Immune response to an adjuvanted influenza A H1N1 vaccine (Pandemrix®) in renal transplant recipients

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Abstract

Background. In the course of the influenza A H1N1 pandemic, transplanted patients were recommended to receive vaccination. In the present study, we evaluated the immune response to an adjuvanted influenza A H1N1 vaccine (Pandemrix®) in renal allograft recipients.

Methods. Sixty patients and 22 healthy controls participated in a prospective observational study and received a single dose of Pandemrix®. H1N1 antibody titres as well as anti-HLA antibodies were determined before and after vaccination. In 19 patients, a booster vaccination was performed and the outcome of all vaccinated renal allograft recipients (n = 107) in our clinic was reviewed.

Results. Two out of sixty patients had an elevated influenza A H1N1 titre before vaccination. Of the remaining 58 patients, only 20/58 (34.5%) developed a protective immune response in contrast to 20/22 (91%) of the control group. After booster vaccination, a protective titre was present in 8/19 (42%) of patients. Of the 107 patients, 6 (5.6%) developed new donor-specific HLA antibodies after vaccination.

Conclusions. These data suggest that Pandemrix® does not provide a protective immune response in the majority of kidney transplant recipients. Therefore, for new vaccines, efficacy as well as safety profiles should be evaluated in this subgroup of patients.

Keywords: H1N1; HLA-antibodies; transplantation; vaccination

Introduction

Viral infections, including influenza infection, occur at higher frequency under effective immunosuppression [1, 2]. Moreover, immunosuppressed populations are at higher risk of influenza-associated complications resulting in a considerably higher death rate [3]. As a consequence, annual vaccination against seasonal flu has been generally recommended for transplant recipients for many years [4].

Already in the early course of the influenza A H1N1 pandemic, surveillance data revealed that immunocompromised patients were at increased risk for influenza A H1N1-associated complications. Early reports describe as many as 20% of patients hospitalized as a result of influenza A H1N1-infection as having an underlying immunosuppressive condition, the majority being on corticosteroid treatment [5–7]. This situation highlighted the urgent need for effective primary prevention, and risk groups were recommended to receive vaccination first in order to minimize morbidity and mortality [8, 9].

Healthy adults develop a sufficient immune response after a single vaccination with an adjuvanted split-virion influenza A H1N1 formulation in the vast majority of individuals (between 80 and 95%) [10–12], thus a single vaccination is deemed appropriate and was recommended for patients under the age of 60.

However, response rates to seasonal influenza vaccination in solid-organ transplant recipients are still a controversial issue. Despite some evidence for comparable influenza vaccine responses in kidney transplant recipients and control individuals [13–15], numerous studies suggest that antibody responses can be diminished in transplant recipients [16–19]. As the different immunosuppressive regimens might considerably contribute to the antibody response, comparability of these studies is limited and interpretation of the results remains difficult [3, 14, 19]. Although influenza A H1N1 is still the dominant influenza strain in a large number of countries [20], only few data on serological response rates to pandemic H1N1 vaccines in immunosuppressed patients have been published so far [21, 22].

The potential induction of anti-HLA antibodies as a result of vaccination has always been a subject of concern in transplant recipients. To date, a direct causal relationship between influenza vaccines and the induction of donor-specific antibodies (DSA) has never been observed in transplant patients [13, 23–25]. However, a de novo DSA rate of 4.8% after seasonal flu vaccination was found in kidney transplant patients. [23]

Therefore, we evaluated the immune response to an adjuvanted influenza A H1N1 vaccine (Pandemrix®) in renal transplant patients after a single vaccination as well as after booster vaccination by monitoring influenza A H1N1 titres.
In addition, we aimed to monitor anti-HLA antibodies, safety and the clinical course in the present study in order to provide a comprehensive analysis of risks and benefits of the recommended adjuvanted H1N1 vaccine.

