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Immunogenicity of an adjuvanted 2009 pandemic influenza A (H1N1) vaccine in haemodialysed patients

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Abstract

Background. The 2009 pandemic of influenza A (H1N1) prompted an urgent worldwide vaccination campaign, especially of high-risk subjects, such as maintenance haemodialysis (HD) patients. Still the immunogenicity of the pandemic A (H1N1) vaccine in HD patients is unknown. **Methods.** We prospectively studied the immunogenicity of a monovalent adjuvanted influenza A/California/2009 (H1N1) vaccine (Pandemrix®, GSK Biologicals, Rixensart, Belgium) in HD patients and controls. Antibody level was measured using a seroneutralization assay before (D₀) and 30 days after (D₃₀) a single 3.75 µg vaccine dose. Specimens were tested in quadruplicates. Geometric mean

(GM) antibody titers were determined in each subject at D₀ and D₃₀. Seroconversion was defined as an increase in GM titers by a factor 4 or more.

Results. Fifty-three adult HD patients [aged 71 ± 10, 58.5% males, on HD for a median of 38 (3–146) months] and 32 control subjects (aged 47.3 ± 14, 31.3% males) were analyzed. Baseline GM titers were similar in HD patients and controls [7.9 (6.6–9.6) vs 10 (6–17); p = 0.69]. Seroconversion was observed in 30 (93.8%) controls and 34 (64.2%) HD patients (p = 0.002). In addition, GM titers at D₃₀ were significantly higher in controls than in HD patients [373 (217–640) vs 75.5 (42.5–134); p = 0.001]. HD patients were significantly older than controls

($p < 0.001$) and more likely to be males ($p = 0.02$). However, by multivariate analysis, HD status [OR 0.13 (0.02–0.78), $p = 0.03$], but neither age [OR 0.99 (0.96 – 1.03); $p = 0.7$] nor male gender [OR 1.31 (0.45 – 3.85); $p = 0.63$] was independently associated with seroconversion. The vaccine was generally well tolerated by HD patients.

Conclusions. Only 64% of chronic HD patients developed seroconversion after a single dose of adjuvanted influenza A (H1N1) vaccine, a much lower rate than in controls (94%). These results underscore the substantial immunodeficiency associated with End-Stage Renal Disease. The persistence of protective antibodies as well as the effect of a booster dose remain to be investigated in HD patients.

Keywords: immunogenicity; influenza A (H1N1); haemodialysis; pandemic influenza A; swine influenza; vaccination

Introduction

Within 7 weeks of the initial report on 24 April 2009 [1], the rapid global spread of pandemic human influenza A (H1N1) originating from the swine, prompted the World Health Organization to declare on 11 June 2009 [2] the first influenza pandemic in 41 years and to call for the urgent development of vaccines [3]. Indeed, this influenza strain appeared to entail a potentially high risk of mortality in children and young adults without (cross-) immunity.

Several adjuvanted and non-adjuvanted vaccines were developed. Vaccination was recommended by the Centers for Disease Control and Prevention (CDC) for pregnant women, people living with or caring for children <6 months of age, health care personnel, persons between the ages of 6 months and 24 years and people from ages 25 through 64 years who are at higher risk because of chronic health disorders or compromised immune system [4]. European guidelines further considered vaccination of healthy adults aged 15–64 years [5].

Trials performed in the general population have shown the development of a protective immune response after vaccination against pandemic human influenza A (H1N1) [6–8]. Nonetheless, the immunogenicity of the influenza A (H1N1) vaccines has not been investigated so far in haemodialysis (HD) patients, despite the potential risk of severe evolution of the disease in this patient group [9].

We conducted a prospective study in order to measure the immune response to the monovalent adjuvanted influenza A/California/2009 (H1N1) vaccine in HD patients and controls.

