Effect of Prednisone on Response to Influenza Virus Vaccine in Asthmatic Children

Mary P. Fairchok, MD; Daniel P. Trementozzi, MD; Patricia S. Carter, MD; Helen L. Regnery, PhD; Edward R. Carter, MD

**Objective:** To evaluate the immunogenicity of the influenza virus vaccine in children receiving short-course (a burst) prednisone therapy for acute asthmatic exacerbations.

**Design:** Prospective cohort study.

**Setting:** Outpatient pediatric clinic of a military medical center.

**Patients:** Children aged 6 months to 18 years requiring the 1996 influenza virus vaccine were eligible for the study. A total of 58 children were enrolled initially. The control group included 37 asthmatic children requiring less than 900 µg/d of inhaled prednisone and their siblings. The prednisone group included 21 children vaccinated at the beginning of a course of prednisone prescribed to treat an asthma exacerbation. Thirty-one control subjects (84%) and 19 patients in the prednisone group (90%) completed the study. Dropout was due to failure to come in for the postvaccination serum sampling.

**Interventions:** All study patients underwent immunization with the 1996-1997 trivalent subvirion influenza virus vaccine (FluShield; Wyeth Laboratories Inc, Marietta, Pa) containing 15-µg hemagglutinin antigens each of A/Texas/36/91 (H1N1) (A/H1), A/Wuhan/359/95 (H3N2) (A/H3), and B/Beijing/184/93 (B). The prednisone cohort received a burst of oral prednisone therapy (2 mg/kg per day for 5 days).

**Main Outcome Measures:** To assess the immunogenicity of the vaccine between both groups, at least a 4-fold rise in titer and end titers of at least 1:40 to each of the 3 antigens were compared. Mean changes in geometric titers to the 3 antigens were also compared.

**Results:** Proportion of patients in each group with at least a 4-fold rise in titer to each of the influenza antigens was as follows: for A/H3N3 antigen, 15 patients (79%) in the prednisone group vs 8 controls (42%) (P = .20); for A/H1N1 antigen, 16 patients in the prednisone group (84%) vs 27 controls (83%) (P = .53). Proportion of patients in each group with an end titer of at least 1:40 to each of the antigens was as follows: for A/H3N2 antigen, 11 patients in the prednisone group (58%) vs 23 controls (75%) (P = .99); for B antigen, 7 patients in the prednisone group (35%) vs 15 controls (67%) (P = .2). There were also no significant differences between groups in the mean changes in geometric titers to any of the 3 antigens.

**Conclusions:** Prednisone bursts did not diminish the response of asthmatic children to the 1996 influenza virus vaccine, compared with controls. Children can be effectively vaccinated against influenza virus while they are receiving prednisone therapy bursts for asthmatic exacerbations.

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**Editor’s Note:** Another supposed reason NOT to immunize against influenza goes down the drain. I hope this leads to more asthmatics receiving the recommended vaccine.

_Catherine D. DeAngelis, MD_
PATIENTS AND METHODS

PATIENTS

From October 1 to December 31, 1996, children aged 6 months to 18 years with a known diagnosis of moderate to severe asthma and their siblings who presented to Madigan Army Medical Center Pediatric Clinic, Tacoma, Wash, were invited to participate in the study. All children met criteria for routine vaccination against influenza on the basis of a known history of moderate to severe asthma or being the sibling of an asthmatic child. Asthmatic children who did not require a glucocorticoid burst at the time of influenza vaccination and their healthy siblings comprised the control group. The prednisone group consisted of asthmatic children presenting to the clinic with an acute exacerbation of asthma requiring treatment with glucocorticoids. These patients started a 5-day course of prednisone or prednisolone (2 mg/kg per day) within 48 hours of enrollment into the study. Children were excluded from the study if they had a known contraindication to influenza virus vaccination or known immunocompromise or had received oral or intravenous glucocorticoid therapy within the 3 weeks preceding enrollment. Asthmatic subjects requiring greater than 900 µg/d inhaled glucocorticoids or long-term oral glucocorticoid therapy were also excluded, since the scope of our study was not large enough to address the potential effects of long-term glucocorticoid use on the influenza virus vaccine response.