Materials and methods

Subjects and study procedures

The current single-centre study started in October 2009, when the adjuvanted influenza A H1N1 vaccine (Pandemrix®) became available in Germany and ended in June 2010. At that time, the adjuvanted H1N1 vaccine Pandemrix® was the only available vaccine in Germany. All maintenance patients >18 years with stable graft function who received their transplant >6 months previously and who were free of rejection in the last 6 months (n = 767) were informed in a letter about the recommendations on H1N1 vaccination, especially for risk groups, and were asked to participate in the observational study. Vaccination was performed in our outpatient clinic; 22 healthy subjects served as controls. The study was approved by the local ethics committee. All patients gave written informed consent.

A single dose of Pandemrix® (3.75 μg per dose, adjuvanted) was administered intramuscularly into the deltoid muscle at Day 0 according to manufacturer’s instructions. Because of the unknown response rate and the initial recommendation by health authorities for a booster vaccination for all patients >60 years of age, we offered all patients a second dose of Pandemrix® (3.75 μg) 3 weeks after the first vaccination. Nineteen of the 60 patients decided in favour of a second vaccination.

In participants of the observational study, we collected prospectively blood samples for influenza A H1N1 titres immediately before vaccination as well as 3–4 weeks after vaccination. In the subgroup of patients having received a second dose of Pandemrix®, booster titres were analysed 2 months after the second vaccination. Anti-HLA antibodies were analysed in parallel to influenza A H1N1 titres and serum samples were separated and stored at −20°C. It is important to note that all sera were frozen and titres were determined together in batches, after vaccination was completed.

Vaccine

Pandemrix® is a monovalent, adjuvanted inactivated split-virus vaccine (Glaxo Smith Kline, Dresden, Germany). One dose (0.5 mL) contains 3.75 μg of antigen (A/California/7/2009 (H1N1)v-like strain X-179A), 5 μg thimerosal added as preservative and the adjuvant AS03 composed of squalene (10.69 mg), DL-α-tocopherol (11.86 mg) and polysorbate 80 (4.86 mg). The vaccine was prepared in embryonated chicken eggs with the same standard techniques that are used for the production of seasonal trivalent-inactivated vaccine [26] and was presented in 5 mL multidose vials.

Local and systemic reactions after vaccination

Solicited local and systemic reactions during the first 7 days after vaccination were documented at the next outpatient visit. All renal transplant recipients treated in our Department are listed with their patient records in our electronic database Tbase [27]. Starting in 1999, all medications, laboratory data and the clinical course of all renal transplant patients are compiled in the database. All outcome data were retrieved from the database.

Anti-influenza A H1N1 antibodies

Influenza-specific antibody levels were measured by a standard hemagglutination inhibition assay. Prior testing, naturally occurring nonspecific inhibitors were removed from the sera according to the WHO guidance [28] achieving a final serum dilution of 1:10.

The sera were then diluted serially 2-fold into microtitre plates with V-bottom format. The H1N1-Virus split antigen (A/California/7/2009 NYMC X-179A, Pandemrix; GSK Dresden) was adjusted to 4 HA U/25 μL which was verified by back titration and 25 μL of this virus suspension was added to each of the 96 wells. After incubation at room temperature (RT) for 30 min, freshly prepared 0.5% turkey red blood cells were added and the plates were mixed for agitation followed by incubation at RT for 30 min. Human sera serving as positive controls and negative controls were included on each plate.

Titres were expressed as the reciprocal of the highest dilution of serum that inhibited hemagglutination and given on a log2 scale.

According to European and International guidance, seroconversion after vaccination was defined by either an H1N1 Ab titre of ≤1:10 before and of at least 1:40 after or at least 1:10 before and at least 4-fold increase in antibody titre 21 days after vaccination [29, 30].

Anti-HLA antibodies

The HLA antibody status of the patient was assessed using a combination of different tests including complement-dependent lymphocytotoxicity (CDC) test (Biotest, Dreieich, Germany) and the LABScreen™ test (One Lambda, Canoga Park, CA) according to previously published methods [31].

