Serum Antibody Response to Influenza Vaccine in Pulmonary Patients Receiving Corticosteroids*

Martin A. Kubiet, MD; Ricardo J. Gonzalez-Rothi, MD, FCCP; Rob Cottee, BS; and Bradley S. Bender, MD

Objective: Despite the recommendation that patients with chronic lung diseases—many of whom receive corticosteroids—receive annual influenza vaccination, it is not known whether corticosteroids influence antibody response to influenza vaccine in this population. The purpose of this study was to assess whether patients with pulmonary conditions receiving long-term corticosteroid therapy develop an adequate antibody response.
Design: We prospectively studied 39 consecutive candidates for influenza vaccination, 25 of whom were receiving corticosteroids for underlying lung diseases. Patients with immunosuppression besides corticosteroids were excluded. Serum samples were obtained prior to and 1 month after vaccination with inactivated trivalent influenza vaccine and assayed for antibodies to the three strains using a hemagglutination inhibition assay. No patients had any intercurrent illness compatible with influenza during the study period and patients receiving corticosteroids continued treatment with them during this time.
Results: A fourfold rise in antibody titer at 1 month to at least one component was seen in 21 of 25 (84%) of corticosteroid-treated patients, which was similar to patients not receiving corticosteroids (11/14, 79%). There was no corticosteroid-antibody, dose-response relationship.
Conclusions: Patients with pulmonary conditions receiving corticosteroids can generate an adequate antibody response to killed influenza virus vaccine. Long-term therapy with corticosteroids should not preclude influenza vaccination in patients with chronic pulmonary diseases who are deemed vaccine candidates.

Key words: antibody response; corticosteroids; influenza vaccine; pulmonary disease

Abbreviations: HAI—hemagglutination inhibition

Influenza is a major contributor to morbidity and mortality worldwide. Influenza vaccine is recommended for persons who because of age or underlying predisposing medical conditions are at increased risk for developing complications from influenza. Under current Centers for Disease Control and Prevention guidelines, patients with chronic pulmonary diseases would be considered candidates for yearly influenza vaccination.1 Many such patients receive long-term corticosteroid therapy as treatment for their underlying pulmonary disease. Corticosteroids suppress several aspects of the immune response, including antibody production,2,3 and the influenza vaccine manufacturer's package insert states that patients who are immunocompromised—including patients receiving long-term corticosteroid therapy—may have reduced antibody responses following influenza vaccine.4 However, we could not find any published studies that specifically addressed whether patients with pulmonary disease who are receiving corticosteroids long term can generate an adequate antibody response to influenza vaccine. This could be clinically relevant if either patients receiving corticosteroids received influenza vaccination without protective effect or if vaccinations were withheld on the presumption of an impaired antibody response. In addition, if a group of patients who fail to develop an appropriate antibody response could be identified, they might be candidates for antiviral prophylaxis with amantadine or rimantadine.5 The present prospective study was designed to assess the efficacy of antibody response to influenza vaccine in corticosteroid-dependent patients with chronic lung disease.

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Table 1—Descriptive Characteristics of Vaccinees

<table>
<thead>
<tr>
<th></th>
<th>No Steroids (n=14)</th>
<th>Steroids* (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>Gender, M:F</td>
<td>1:8:1</td>
<td>4:1</td>
</tr>
<tr>
<td>COPD, No.</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>ILD, No.</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Asthma, No.</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Bronchiolitis, No.</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Previously vaccinated, No.</td>
<td>14</td>
<td>25</td>
</tr>
</tbody>
</table>

*Patients receiving corticosteroids had been receiving corticosteroids for at least 1 month prior to the study and steroid doses were stable through the conclusion of the study.

1ILD=interstitial lung disease (eg, idiopathic fibrosing alveolitis).

MATERIALS AND METHODS

Patient Selection

This was a prospective study conducted in the fall of 1993 of consecutive patients deemed candidates for influenza vaccine by their respective physicians. Patients were recruited from the pulmonary clinics at Shands Teaching Hospital and the Gainesville (Fla) Veterans Administration Medical Center. Patients with a serious previous adverse reaction to influenza vaccine or egg products, or those with acute febrile illnesses during the initial evaluation were excluded. Patient characteristics are listed in Table 1. The study was approved by the Institutional Review Board at both hospitals. Written informed consent was obtained from all participants.

Protocol

Participants were immunized with trivalent influenza virus vaccine from the same lot containing 15 μg/0.5 mL each of the hemagglutinin of influenza A/Beijing/32/92, A/Taiwan/1/86, and B/Panama/45/90 (Wyeth Laboratories Inc; Marietta, Pa). Each individual received a single IM inoculation of the vaccine in the deltoid muscle. All were evaluated for the presence of an influenza-like illness preceding each collection of blood samples for serologic testing.

Serum for determination of antibody titers was obtained by venipuncture from all subjects just prior to administration of the vaccine and at 4 weeks following vaccination. Serum samples were separated immediately after blood collection and stored at −20°C until assayed.

Serum antibody titers were determined by standard laboratory procedures. Briefly, duplicate serum samples were incubated overnight with a receptor-destroying enzyme. The 1:10 diluted samples were then diluted twofold in phosphate-buffered saline solution in microtiter plates and tested in parallel. Four hemagglutination units of the 1993-1994 vaccine antigen (Atlanta Biological Products; Atlanta, Ga) were added to each serum dilution; the contents of the plates were mixed and incubated for 1 h at room temperature. A 0.5% chicken RBC suspension was added and the plate contents were mixed and allowed to settle at room temperature until control (serum-free) wells demonstrated agglutination. Serum hemagglutination inhibition (HAI) antibody titers were recorded as the reciprocal of the greatest serum dilution resulting in nonagglutination of RBCs.

