Pandemic unadjuvanted influenza A (H1N1) vaccine in dermatomyositis and polymyositis: Immunogenicity independent of therapy and no harmful effect in disease

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ABSTRACT

The goal of the present study was to evaluate the influence of the influenza A H1N1/2009 vaccine on dermatomyositis/polymyositis (DM/PM) disease parameters and the potential deleterious effect of therapy on immune response. Thirty-seven DM and 21 PM patients (Bohan and Peter’s criteria) were gender- and age-matched to 116 healthy controls. Seroprotection, seroconversion, the geometric mean titers (GMTs) and the factor increase (FI) in the GMTs were calculated. Disease safety was determined from a muscle enzyme analysis and the DM/PM scores [patient’s visual analog scale (VAS), physician’s VAS, manual muscle strength (MMT-8)] evaluated pre- and post-vaccination. The mean age (43.1 ± 9.9 vs. 43.8 ± 8.4 years, p = 0.607) and gender distribution (p = 1.00) were comparable between the patients and controls. After 21 days, seroconversion (p = 0.394), seroprotection (p = 0.08), GMT (p = 0.573) and the FI in the GMT (p = 0.496) were similar in both groups. The disease and muscle parameters remained stable throughout the study, including the creatine kinase (p = 0.20) and aldolase levels (p = 0.98), the physicians’ VAS (p = 1.00), the patients’ VAS (p = 1.00) and the MMT-8 (p = 1.00). Regarding the influence of treatment, the seroconversion rates were comparable between the controls and patients undergoing treatment with glucocorticoid (GC) (p = 0.960), GC >0.5 mg/kg/day (p = 0.395) and GC + immunosuppressors (p = 0.285). Vaccine-related adverse events were mild and similar in the DM/PM and control groups (p > 0.05). Our data support the administration of the pandemic influenza A H1N1/2009 vaccination in DM/PM, as we found no short-term harmful effects related to the disease itself and adequate immunogenicity in spite of therapy. Further studies are necessary to identify any long-term adverse effects in patients with these diseases.

1. Introduction

The pandemic influenza A (H1N1) emerged and rapidly spread worldwide in 2009, affecting mainly young population [1]. Its spectrum of clinical presentation varied from asymptomatic to respiratory failure and death [2]. Serious outcomes of influenza disease have been associated with risk factors such as underlying medical conditions, including obesity, pregnancy, cardiovascular diseases and immunosuppressive therapy [3]. Impairment of immune function inherent to the disease itself or secondary to drugs seems to underlie the higher risk in patients under immunosuppressant treatment [4], supporting the recent recommendations of the Advisory Committee on Immunization Practices and the European League Against Rheumatism that immunocompromised patients should receive the flu vaccine [5,6].

The efficacy and safety of vaccination with the monovalent pandemic adjuvanted H1N1 influenza were demonstrated by Elyayam et al. [7] and Gabay et al. [8] in a limited number of patients with rheumatic diseases. Previous seasonal vaccine studies did not include patients with idiopathic inflammatory myopathies, and evaluations of the safety of vaccines against other microbial agents for these patients are also scarce [9–13]. Another uncertain topic is the potential risk of flares of DM/PM following vaccination.

More recently, we reported the overall short-term safety, but reduced immunogenicity, of an adjuvant-free influenza A
(H1N1) vaccine in a cohort of 1668 autoimmune rheumatic disease patients, including for the first time 73 dermatomyositis (DM)/polymyositis (PM) patients [14]. However, the vaccine’s potential deleterious effects on the disease parameters and the possible influence of therapy on the vaccine antibody response have not been explored.

Therefore, the objectives of the present study were to evaluate the influence of influenza A H1N1/2009 vaccine in DM/PM disease parameters and the potential deleterious effect of therapy on the immunoresponse.

2. Materials and methods

2.1. Study design and participants

The present study was prospective and was conducted at a single center during the Public National Health pandemic 2009 influenza A (H1N1) vaccination campaign in Brazil. It was approved by the institutional review board of our university hospital and registered at ClinicalTrials.gov number: NCT01151644. The study included two stages: vaccination (March 22nd to April 2nd, 2010) and a follow-up period of 21 days with a personal diary card for reporting adverse events.

Out of 73 adult DM/PM patients (Bohan and Peter’s criteria [15] who received the vaccination and regularly attended at the Idiopathic Inflammatory Myopathies Outpatient Clinics, 58 adult patients (37 DM and 21 PM) had complete serology, clinical and therapeutic data and were included in the study. Out of 234 healthy vaccinated individuals recruited from the hospital’s immunization center, 116 gender- and age-matched individuals were randomly selected as controls.