CDC test.

Sera were screened for the presence of lymphocytotoxic HLA antibodies by CDC according to the National Institute of Health as described in detail elsewhere [31, 32]. In brief, 1 μL of patient serum was incubated for 30 min with 1 μL of a lymphocyte suspension, followed by the addition of 5 μL rabbit complement. After further 60-min incubation time at RT, a fluorescence dye (fluorochrome; One Lambda) was added. The test result was read under a fluorescence microscope. To differentiate between specific HLA-IgG antibodies and non-HLA-specific IgM antibodies, the CDC test was performed in parallel by adding dithiothreitol to reduce the IgM antibodies. For the detection and specification of panel-reactive HLA antibodies (PRA), a lymphocyte panel of HLA-typed blood donors was used.

Solid-phase assay LABScreen™.

LABScreen™ products use micro beads coated with purified Class I or Class II HLA antigens and pre-optimized reagents for the detection of Class I or Class II HLA antibodies in human sera. LABScreen™ products utilize the Lambda Array Beads Multi-Analyte System® (LABMAS), which features the LABScan™ 100 flow analyzer, for data acquisition and analysis.

Samples were tested first by using the sensitive LABScreen™ Mixed test and specified if needed by LABScreen Single Antigen beads similar to a previous publication [31].

The tests were performed according the instructions of the manufacturer. In brief, incubation of 5 μL LABScreen® beads with 20 μL of patient, negative and positive control sera in separate 1.5 mL microfuge tubes in the dark for 30 min at 20–25°C with gentle shaking. After two washing steps, a secondary antibody, R-Phycocyanin-conjugated anti-human IgG, was added and incubated for 30 min in the dark. Another washing step stopped the reaction. The test result was read in the flow analyzer.

Clinical definitions

Seroconversion rate was defined as the rate of patients with ≥4-fold increase in antibody titres against influenza A H1N1 after vaccination. Seroconversion factor was defined as the level of increase in antibody titres before and after vaccination. Seroprotection rate was defined as the percentage of patients with an antibody titre of ≥40 after vaccination.

Statistical analysis

Student’s t-test was used to compare continuous parameters, and χ2 test was used for categorical data. P-values <0.05 were considered to be significant.

Logistic regression was used to analyze the association of clinical outcome (defined as a protective immune response) with the following parameters (metric variables): age, dose of immunosuppression (steroid, mycophenolic acid (MPA), mammalian target of rapamycin inhibitors and calcineurin inhibitors (CNI)), gender, time after transplantation and PRA before vaccination. Only variables with a P-value <0.15 were retained in the final model. All analyses were performed using PASW Statistics 18 software (SPSS).

Results

Of the 767 patients in our outpatient clinic who were informed about the vaccination and the observational study, a total of 107 patients were vaccinated in our centre. Of these, after giving informed consent, a total of 60 patients (12 females/48 males) agreed to participate in the observational study. Patient characteristics as well as immunosuppressive regimens are given in Table 1.

influenza A H1N1 titres after a single dose of Pandemrix®

Two of the 60 patients (3.3%) had an elevated influenza A H1N1 titre before vaccination suggesting previous immunization, although being completely asymptomatic.
Of the remaining 58 patients, only 20 (34.5%) developed a titre of ≥1:40 after 25.8 ± 2.8 days, a titre which is considered as a protective immune response. Thirty-eight patients (65.5%) showed no (n = 27) or only a weak (n = 11 titre >1:10 but <1:40) response. In contrast to this, 20/22 subjects (91%) of the control group developed a protective titre of ≥1:40 after 21 days (Figure 1). Data on seroprotection rate, seroprotection factor, seroconversion factor and geometric mean titre are given in Tables 1 and 2. None of the vaccinated patients was diagnosed with influenza A H1N1 until the end of the observation period.