Materials and methods

In November 2009, we decided to recommend influenza A (H1N1) vaccination to all patients under maintenance HD in our hospital HD unit. They were all dialysed three times a week for 3.5–5 h per session using hollow-fiber Superflux polysulfone dialysers (FX50 to FX 100 series from Fresenius, Bad Homburg, Germany). Of note, 18 patients were not vaccinated: 3 patients had an active bacterial infection, 2 patients had just been vaccinated by their general practitioner and 13 patients de-

clined the vaccination. Overall, 58 HD patients were vaccinated. Thirty-two volunteers without significant health disorder resulting in immunodeficiency were recruited as controls: 10 close relatives of HD patients and 22 non-related hospital staff members. All participants provided informed consent. Approval was obtained from the Biomedical Ethics Committee of the Cliniques Universitaires Saint-Luc and UCL Faculty of Medicine, Brussels, Belgium.

All subjects received a single intramuscular (deltoid muscle) dose of the monovalent adjuvanted influenza A/California/2009 (H1N1) vaccine commercialized in Belgium (Pandemrix®; GlaxoSmithKline Biologicals, Rixensart, Belgium). Each vaccine dose (0.5 ml) contains 3.75 µg of antigen of split-inactivated pandemic (H1N1) 2009 influenza virus and adjuvant system AS03 (10.69 mg of squalene, 11.86 mg of DL- α -tocopherol and 4.86 mg of polysorbate 80). Participants were monitored for the occurrence of adverse events during the 30 days after vaccination.

Serum samples were obtained immediately before [Day 0 (D_0)] and 30 days after [Day 30 (D_{30})] vaccination, for antibody titration against the Influenza A/California/7/2009 (H1N1) using a seroneutralization (SN) assay, performed at the National Influenza Centre, Scientific Institute of Public Health, Brussels, Belgium. The SN assay is based on the ability of antibodies to inhibit the infection of Madin–Darby canine kidney (MDCK) cell culture by influenza virus, as previously described [10]. Briefly, 1:2 serial dilutions of inactivated human serum samples were pre-incubated with a standardized amount of virus (100TCID₅₀) prior to the addition of MDCK cells (25000 cells per well). After overnight incubation, enzyme-linked immunosorbent assay (ELISA) was used to measure influenza A viral nucleoprotein in infected MDCK cells. Since serum antibodies against influenza virus inhibit the viral infection of MDCK cells, the optical density (OD) results of the ELISA are inversely proportional to the serum antibody concentration. The initial dilution and lowest detection limit of this assay was 1:10. Suitable control serum samples were included in all analyses, with a post-infection sheep serum sample raised against the A/California/7/2009 (H1N1) strain (FR-188, CDC), and a human serum of convalescent cases of pandemic influenza A (H1N1) and human recipients of A/California/7/2009 (H1N1) (NYMC X179A) vaccine (ref 09/194; NIBSC, London, England) as positive controls. Influenza normal control serum from sheep (FR-49, CDC) was used as negative control. Samples were tested in duplicate in each assay, and assays were independently repeated once. The titer analysed was the geometric mean (GM) of these four test results, expressed as the reciprocal of the strongest serum dilution with OD₄₅₀ value less than X , where $X = [(average\ OD_{450}\ of\ VC\ wells) - (average\ A_{450}\ of\ CC\ wells)]/2 + (average\ OD_{450}\ of\ CC\ cells)$, with VC = virus control and CC = cell control [10]. Samples without detectable antibody activity were assigned the titer of half the assay detection limit (1:5). Titers were expressed as the reciprocal of the dilution.

GM titers were determined at subject level by individual GM of four test results at each time point and at group level by GM of all subject GM titers. In addition, individual and group level geometric mean titer ratios (GMTRs) (GM titer D_{30}/D_0) were determined to measure the factor increase in GM titers. For each variable, the result is expressed as point estimate with corresponding 95% confidence intervals. Seroconversion was defined as an increase in GM titers by a factor ≥ 4 . Mann–Whitney U -tests were used to compare group GM titers at D_0 and D_{30} and GMTR. The proportion of seroconversions in each group at each time point was compared by Fisher's exact tests. Demographic variables are presented as mean \pm SD, median and range (if the distribution is not Gaussian) or percentage, as appropriate. A logistic regression multivariate analysis controlling for age, gender and status (chronic HD patient or control) was further performed, using the PASW (SPSS), version 18. Statistical significance level was set at $P < 0.05$.