2.2. Exclusion criteria

The exclusion criteria were a previous known infection with pandemic 2009 influenza A H1N1; a history of anaphylactic response to vaccine components or to eggs; an acute infection resulting in a fever of over 38 °C at the time of vaccination; a history of Guillain–Barré syndrome or demyelination syndromes, cancer, or other associated autoimmune diseases; vaccination with any live vaccine within a period of 4 weeks prior to the study, any inactivated vaccine within a period of 2 weeks prior to the study, or the 2010 seasonal influenza vaccine; a blood transfusion within a period of 6 months prior to the study; less than 8 weeks of anti-TNF therapy, hospitalization during the study; or failure to complete the protocol [14].

2.3. Vaccine

The vaccine, Sanofi Pasteur 2009 influenza A (H1N1) was a novel monovalent adjuvant-free vaccine (A/California/7/2009/Butantan Institute/Sanofi Pasteur). The active component was a split inactivated influenza virus containing 15 μg hemagglutinin (HA) from an influenza A/California/07/2009 (H1N1) virus-like strain (NYMCx-179A) per 0.5 mL dose [9]. It was available as 5 mL multidose vials with thimerosal (45 μg/0.5 mL dose) added as preservative and was stored at 2–8 °C until used.

2.4. Study procedures

All subjects were vaccinated with a single intramuscular dose (deltoid muscle) of the H1N1 vaccine using a 22Gx1.14 in. needle. The patient’s visual analog score (VAS) and physician’s VAS [16,17], the manual muscle testing score (MMT-8) [18,19], and the blood sample collection were assessed before and 21 days after the vaccination. Muscle enzymes were determined using an automated kinetic method [creatinine kinase (normal range: 24–173 IU/L) and aldolase (normal range: 1.0–7.5 IU/L)].

2.5. Safety assessments

A 21-day symptom diary-card for prospective completion was given to each participant following vaccination and returned 21 days later. All new symptoms, recorded or not, in the diary were reviewed by the investigators, and the causal relationship with the vaccine was assessed. All patients answered one specific (yes or no) question about their perception of the vaccine’s interference with their disease activity. Local reactions were defined as local pain, redness, swelling and itching, whereas systemic reactions included arthralgia, fever, headache, myalgia, sore throat, cough, diarrhea, rhinorrhea and nasal congestion.

2.6. Laboratory assays

The immunogenicity of the H1N1 A/California/7/2009-like virus vaccine was evaluated (hemagglutination inhibition assay-HIA) at Adolfo Lutz Institute [13]. The antibody titers were assessed at baseline and 21 days post-immunization. The following serologic endpoints were evaluated: the seroprotection rate, defined as the percentage of patients with a titer ≥1:40, and the seroconversion rate, defined as the percentage of patients with a 4-fold increase in vaccination titer if the pre-vaccination titer was ≥1:10 or a post-vaccination titer ≥1:40 if the pre-vaccination titer was <1:10.

2.7. Statistical analysis

Two-sided 95% confidence intervals (CI) were calculated assuming binomial distributions for dichotomous variables and a log-normal distribution for hemagglutination inhibition titers. For the categorical variables, the statistical summaries included the rates of seroconversion and seroprotection; these rates were compared using Fisher’s exact test. For every subgroup, the hemagglutination inhibition geometric mean titers (GMTs) were calculated before vaccination and 21 days after vaccination. The factor increase in the GMTs (i.e., the ratio of the titers after vaccination to the titers before vaccination) was also obtained. The factor increases and the GMTs were compared between DM/PM patients and controls using Student’s two-sided t-test with the log-transformed titers. The Wilcoxon signed rank test was performed to analyze paired and non-parametric data.

3. Results

3.1. Demographic characteristics

The mean current age was comparable in the DM/PM patients and controls (43.1 ± 9.9 vs. 43.8 ± 9.4 years, p = 0.607), with a similar frequency (75.9%) of female gender in both groups (p = 1.00). The disease duration was 7.3 ± 6.3 years.

3.2. The influence of the vaccine on disease parameters

Table 1 illustrates the DM/PM parameters and treatment status before and after the influenza A H1N1/2009 vaccination. The pre- and post-vaccination disease and muscle parameters were comparable [patients’ VAS (p = 1.00), physicians’ VAS (p = 1.00), MMT-8 (p = 1.00), creatine kinase (p = 0.19) and aldolase (p = 0.98)].