Influenza A H1N1 titres after booster vaccination

A subgroup of 19 patients received a second dose of Pandemrix® 21.8 ± 3.5 days after the first vaccination. In the booster subgroup (n = 19), a titre of 1:40 or more was present in 7/19 (36.8%) of patients after the first vaccination. 71 ± 25 days after the second vaccination only one additional patient had a protective titre. A total of 11/19 patients (58%) showed no (n = 9) or only a weak (n = 2 titre >1:10 but <1:40) response. Thus, only 8/19 (42%) showed a protective immune response after the second vaccination indicating that booster vaccination is not efficacious in improving the response rate (Figure 2). In 11 patients, H1N1 titres remained stable after the second vaccination, in 6 patients, the H1N1 titres increased and in 2 patients, H1N1 titres were lower compared to the first vaccination.

Table 1. Clinical definitions to evaluate the immune response to Pandemrix® in kidney transplant patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>NTx patients, n = 58</th>
<th>Controls, n = 20</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroconversion rate (% of subjects)</td>
<td>32.7 (19/58)</td>
<td>86.4 (19/22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Geometric mean titre (95% CI)</td>
<td>96.5 (72.1–120.9)</td>
<td>406.4 (366.3–445.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seroconversion factor (95% CI)</td>
<td>9.7 (3.2–16.2)</td>
<td>34.8 (18.9–50.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seroprotection rate (% of subjects)</td>
<td>34.5 (20/58)</td>
<td>91 (20/22)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*NTx, kidney transplant. Titres were measured by hemagglutination inhibition assay.

Subgroup analysis of responders

Comparing patient characteristics and level of immunosuppression between patients with a titre of ≥1:40 (responders, n = 20) and patients with titres <1:40 (non-responders, n = 38), significant differences were seen in patient age (44.0 ± 14.4 versus 57.1 ± 13.4 years; P = 0.001) tacrolimus trough levels (3.8 ± 1.2 versus 6.6 ± 1.5 ng/mL; P = 0.002), MPA dosage (603 ± 510 versus 985 ± 493 mg/day; P = 0.007) and gender. A total of 8/12 (66.7%) female patients developed a protective titre, whereas in male patients, only 12/48 (25%) responded to the vaccine (P < 0.05, χ²-test). Trough levels of cyclosporine, everolimus and sirolimus as well as the median steroid dosage were not different (Table 3).

Whether immunosuppression consisted of mTOR-inhibitors or not did not influence the immune response to the vaccine. Similarly, no difference was observed whether patients were on steroids, received MPA or were on a CNI. Patients already showing PRA before vaccination showed no differences in response rates compared to PRA-negative patients (χ² test, Table 3).

In the multivariable logistic regression analysis, only age >60 years [odds ratio (OR) 0.129; 95% confidence interval (CI) 0.022–0.745; P = 0.022], MPA standard dosage (1440 mg/day) (OR 0.347; CI 0.122–0.988; P = 0.048) and female gender (OR 5.563; CI 1.095–28.258; P = 0.039) remained significant factors for vaccination response.

Safety and tolerability of the vaccination

Flu-like symptoms, local pain and fatigue lasting <72 h were reported by nine patients (15%), eight patients (13.3%), and two patients (3.3%), respectively. By far, most patients [41/60 (68.3%)] reported no clinical notable side effects.

Fig. 1. Reverse cumulative distribution curves of H1N1 antibody titres in serum. Titres ≥1:40 were regarded as protective immune response; titres are expressed as the reciprocal of the dilution.
Clinical course and anti HLA-antibodies

Patients (3/60; 5%) in the observational study developed new DSA after vaccination with Pandemrix®. DSA were detected on day 61, 117 and 118 after vaccination, with a maximum fluorescence intensity (MFI) of 1265, 350 and 443, respectively. Two of the three patients developed histologically confirmed acute antibody-mediated rejection after vaccination and one patient lost the graft within 10 weeks after vaccination due to refractory acute humoral rejection.