The primary endpoint was the proportion of subjects reaching seroconversion in each group. Secondary endpoints were GM titers and GMTR reached in both groups and the occurrence of severe adverse reactions.

Results

Study population

Fifty-eight adult chronic HD patients and 32 controls were vaccinated. Serum samples on D_{30} were not collected in five HD patients: three patients had died be-

Table 1. Baseline demographic characteristics

	HD patients, <i>n</i> = 53	Controls, <i>n</i> = 32	P-value
Age (years)			
Mean \pm SD	71 \pm 10	47 \pm 14	<0.001
Median	72 (20–90)	46 (22–83)	
Sex <i>n</i> (%)			
Males	31 (58.5)	10 (31.3)	0.02
Females	22 (41.5)	22 (68.7)	
Ethnicity <i>n</i> (%)			
Caucasian	49 (92.5)	27 (84.4)	0.29
Black	4 (7.5)	5 (15.6)	
HD vintage (months)			
Median (range)	38 (3–146)		

tween D₀ and D₃₀ (two died from sepsis caused by *Klebsiella pneumoniae* and *Escherichia coli*, respectively, and one died from pulmonary carcinomatous lymphangitis), one patient had received a kidney transplant and blood sampling was unfortunately forgotten on D₃₀ in the last one. Fifty-three HD patients were thus included in the final analysis. The main characteristics of HD patients and controls are depicted in Table 1. Of note, HD patients were older ($P < 0.001$) and more likely to be males ($P = 0.02$) than controls.

Immunogenicity of the 2009 influenza A (H1N1) vaccine

As shown in Figure 1A, GM titers before vaccination (D₀) were similar in HD patients and controls [7.9 (6.6–9.6) versus 10 (6–17); $P = 0.69$]. Only 34 (64.2%) HD patients had seroconversion on D₃₀, compared with 30 (93.8%) controls (Figure 1C). This difference was significant ($P = 0.002$). Moreover, GM titers were significantly higher in controls than in HD patients [373

(217–640) versus 75.5 (42.5–134); $P = 0.001$] (Figure 1B). Similarly, a significant difference in increase of GM titers (GMTR) between both groups was observed [38 (22–63) in controls versus 9.5 (6–16) in HD patients; $P = 0.001$] (Figure 1D).

One control subject aged 22 presented very high baseline GM titers (7611). After vaccination, his GM titers increased to 15222. Two HD patients (aged 56 and 65) had GM titers at D₀ comparable to controls, which increased dramatically to 3044 and 7610, respectively, at D₃₀.

By logistic regression, only HD status [odds ratio (OR) 0.13 (0.02–0.78), $P = 0.03$], but neither age [OR 0.99 (0.96–1.03); $P = 0.7$] nor male gender [OR 1.31 (0.45–3.85); $P = 0.63$] was independently associated with seroconversion.

Adverse effects

With the exception of two HD patients, who presented moderate local pain at the site of injection, no other side effects associated with the vaccine were observed in HD patients.

Discussion

To the best of our knowledge, this is the first study assessing the immunogenicity of an adjuvanted influenza A (H1N1) vaccine in HD patients in comparison to controls. Seroconversion was observed in only 64% of the HD patients, in contrast to the 94% rate in controls, the latter in accordance with those recently reported in the general population after one dose of adjuvanted vaccine [6,8]. In this study, HD patients which responded to the 2009 influenza A (H1N1) vaccine, further had lower antibody titers