Glucocorticoid and immunosuppressive treatments remained unchanged throughout the study (p > 0.05), as shown in Table 1. The frequencies of the use of immunosuppressive therapy were as follows: methotrexate (39.7%), azathioprine (32.8%), chloroquine diphosphate (15.5%), cyclosporine (13.8%), mycophenolate
Dermatomyositis/polymyositis parameters and treatment before and after influenza A H1N1/2009 vaccine.

<table>
<thead>
<tr>
<th>Variables (reference values)</th>
<th>Pre-vaccination (n = 58)</th>
<th>Post-vaccination (n = 58)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DM/PM parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient’s VAS (0–10)</td>
<td>0 [0–1]</td>
<td>0 [0–1]</td>
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<tr>
<td>Physician’s VAS (0–10)</td>
<td>0 [0–1]</td>
<td>0 [0–1]</td>
<td>1.000</td>
</tr>
<tr>
<td>MMT-8 (0–80)</td>
<td>80 [80]</td>
<td>80 [80]</td>
<td>0.500</td>
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<tr>
<td>Creatine kinase, IU/L (24–173)</td>
<td>145.5 [121–186]</td>
<td>167.5 [98–321]</td>
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<tr>
<td>Aldolase, IU/L (1.0–7.5)</td>
<td>4.6 [3.6–5.5]</td>
<td>4.4 [3.4–7.7]</td>
<td>0.980</td>
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<tr>
<td><strong>Treatment</strong></td>
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<td></td>
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<tr>
<td>Prednisone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>32 [55.2]</td>
<td>32 [55.2]</td>
<td>1.000</td>
</tr>
<tr>
<td>Dose, mg/day</td>
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<td>9.7 [2.5–60]</td>
<td>1.000</td>
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<tr>
<td>Prednisone ≥0.5 mg/kg/day</td>
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<td>Methotrexate</td>
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<td>Dose, mg/week</td>
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<td>8.5 [7.5–30]</td>
<td>1.000</td>
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<tr>
<td>Azathioprine</td>
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<td>Current use</td>
<td>19 [32.8]</td>
<td>19 [32.8]</td>
<td>1.000</td>
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<tr>
<td>Dose, mg/day</td>
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<td>62.1 [100–300]</td>
<td>1.000</td>
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<tr>
<td>Cyclosporine</td>
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<td>Current use</td>
<td>8 [13.8]</td>
<td>8 [13.8]</td>
<td>1.000</td>
</tr>
<tr>
<td>Dose, mg/day</td>
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<td>1.000</td>
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<td>Mycophenolate mofetil</td>
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<td>Current use</td>
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<td>1.000</td>
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<tr>
<td>Dose, g/day</td>
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<td>0.1 [1.5–2.0]</td>
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<td>Cyclophosphamide</td>
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<td>Current use</td>
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<td>1 [1.7]</td>
<td>1.000</td>
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<td>Dose (g/m² body surface)</td>
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<td>1.2</td>
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<td>Chloroquine diphosphate</td>
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<tr>
<td>Current use</td>
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<td>9 [15.5]</td>
<td>1.000</td>
</tr>
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<td>Leflunomide</td>
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<tr>
<td>Current use</td>
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<td>2 [3.4]</td>
<td>1.000</td>
</tr>
<tr>
<td>Dose, mg/day</td>
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<td>20</td>
<td>1.000</td>
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<tr>
<td><strong>Immunosuppressive current use</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19 [32.8]</td>
<td>19 [32.8]</td>
<td>1.000</td>
</tr>
<tr>
<td>Two immunosuppressive</td>
<td>16 [27.6]</td>
<td>16 [27.6]</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are expressed in n (%) or median [interquartile range], median (range) or mean ± standard deviation (SD). DM, dermatomyositis; PM, polymyositis; MMT, manual muscle testing score.

mofetil (3.4%) and leflunomide (3.4%). Twenty-three (39.7%) out of 58 patients were using one immunosuppressive, six (27.6%) were receiving two immunosuppressives and 42 (74.1%) were simultaneously using immunosuppressive and glucocorticoid therapies. In addition, 32 (55.2%) patients were using prednisone with a mean dose at 9.7 mg/day, and nine (15.5%) of them were receiving ≥0.5 mg/kg/day.

3.3. Vaccine immunogenicity in DM/PM patients

The seroconversion rate (p = 0.394), the seroprotection rate (pre- and post-vaccination: p = 0.234 and p = 0.08, respectively), the GMTs (p = 0.932 and p = 0.573) and the factor increases in the GMTs (p = 0.496) were similar in the DM/PM patients and control groups (Table 2).