Statistical Analysis

Changes in antibody titers were expressed as mean fold increase in antibody titer from baseline. Subjects were categorized as “responders” or “nonresponders” according to whether they developed a fourfold or greater increase in antibody titer. Data were analyzed using software (Instat; GraphPad Software; San Diego, Calif).

RESULTS

Of 41 participants initially enrolled in the study, 39 individuals completed the protocol (2 did not return in time to obtain follow-up serum antibody titers). Descriptive characteristics were similar in patients with pulmonary disease receiving and not receiving corticosteroids with the exception that there were relatively twice as many men as women in the corticosteroid group (Table 1).

Serum HAI antibody responses were similar in the two groups. Overall, 21 of 25 (84%) of the subjects receiving corticosteroids developed a fourfold or greater increase in titer to at least one component as compared with 11 of 14 (79%) of the subjects not receiving corticosteroids. The number of the subjects responding to the individual components and the

Figure 1. Geometric mean titer for patients with pulmonary conditions prevaccination (open bars) and postvaccination (solid bars) with trivalent influenza vaccine. Responses are shown for all three antigens for patients not receiving steroids and receiving steroids. Numbers are those responding (fourfold or greater increase in titer)/total vaccinated.
geometric mean HAI titers are shown in Figure 1. Responses were highest for A/Beijing—8 of 14 (57%) for the no steroid group vs 8 of 25 (32%) for the steroid group; intermediate for A/Taiwan—4 of 14 (29%) vs 11 of 25 (44%); and lowest for B/Panama—4 of 14 (29%) vs 5 of 25 (20%). None of these values were significantly different (Fisher’s exact test).

The daily corticosteroid dose (prednisone equivalent) ranged from 2.5 to 60 mg (mean±SD=17±15 mg; median=10 mg). Despite this wide range of doses, there was no correlation between the dose of corticosteroids and the magnitude of the antibody response (data not shown).

**DISCUSSION**

Corticosteroids have multiple effects on the immune system, including inhibition of endocytosis by antigen-presenting cells, cytokine production, and helper T-cell function.8-10 In addition, corticosteroids may alter antibody production.3 The antibody response to influenza vaccine was found by Herron and coworkers11 to be diminished in patients with rheumatologic conditions receiving immunosuppressive therapies, including corticosteroids. A more recent study by Chalmers and associates12 in a population of patients with rheumatoid arthritis demonstrated that influenza vaccination produced a sufficient antibody response. The patient population in both studies differed from ours in that the above studies involved younger patients with connective tissue disorders, many of whom also received other forms of immunosuppressive therapy besides corticosteroids. A review of 12 studies that assessed the immune responses to influenza vaccine in patients receiving cancer chemotherapy likewise concluded that the serum antibody response to influenza vaccine tends to be weaker in patients undergoing cancer chemotherapy.13

Our study excluded patients with other pharmacologic immunosuppression besides corticosteroids. Our data clearly demonstrate that patients with a variety of pulmonary diseases who are receiving long-term corticosteroid therapy have the capacity to generate adequate antibody responses to inactivated influenza vaccine. The difference in the proportion of men to women in each group (corticosteroids vs no corticosteroids) should not be expected to affect the results as the postvaccination change from baseline titers was tabulated for each patient as his or her own control subject. The consistently lower levels of antibody noted for the B/Panama strains irrespective of corticosteroid treatment are similar to those in previous studies that have observed that the intensity of antibody production as stimulated by influenza B virus vaccine (and measured by HAI) is less than that conferred by the influenza A vaccine.14-17

The ability to develop HAI antibodies was not altered by doses of corticosteroids in prednisone equivalents ranging from 2.5 to 60 mg/d in our study. This is similar to a recent study in adult steroid-dependent asthmatics which showed that long-term prednisone therapy (10 to 35 mg daily) does not appear to alter the specific antipneumococcal antibody-generating capacity responses to a polyvalent pneumococcal vaccine when compared with a group of similar nonsteroid-dependent asthmatic patients.18

There are three potential limitations of this study. First, it was not designed to test efficacy, ie, protection from subsequent influenza infection. Serologic responses are indirect markers of actual protection against influenza, and data from other studies support the paradigm that serologic responses to influenza vaccine are associated with a protective response against illness.19,20

Second, there were a relatively small number of subjects. There was, however, a higher response in the corticosteroid group as assessed overall or individually to two of the three antigens. It would also be very difficult to detect only small differences in response rates. If we assume that the overall response rate of 79% is representative for patients with pulmonary disease not receiving corticosteroids, then a sample size of 94 subjects (per group) would be needed to detect a difference of 15% with 80% power and α<0.05. We believe that the expense of such a study would far outweigh any possible clinical benefits.

Third, all of the subjects in this study had received influenza vaccination previously and it is possible that subjects with low titers receiving corticosteroids may not develop significant titers. However, four of our subjects receiving corticosteroids had at least one pre-vaccination titer of 1:40 or less, and three of them had a fourfold or greater response to that antigen. We conclude that corticosteroid therapy should not dissuade clinicians from routinely immunizing patients with pulmonary diseases who are deemed to be influenza vaccine candidates. Since seasonal timing of influenza vaccination is crucial, corticosteroid therapy should neither preclude nor be a reason to delay or withhold vaccination in this high-risk group of patients.

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**REFERENCES**

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