All children were immunized using standard methods with the trivalent subvirion influenza vaccine (FluShield; Wyeth Laboratories Inc, Marietta, Pa; lot 4968264) containing 15-µg hemagglutinin antigens each of A/Texas/36/91 (H1N1)(A/H1), A/Wuhan/359/95 (H3N2)(A/H3), and B/Beijing/184/93 (B). This product was not subject to the influenza virus vaccine lot recall issued in 1996 for decreased potency. In accordance with the guidelines of the American Academy of Pediatrics for immunization against influenza, patients who were younger than 9 years and had not received an influenza virus vaccination previously received a booster dose after a 4- to 6-week interval. Vaccination serum samples were obtained from each subject on enrollment, and postvaccination samples were obtained 3 to 6 weeks after the last vaccination dose. Children were monitored in the clinic for 20 minutes after vaccination for severe reactions. Parents were instructed to note any reactions to the immunization within the first 24 hours, including injection-site pain and fever. On the follow-up visit for the final serum sampling, any immunization reaction and interim illnesses and asthma exacerbations during the study were recorded by the investigators.

LABORATORY ANALYSIS

Serum samples were frozen, paired, and shipped to the Influenza Branch, Centers for Disease Control and Prevention, Atlanta, Ga, for analysis. Samples collected from both groups before and after vaccination were identically treated with receptor-destroying enzyme, and all samples were assayed using the hemagglutination inhibition (HAI) test with standard methods. The HA antigen for B/Harbin/07/94 was treated with ether to obtain optimal sensitivity. Serum samples were run simultaneously in pairs. We defined an immunologic response as a titer rise of at least 4-fold from baseline. Starting dilutions of HAI were set at 1:5. A post-vaccination titer of at least 1:40 was considered a protective response. Although the exact correlation between an absolute HAI serum titer and protection is unclear, there is evidence that a titer of at least 1:40 confers protection against influenza virus infection. Previous studies also have used this level as a marker for protection.

STATISTICAL ANALYSIS

The Fisher exact test was used to analyze race and sex differences and to compare the proportion of patients in each group achieving an immunologic postvaccination titer of at least 1:40. The Fisher exact test was also used to compare the proportion of patients in each group requiring booster doses. Because of the geometric nature of the titer assays, titer responses were expressed as the difference between prevaccination and postvaccination log2 (titer/5) for each patient. Mean values for the group were obtained for the purpose of comparison. For example, a change in titer response in a patient from 1:40 to 1:160 would be expressed as 2. Mean titer rises, mean age, and mean number of days between last vaccine dose and serologic sampling were evaluated using the unpaired t test.

For a protective end titer of at least 1:40, our study had a power of 0.8 to detect a difference of greater than 34% between the prednisone and control groups for the A/H1N1 antigen, a difference of greater than 37% for the A/H3N2 antigen, and a difference of greater than 34% for the B antigen. The power analysis was performed using an α of .05 and normal approximations for a 2-sided test.

pressed response to the influenza virus vaccination among asthmatics who require a short course (a burst) of high-dose glucocorticoids for treatment of an asthma exacerbation. The manufacturer’s insert for the influenza virus vaccine highlights this concern with a warning that “patients with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including . . . corticosteroids . . . ) may have a reduced antibody response. . . .” Since the parenteral influenza virus vaccine is not a live virus, there is no specific contraindication to concurrent administration in patients receiving high-dose glucocorticoids, but concern over the effect on immunogenicity remains.

We hypothesized that administration of short-term glucocorticoid therapy would not diminish antibody responses of asthmatic children to the influenza virus vaccine. We evaluated the immunogenicity of the vaccine when administered to children receiving a burst of high-dose prednisone for treatment of their asthma.
Table 1. Demographic Characteristics of Subjects*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Prednisone Group† (n = 19)</th>
<th>Control Group† (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15 (79)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (79)</td>
<td>26 (84)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (16)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>9.8 (4.0)</td>
<td>9.3 (4.4)</td>
</tr>
<tr>
<td>Patients without history of influenza virus vaccination</td>
<td>3 (16)</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as number (percentage) of patients.
† Groups are described in the “Patients” subsection of the “Subjects and Methods” section.

compared with a group of control children who did not receive prednisone.

