responsive chronic dialysis patients showed that repeated low-dose i.d. inoculations provided seroprotection in almost all patients who had not previously responded to a reinforced HB vaccination protocol by the i.m. route. In spite of the same dose level of HBsAg selected, supplementary inoculations by the i.m. route produced seroprotection in a significantly lower proportion of non-responder patients during the 1-year follow-up.

We administered the same amount of HBsAg in both the groups. Indeed, the dose selected for the hepatitis B vaccination can strongly influence the immune response, as observed by other authors. Therefore we eliminated the confounding influence of such a factor [30].

Our low-dose intradermal re-vaccination protocol gave better results than those of Jungers et al. [14] and Donati and Gastaldi [12]. In fact they observed a
seroprotection rate of 56 and 86% respectively in their non-responder patients after re-vaccination with HB vaccine and interleukin (IL-2) or thymopentin as immunoadjuvant. In the trial of Jungers et al. [14], the immunoadjuvant effect of human recombinant IL-2 on the response to a booster injection of hepatitis B vaccine in previously non-responder uraemic patients was not confirmed. But is the very high seroprotection rate obtained by i.d. re-vaccination really a function of the changes in the route of administration or merely the cumulative effect of multiple vaccinations? Re-vaccinating many times might partially explain our findings. Indeed, we believe that every inoculation gives us a chance that one patient shows detectable antibody to hepatitis B surface antigen, as other authors previously suggested [31].

However, we have previously observed a high seroprotection rate (81%, 17/21) with a lower number (10 injections) of intradermal inoculations in HD patients who had not previously vaccinated [32]. Moreover, only 41% [33] of non-responder homosexual men showed seroconversion after vaccination with three supplementary i.m. doses. Also, the seroconversion rate [6] with three double doses of HBV vaccine by the i.m. route was 69% (81/118), 36 (44%) of them being low-responders, in our HD patients. Although not conclusive, these data strongly suggest that the change in the route of administration may be an important factor in obtaining complete seroconversion in the i.d. group of our trial.

In addition to the immunogenicity of our re-vaccination schedule, several factors might explain the very high seroprotection rate observed in our i.d. patients—the patients did not show abnormal biochemical markers of nutritional status, and the influence of malnutrition on vaccine response of HD patients has been emphasized by several authors [6,34,35], the median duration of dialysis treatment in our i.d. group was more than 3 years, and previous authors [36] suggested that antibody response rates increase with increasing length of time on dialysis prior to receipt of vaccine. There were no patients in our study showing antibodies against HIV, and no intravenous drug users, and that supports the strong immune response we have detected. Further, the prevalence of HCV infection in our patients was not very high [37], and HCV infection might negatively influence the antibody levels after HB vaccination [38].

On the other hand, in our i.d. group there were many patients (8/25, 30%) affected with diabetes mellitus, an important cause of unresponsiveness to HBV vaccine [6,39], the mean age of the i.d. group (67.4 years) was high and a decreased response rate with increasing age is in agreement with other studies [35]. Furthermore, i.d. and i.m. patient groups showed similar demographic and clinical features except for transfusion requirement, that was significantly higher in the i.d. compared to the i.m. group. Transfusion avoidance could contribute to the improved serological response after hepatitis B vaccination, as other authors previously suggested [40]; therefore, the larger transfusion requirement of the i.d. group highlights the higher immunogenicity of our i.d. re-vaccination strategy compared to i.m. hepatitis B administration.

The mechanisms responsible for inducing the potential immunogenicity of intradermal HB vaccination are unclear. The antigen might be trapped in cutaneous tissue for a longer period of time than in an i.m. inoculation. The i.d. presentation of antigen to the immune system might result in a macrophage-dependent T-lymphocyte response via specific epidermal cells [41].

In our current study the administration of two supplementary doses of HB vaccine by the i.m. route resulted in a 40% seroprotection rate in previous non-responsive patients. It is likely that the seroprotection of all non-responsive patients might be also obtained with further supplementary i.m. doses, but with such a schedule a very large amount of HB vaccine should be administered, with very high costs. Similarly, the patient who showed only seroconversion after completion of the re-vaccination schedule by the i.d. route might produce detectable anti-HBs antibody with supplementary i.d. inoculations.

An important question is the duration of anti-HBs titres afforded by the i.d. route. Such a question has been raised by other authors [41]. Our long-term evaluation showed that 20 months after completion of the re-vaccination schedule the seroconversion and seroprotection rates were higher in i.d. compared to i.m. individuals; the differences did not reach statistical significance, and this is probably related to the small number (n=20) of patients evaluated at the end of the 20-month period. Therefore it is necessary to re-evaluate this on larger patient groups.

At the present time, we do not give booster doses to responder dialysis patients who lose detectable anti-HBs antibodies, but we rely on the immunological memory of dialysis patients to protect against late infections. Providing booster doses is a very expensive strategy and it is not clear if disappearance of antibody equates with becoming susceptible again, either in dialysis patient or healthy populations [42]. The answer to this question lies in long-term follow-up studies of immunized populations who continue to have a high risk of exposure and in whom surveillance of serological events and acute hepatitis is possible; further surveys concerning chronic dialysis individuals might be very interesting to this end.

Several authors [41] cast some doubt on the efficacy of anti-HBs antibody produced after i.d. administration of HB vaccine. However, we did not observe breakthrough HB infections either in patients re-vaccinated with i.d. schedule or in individuals who received intradermal HB vaccine as primary active immunization [32].

The intradermal route might be less practical compared to i.m. administration, as it requires individuals experienced in the technique of intradermal inoculation. Subcutaneous injection into fat results in a very poor immune response, as previously observed [43]. Furthermore, we use a reinforced vaccination schedule.
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HB re-vaccination by intradermal and intramuscular routes with analysis of costs


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