In all other patients, transplant function was stable with a mean serum creatinine of 1.83 ± 0.8 mg/dL at time of vaccination and of 1.85 ± 0.83 mg/dL at the end of the study in June 2010.

A total of 9/60; patients (15%) already had DSA at the time of vaccination. MFI of DSA as well as the antibody pattern remained unchanged in all patients after vaccination with Pandemrix® during a follow-up time of 250 days. Transplant function was stable in all these patients during follow-up. A total of 15/60 patients (25%) showed non-donor-specific antibodies (NDSAs) at the time of vaccination. In two of these patients, a transient unspecific rise in NDSA could be determined; in all 15 patients, transplant

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**Table 2.** Booster subgroup: clinical definitions to evaluate the immune response to Pandemrix® in kidney transplant patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>After 1. vaccination, n = 19</th>
<th>After 2. vaccination, n = 19</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroconversion rate (95% CI)</td>
<td>36.8 (11.2–81.4)</td>
<td>67.4 (5.9–128.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Seroconversion factor (95% CI)</td>
<td>4.6 (0.9–8.3)</td>
<td>6.7 (0.6–13.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Seroprotection rate (95% CI)</td>
<td>36.8 (7/19)</td>
<td>42.1 (8/19)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Titres were measured by hemagglutination inhibition assay n.s.: not significant.

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**Fig. 2.** Booster subgroup: reverse cumulative distribution curves of H1N1 antibody titres in serum after booster vaccination. Titres ≥ 1:40 were regarded as protective immune response; titres are expressed as the reciprocal of the dilution.

**Table 3.** Patient characteristics of responders (titre ≥ 1:40 after vaccination) and non-responders

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total</th>
<th>Responder</th>
<th>Non-responder</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.2 ± 5.6</td>
<td>44.0 ± 14.1</td>
<td>57.1 ± 13.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Time after NTx (years)</td>
<td>5.4 ± 6.0</td>
<td>4.1 ± 4.7</td>
<td>6.3 ± 6.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female</td>
<td>8/20 (40%)</td>
<td>11/20 (55%)</td>
<td>14/20 (66%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>IS-containing mTOR</td>
<td>6/20 (30%)</td>
<td>6/20 (30%)</td>
<td>6/20 (30%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>PRA before vaccination</td>
<td>7/19 (37%)</td>
<td>3/19 (16%)</td>
<td>4/19 (21%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tacrolimus (ng/mL)</td>
<td>5.5 ± 1.9</td>
<td>3.8 ± 1.2</td>
<td>6.0 ± 1.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Cyclosporin (ng/mL)</td>
<td>92.4 ± 34.7</td>
<td>84 ± 25.2</td>
<td>95.7 ± 38.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Everolimus (ng/mL)</td>
<td>6.8 ± 2.1</td>
<td>5.6 ± 2.1</td>
<td>7.6 ± 1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sirolimus (ng/mL)</td>
<td>7.4 ± 1.7</td>
<td>7.4 ± 1.7</td>
<td>7.5 ± 0.14</td>
<td>n.s.</td>
</tr>
<tr>
<td>MMF/MPA (mg/day)</td>
<td>861 ± 524</td>
<td>603 ± 510</td>
<td>986 ± 492.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Steroids (mg/day)</td>
<td>1.9 ± 2</td>
<td>2.4 ± 2</td>
<td>1.6 ± 2</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Titres were measured by hemagglutination inhibition assay n.s.: not significant.
function was stable. The remaining 32/60 patients (53.3%) were antibody-negative during the whole observation period. There were no further cellular or antibody-mediated rejection episodes detected in the study population between November 2009 and June 2010.

In order to further describe the clinical risks associated with the adjuvanted H1N1 vaccination, we reviewed the charts of 47 additional vaccinated patients, who did not participate in the observational study on H1N1 titres. In these patients, we found three additional patients who developed de novo DSA (MFI of 904, 4528, and 14653, respectively), with one further patient developing an acute humoral rejection, who subsequently lost his graft. The other two patients had a stable graft function during the observation period.