RESULTS

PATIENTS

From October 1 to December 31, 1996, we enrolled 58 children. Fifty patients completed the study, including 19 in the prednisone group and 31 in the control group. There were no significant differences between groups for sex, age, race, or percentage of children without a history of immunization against influenza (Table 1). The mean interval between the last vaccination and serologic sampling for the postvaccination titer was 33.4 days for the prednisone group and 32.3 days for the control group (P = .63). Both groups reported less than 3% incidence of adverse effects to the vaccination. The most frequent adverse event in each group was tenderness at the injection site. No patients in either group had worsening in their asthma symptoms following the immunization. We observed no significant increase in use of asthma medications following the vaccination. Following immunization, 4 patients required interim prednisone bursts before obtaining the postvaccination titer; 3 children were in the prednisone group and 1 child was in the control group (P = .15). Each of these prednisone bursts was prescribed more than 2 weeks after the initial vaccination. Excluding these 4 patients did not alter the results of the statistical analysis.

All of our subjects had their postvaccination serum samples drawn later than November 25, 1996, ie, after the onset of the influenza season in Washington State. Influenza activity in Washington State during the 1996-1997 season began earlier than usual, with peak number of cases occurring from November 25 to December 19. Seventy-six percent of influenza cases isolated by the Washington State Department of Health, Seattle, during the season were attributable to A/H3N2 antigen, 24% to B antigen, and none to A/H1N1 antigen.9 The influenza B antigen cases did not occur until late December. The influenza A/H3N2 and B strains isolated in the United States during the 1996-1997 season were antigenically similar to the strains included in the 1996-1997 vacc-

cine. Since all of our subjects underwent postvaccination serologic study after the onset of influenza season, some of the study participants may have been infected, thus affecting their titer results. To evaluate for this possibility, we analyzed data on interim illnesses between groups. Five subjects (16%) in the control group and 4 subjects (21%) in the prednisone group experienced interim illnesses between initial immunization and the postimmunization titer. This did not represent a significant difference. All of the illnesses were respiratory and included otitis media (n = 1), sinusitis (n = 2), mild upper respiratory tract infection (n = 2), and asthma exacerbation (n = 4). None of the illnesses were clinically suggestive of influenza. Viral washings for influenza culture were submitted for 1 of the patients with an upper respiratory tract infection, with negative results for influenza virus. Excluding data from these patients from analysis did not alter the results of the study.

SEROLOGY

There were excellent responses in both groups to the A/H1N1 and A/H3N2 antigens, but the response to the B antigen in both groups was poor. There were no statistically significant differences in the responses of both groups to the 3 components of the vaccine in the proportion achieving a 4-fold rise in titer (Figure 1) or the proportion with protective titers of at least 1:40 (Figure 2). The prednisone group actually had greater immunologic responses to all 3 components of the vaccine, but these did not reach statistical significance.

Both groups had strong quantitative titer rises to the A antigens, with a weaker response to the B antigen (Table 2). Although the differences between groups in mean titer rise to the 3 antigens were not statistically significant, there was a trend toward a better response to the A/H1N1 antigen in the prednisone group. There were no significant differences in the proportion of patients in each group with prevaccination titers of less than 1:40 to both of the A antigens. For A/H3N2 antigen, 20 con-
trols (64%) vs 13 patients in the prednisone group (68%) had prevaccination titers of less than 1:40 (P < .99); for A/H1N1 antigen, 20 controls (64%) vs 15 patients in the prednisone group (79%) began with titers of less than 1:40 (P = .35). However, for the B antigen, there was a significant difference in the levels of preexisting antibody, with significantly more patients in the predni-

We found that a burst of high-dose prednisone did not affect the immunogenicity of any of the 3 components of the 1996 influenza virus vaccination in asthmatic children. Both groups in the study had excellent responses to the A antigens, which strengthened the power of our study to detect a potential difference. Response to the B antigen was equally poor in both groups.

Variables affecting the response to the influenza virus vaccine include age, a history of vaccination, and previous influenza virus infection. Both patient groups in our study were comparable for these factors on demographic analysis. There were no statistical differences between groups in mean age or previous influenza virus vaccination experience. None of our subjects had a documented or known history of influenza infection. Although it is likely that some subjects did have previous experience with influenza virus infection, this possibility should not have been significantly different between both groups regarding the A antigens, based on the lack of difference in proportion with baseline titers of less than 1:40 for the A antigens. The prednisone group had a significantly lower proportion with prevaccination titers to B antigen of less than 1:40, which would put them at a potential disadvantage in responding to this antigen, yet no difference was seen in response.