3.4. The influence of treatment on the vaccine immune response

The analysis of the patients’ therapies revealed that DM/PM patients receiving glucocorticoid treatment had similar seroconversion rates (p = 0.969), seroprotection rates (pre- and post-vaccination: p = 0.273 and p = 0.27, respectively), the GMTs (p = 0.952 and p = 0.435) and factor increases in the GMTs (p = 0.403) to the control group. Likewise, patients receiving a high dose of glucocorticoid treatment (≥0.5 mg/kg/day) had seroconversion rates (p = 0.395), seroprotection rates (pre- and post-vaccination: p = 0.209 and p = 0.667, respectively), GMTs (p = 0.446 and p = 0.292) and factor increases in the GMTs (p = 0.501) comparable to those of controls. The concomitant use of glucocorticoid and immunosuppressive therapy also resulted in a comparable immune response to controls [seroconversion rate (p = 0.285), seroprotection rate (pre- and post-vaccination: p = 0.553 and p = 0.066, respectively), GMTs (p = 0.786 and p = 0.846) and factor increases in the GMTs (p = 0.714)], Table 2.

Moreover, the disease parameters (patients’ VAS, physicians’ VAS, MMT-8, creatine-kinase and aldolase) were comparable between seroconverted and non-seroconverted patients (p > 0.05) (data not shown).

3.5. Adverse events

The vaccine was well tolerated without any severe adverse effects during the follow-up. The frequencies of minor local reactions (8.6 vs. 11.2%, p = 0.597) and of mild systemic reactions (15.5 vs. 25.7%, p = 0.123) were similar between the patients and controls.

4. Discussion

To our knowledge, this is the largest study addressing short-term disease safety of adjuvant-free 2009 influenza A (H1N1) vaccine in patients with DM/PM. The vaccine did not seem to have a deleterious effect on disease and immunoresponsiveness was not affected by therapy.

The advantages of the present study were the prospective design and the inclusion of well-defined DM/PM [14] patients with the careful exclusion of patients with cancer and other associated-autoimmune diseases. In addition, the patients were age- and gender-matched with the control group because
immunogenicity varies according to age [13] and gender [20]. We also choose the non-adjuvanted preparation to minimize the potential risk of flares of underlying autoimmune diseases and the risk of "adjuvant disease" in genetically susceptible individuals [21] is defined as autoimmune syndrome induced by adjuvants (ASIA syndrome) [22,23].

We have established the disease safety of the pandemic H1N1 influenza vaccine on the basis of the result that muscle enzymes and DM/PM scores remained stable throughout the study; muscle enzymes and DM/PM scores are well-known indicators of myositis activity in the clinical management of these idiopathic inflammatory myopathies [16–19].

Additionally, we have confirmed our previous finding that the seroconversion of the H1N1 pandemic vaccine is adequate and comparable in age-matched healthy controls in contrast to the reduced vaccine response in patients with juvenile autoimmune rheumatic diseases [24], systemic lupus erythematosus [25] and rheumatoid arthritis [7,26]. One possible explanation for this discrepancy is the fact that the majority of the patients were stable with respect to laboratory and clinical parameters. Notably, the seroconversion rate was also not affected by glucocorticoid and immunosuppressive therapies whereas a deleterious effect of these drugs was reported in patients with systemic lupus erythematosus [8], rheumatoid arthritis [7,26], ankylosing spondylitis [7] and pediatric rheumatic diseases [24].

We further demonstrated that post-vaccination seroprotection in DM/PM patients was in fact similar to that in controls when compared to a rigorously gender- and age-matched group. The non-attendance for each subgroup analyzed in our previous study evaluating a large cohort of rheumatic disease patients may explain the reduced response reported for DM patients [14].

No serious short-term adverse events were observed, as reported previously in patients with autoimmune rheumatic disease who received seasonal influenza [7] and pandemic vaccines [8,24–26]. Long term effects on DM/PM could not be ruled out on the basis of the data presented because of the limited observation period of this study. This result should be interpreted with caution because the overall number of DM/PM patients was relatively small to detect relatively infrequent adverse events.

In summary, our data support the administration of the pandemic unadjuvanted influenza A H1N1 2009 vaccine in DM/PM patients on the basis of our findings of no short-term harmful effects related to the disease itself and the adequate immunogenicity of the vaccine in spite of therapy.

Acknowledgments

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