Finally, we queried our database on any positive H1N1 cases. Only one of our patients (1/767) was diagnosed during the observational period with a positive influenza A H1N1 polymerase chain reaction. This patient was hospitalized for cough and mild bronchitis and treated with antibiotics. The H1N1 infection was detected by routine smear on the day of discharge (Day 3).

Discussion

The present study shows that a single dose as well as booster vaccination against influenza A H1N1 with Pandemrix® does not induce a sufficient immune response in the majority of renal transplant recipients. Although we cannot exclude that lower titres may provide some protection, our study raises serious concerns about the efficacy of primary vaccination in these patients at risk especially as influenza A H1N1 still is the dominant influenza strain in a large number of countries [20].

The considerably low seroprotection rate is confirmed by Meyer et al. [22] in heart transplant recipients. In contrast, a higher seroprotection rate of 72% in kidney transplant patients after vaccination with Pandemrix® was reported by Manuel et al. [21]. However, in this study with 29 subjects, 24% of patients were already H1N1 antibody-positive before vaccination.

During the influenza A H1N1 pandemic, health authorities recommended to vaccinate risk groups first in order to minimize morbidity and mortality [8, 9]. Although the number of patients in our study is small, the low response rates in kidney transplant patients raise the question if this strategy should be maintained in a pandemic setting. It is conceivable that immunocompromised patients would be better protected by environmental vaccination. To answer these questions, larger studies are needed and the results of our study emphasize the necessity for testing new vaccines in risk groups such as immunosuppressed transplanted patients especially before primarily recommending pandemic vaccination.

Subgroup analysis of our data supports previous observations, indicating that the level of immunosuppression seems to be an important variable determining the antibody response to a vaccine [3, 14, 19]. In particular, MPA doses were of importance in our cohort. Therefore, comparing response rates to a vaccine in transplant patients remains to be a difficult issue, and further research should be directed into this field.

Long-term H1N1 titres were not different compared to titres after 21 days without booster vaccination ruling out any delay in antibody production in immunosuppressed kidney-transplanted patients. Antibody titres remained stable in those patients who responded to the vaccine indicating a stable protective immune response.

Overall, vaccination with Pandemrix® was well tolerated and only a few mild reactions were described. Overall, renal function remained stable, however, we observed 3/107 humoral rejections in the vaccinated patients. Furthermore, we observed de novo DSA in 5.6% (6/107) of renal transplant patients shortly after vaccination which is comparable to the de novo DSA rate seen after a non-adjuvanted seasonal flu vaccine [23]. A limitation in interpreting these HLA antibody results is the lack of a control group in both studies.

Candon et al. [23] reported no rejection episodes during a follow-up time of 3 months, however, it has been shown that there might be a wide window of time between the initial detection of HLA antibodies and failure of the graft underlining the need of a long-term follow-up in vaccination studies [31].

The overall incidence of de novo DSA in different transplant cohorts is still a subject of research. In comparison to results of an earlier study with our renal transplant cohort, presenting an overall incidence of DSA of 9.2% (93/1014 patients) after a median of 6 years after transplantation [31], the rate of de novo DSA in our vaccination study seems considerably higher. But unless these findings are confirmed in a larger number of patients including a control group, general recommendation for influenza vaccination should not be questioned.

The new sensitive methods for the detection of HLA antibodies offer unique possibilities to study the humoral immune response in greater detail. So far, there is no study investigating the immunological long-term risk of different vaccines in transplant patients. This might be of greater importance than previous estimations as HLA antibodies and especially DSA have been shown to be directly correlated to the long-term survival of renal allografts [31].

We believe that our study demonstrates a serious challenge in the primary prevention of influenza A H1N1 in kidney transplant patients. Especially in a pandemic setting, efficacy of a new vaccine should be evaluated in this subgroup before a general recommendation is given.

Conflict of interest statement. None declared.

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