The humoral and cellular components of the immune system interact to protect against influenza virus infection. Specific antibody against the hemagglutinin antigen is necessary for protection, and the formation of these antibodies is T-lymphocyte dependent. As the extent and scope of immunosuppression in humans receiving 5- to 10-day bursts of high-dose oral prednisone is still unclear, there is some concern that this therapy might interfere with a successful response to influenza virus immunization. Serum IgG levels in humans decline by 50% after 5 days of methylprednisolone administered at 16 mg/d, and large doses of glucocorticoids can cause lymphocytopenia and reduction in cytolyis. Delayed-type hypersensitivity also decreases, although this is due to decreased macrophage recruitment rather than impaired T-cell function. Despite these detrimental effects on humoral and cellular immunity, other studies have shown that there is no inhibition of primary or secondary responses to antigens in humans taking high-dose glucocorticoids. Claman has shown that patients who were taking 15 to 20 mg/d of prednisone had a normal response to immunization.

There has been only 1 other prospective study that assessed the antibody responses to the influenza virus vaccine in asthmatic patients receiving bursts of high-dose prednisone therapy for asthma exacerbations compared with controls. In that study, Park et al found no differences in the antibody responses to the A/H3N2 and A/H1N1 antigens between both groups and no difference in the rate of adverse events. However, they found a significantly better response to the B antigen in their prednisone group. Two other studies of children with asthma receiving long-term daily prednisone therapy also failed to find an association between prednisone and vaccine failure.

Several studies have assessed the immunogenicity of the influenza vaccine in other patient populations exposed to glucocorticoids. Chalmers et al conducted a placebo-controlled study that evaluated the immunogenicity and safety of the influenza virus vaccine in patients with rheumatoid arthritis. One of the groups consisted of patients receiving immunosuppressive therapy, including daily prednisone use of greater than 7.5 mg/kg. There was no difference in the response to the vaccine between this group and healthy age-matched controls. Studies investigating influenza virus vaccine response in adults receiving steroids and other immunosuppressive agents documented a decreased
response to the vaccine, but the effect may have been
due to the other immunosuppressive agents.21,22 Mauch
et al20 investigated the response of children with solid
organ transplants to the influenza virus vaccine using
healthy siblings as controls. Many of these patients were
receiving prednisone, 0.5 to 1 mg/kg per day, in addition
to other immunosuppressive agents. There was no
difference seen between controls and patients who had
undergone transplantation, and regression analysis did
not demonstrate that prednisone use correlated with
response.

Immunization against influenza virus infection in
children with asthma is recommended by the American
Academy of Pediatrics. It has been demonstrated that
even with the use of tracking systems to provide influ-
enza virus vaccine to children with asthma, the immu-
nization rates have been poor.3 Factors that affect
parental compliance with the vaccination include
providers’ attitudes and recommendations.23 Parents and
providers may perceive that adverse effects of the vac-
cine will be more likely during an acute asthmatic exac-
erbation. However, several other studies have demon-
strated that the influenza virus vaccine does not cause
an increase in asthmatic symptoms,17,24,25 and this was
also the case with our study. Also, the providers may be
hesitant to trust the immunogenicity of the vaccine
when given in conjunction with glucocorticoid bursts.
The results of our study suggest that barriers to influ-
enza immunization during an asthmatic exacerbation
are unnecessary. Discarding these barriers should be
an effective step toward improving overall compliance
rates with the vaccine.

Drawbacks to our step include the use of inhaled
glucocorticoids, limited numbers of subjects, and the con-
cern that the study was not completed before the onset
of the influenza season in Washington State. Although
we did not exclude patients receiving inhaled glucocor-
ticoids from the study, we did exclude patients who re-
duced doses that were potentially physiologic. The
number of subjects enrolled was small but sufficient on
power analysis to detect a clinically significant difference in
response to the A antigens. Another limitation of our study
is that all of the postimmunization serum samples were
obtained after the onset of the influenza season. The re-
sponse to the vaccination may have been augmented in
some cases by natural infection. However, analysis of cli-
cial data on all subjects failed to demonstrate any sub-
jects with clinical evidence of acute influenza during the
study. In addition, since Washington State reported only
influenza A/H3N2 infections during our study, there
should have been no potential effect on the outcome in
our patients’ responses to A/H1N1 or B antigen.

The results of our study suggest that the influenza
virus vaccination can be safely and effectively adminis-
ter to asthmatic patients receiving prednisone bursts.
Thus, children with asthma presenting to clinics or emer-
gency departments with asthma exacerbations should be
offered the influenza virus vaccination.

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Reprints not available from the authors.

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