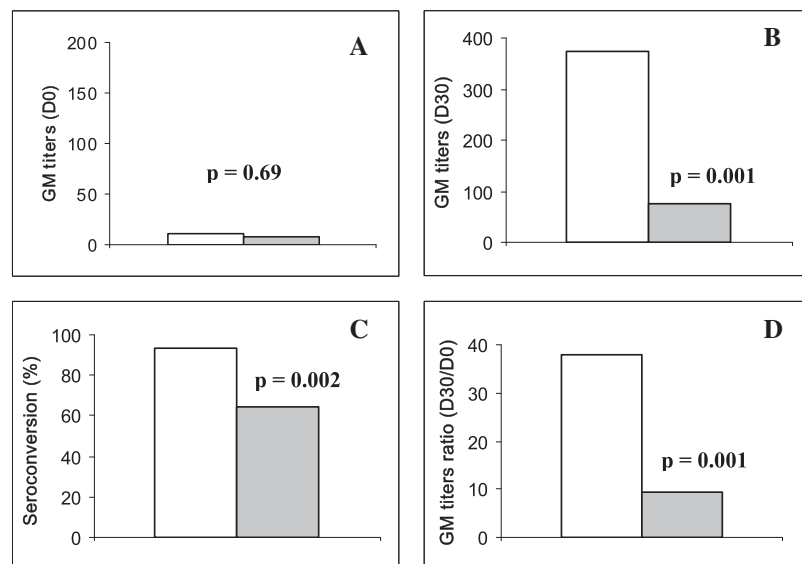


Fig. 1. Antibody responses in HD patients (gray bars) and controls (white bars) at Day 0 (D₀) and Day 30 (D₃₀). (A) Geometric mean antibody titers before vaccination (D₀). (B) Geometric mean antibody titers after vaccination (D₃₀). (C) Seroconversion rate. (D) Geometric mean titers ratio (D₃₀/D₀).

than controls, as observed after hepatitis B (HBV) vaccination [11].

Although the mechanisms of uremia-associated immunodeficiency are still incompletely understood, it is well known that HD is associated with increased susceptibility to infections and decreased response to several vaccines [12]. Seroprotection rates after standard vaccination schedules with current recombinant HBV vaccines are poor in the dialysis population (32–80%), in contrast to the excellent (>95%) efficacy observed in the young general population [13]. In addition to uremia, a clear association between ‘older age’ and no response to primary HBV vaccine was shown in two recent meta-analyses, both in the general population and in ESRD patients (detailed in [ref. 11]). Similarly, some studies showed that age significantly affected the immune response to influenza A (H1N1) vaccine in the general population [6, 8]. Nevertheless, although HD patients vaccinated in our study were significantly older than controls, only HD status but not age was independently associated with seroconversion. Admittedly, our study may not have been powered to detect an independent moderate effect of age. Still, the response rate of a patient sample typical of current in-centre Belgian HD patients to the 2009 influenza A (H1N1) vaccine appears rather poor.

Similarly to some investigational or commercially available HBV vaccines, influenza A (H1N1) vaccines were adjuvanted in order to improve response rates. Adjuvanted HBV vaccines induced a faster onset of seroprotection, greater peak levels of anti-HBs antibodies and longer duration of seroprotection in pre-dialysis and dialysis patients [14,15]. The only influenza A (H1N1) vaccine available in Belgium in 2009 was the adjuvanted vaccine Pandemrix®. Despite the adjuvant, the immunological response was relatively poor in the HD group. These results again underscore the substantial immunodeficiency associated with end-stage renal disease. Whether the administration of two doses (instead of a single one) of adjuvanted vaccine could improve the seroprotection rate of HD patients will require further investigation.

In contrast, Scharpé *et al.* [16] have recently shown that the trivalent vaccine against seasonal influenza elicited high rates (>80%) of seroprotection (defined as a titer of ≥ 40 measured by a hemagglutination inhibition assay) in HD patients, comparable to those observed in healthy controls. These results are, however, difficult to compare with ours, due to different assays (hemagglutination inhibition versus seroneutralization) and endpoints (seroprotection versus seroconversion) used. In addition, as the authors acknowledge, seroprotection rates before influenza vaccination were remarkably high in HD patients (range 53–68%), and significantly higher than in controls, likely reflecting more frequent previous immunizations (or even a survivor bias?), unlike in our HD patients vaccinated for the first time against the 2009 influenza A (H1N1) virus.

Our study has some limitations. Firstly, it was performed in a single centre, and the number of included patients was relatively low. Secondly, we included a predominantly Caucasian population, which may limit the generalizability of the results. Thirdly, the intensity and the type of local adverse reactions were not classified

(local pain, erythema or tenderness). However, as in the general population [6–8], no adverse events of special interest were reported by the participants to our study.

Three subjects presented very high GM titers. High GM titers at baseline in the control subject are likely to be caused by actual asymptomatic or mild infection with the influenza A (H1N1) virus before the vaccination. Two HD patients presented very high GM titers at D₃₀. Given the poor cross-reactivity between influenza A (H1N1) antibodies and the immune response induced by seasonal influenza vaccines [17], the more plausible explanation is that both HD subjects had a very good response to influenza A (H1N1) vaccine.

In conclusion, seroconversion rates and antibody titers elicited by the adjuvanted pandemic influenza A (H1N1) vaccine are significantly lower in HD patients than in controls. The persistence of protective antibodies as well as the effect of a booster dose remain to be investigated in HD patients.

Conflict of interest statement. P. Goubau received from GSK an honorarium for ad hoc consultancy on hepatitis B vaccines in October 2010.

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Clinically unexpected cyclosporine levels using the ACMIA method on the RXL dimension analyser

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Abstract

Safe use of cyclosporine (CsA) in solid organ transplantation relies on regular whole-blood drug monitoring. Several promising immunoassays, e.g. the antibody-conjugated magnetic immunoassay (ACMIA) method, were developed and commercialized during recent years to compete with liquid chromatography coupled to tandem mass spectrometry, which remains the reference method but is labor-intensive. We describe the occurrence of interference in the monitoring of whole-blood CsA after transplantation when using the ACMIA method and discuss the potential mechanisms involved in such interference. Clinically unexpected results of whole-blood CsA require immediate reassessment by another technique to prevent the risk of CsA underdosage and graft rejection.

Keywords: ACMIA; cyclosporine; drug monitoring; transplantation; interference

However, it has been previously shown that some common measurements performed by immunoassays are inherently prone to analytical interference, generally due to the presence of so-called interfering antibodies [2] or endogenous cross-reacting compounds [3]. This kind of interference was described for several immunoassays—e.g. thyroid function tests [4] and cardiac biomarkers—with an approximative occurrence of falsely elevated or false-positive results of 0.4% [2].

Most available immunoassays for CsA monitoring are characterized by a certain extent of cross-reactivity with CsA metabolites, acceptable in clinical practice, and provide lower laboratory workload than liquid chromatography coupled with mass spectrometry (LC-MS/MS), together with good robustness and consistency in the results.

Here, we report a first case of major interference in the monitoring of whole-blood CsA in a heart–kidney transplant recipient when using the antibody-conjugated magnetic immunoassay (ACMIA) method.

Introduction

Cyclosporine (CsA) has been widely used as an immunosuppressant drug in solid organ transplantation for >30 years. Appropriate use of this narrow therapeutic index medication relies on regular whole-blood drug monitoring. Since the years 1990, several immunoassays have been developed and introduced to optimize the care of patients under CsA treatment [1].

Case presentation

A 58-year-old man underwent combined heart and kidney transplantation in August 1995 for Stage IV heart failure resulting from decompensated aortic valvulopathy and chronic kidney disease attributed to chronic glomerulonephritis. Baseline immunosuppression relied on CsA (Neoral; Novartis Pharmaceuticals, Basel, Switzerland), azathioprine and steroids, after rabbit anti-thymocyte glo-