Impact of a Winter Respiratory Virus Season on Patients With COPD and Association With Influenza Vaccination*

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Background: **We assessed the effects of an influenza season on patients with COPD. Data from 2,215 veterans in a multicenter, randomized, double-blind influenza vaccine efficacy study were analyzed for changes in spirometric and functional status, comparing patients with laboratory-documented influenza (LDI)-caused illness, non-LDI-caused respiratory illness, or no illness, and for association with influenza vaccination.**

Methods: **Patients received either IM trivalent inactivated influenza virus vaccine (TIV) plus intranasal trivalent, live attenuated, cold-adapted influenza virus vaccine (TC) or TIV plus intranasal placebo (TP). We performed spirometry, measured the chronic lung disease severity index (CLDSI) score to assess functional status and well-being, and tested for influenza virus infection.**

Results: **Worsening in FEV_1, percentage of predicted FEV_1, and CLDSI score ($p < 0.001$) was associated with acute respiratory illness in 585 illnesses including 94 LDI-caused illnesses. LDI-caused illness was more likely to be associated with worsening in FEV_1 and CLDSI score acutely than non-LDI-caused illness ($p < 0.01$). Logistic regression showed acute respiratory illness (odds ratio [OR], 1.78; 95% confidence limit [CL], 1.40 to 2.26) to be associated with worsening in CLDSI score, and receipt of TC (OR, 1.39; 95% CL, 1.10 to 1.74) and no illness (OR, 0.70; 95% CL, 0.53 to 0.91 for acute respiratory illness) to be associated with better CLDSI score at the end of the study. Hospitalization was more frequent in patients with acute respiratory illness ($p < 0.0001$).**

Conclusions: **Acute respiratory illness was associated with increased health-care utilization and obstruction to airflow, and worse functional status and well-being. At the end of the study, receipt of TC was associated with improvement and acute respiratory illness was associated with worsening in functional status and well-being.** ***(CHEST 2006; 130:1109–1116)***

Key words: COPD; health-related quality of life; influenza virus; pulmonary function; vaccine

Abbreviations: CL = confidence limit; CLDSI = chronic lung disease severity index; LAIV = trivalent, live-attenuated, cold-adapted influenza virus vaccine; LDI = laboratory-documented influenza; OR = odds ratio; $PPFEV_1$ = percentage of predicted FEV_1; TC = trivalent inactivated influenza virus vaccine and intranasal trivalent, live-attenuated, cold-adapted influenza virus vaccine; TIV = trivalent inactivated influenza virus vaccine; TP = trivalent inactivated influenza virus vaccine plus intranasal placebo; VA = Veterans Affairs

Influenza virus infections cause significant morbidity and mortality particularly in patients with underlying chronic diseases.[1–12] Influenza causes exacerbations of COPD and reduced pulmonary function, and as many as 24 million persons in the United States may have underlying COPD.[10,13–16] Immunization with standard influenza virus vaccine is associated with reduced risk of influenza-related illness, reduced hospitalization rates, fewer outpatient visits, less severe illness, and lower mortality related to pneumonia and influenza in older patients and in those with chronic lung disease.[7–9,17–21] Besides influenza virus, other respiratory pathogens are associated with influenza-like illness and acute respiratory illness; and respiratory viruses are associated with 15 to 50% of acute exacerbations of COPD.[22–36]

The effect of a winter respiratory virus season on pulmonary function, performance status, and health-

related quality of life in a large cohort of patients with COPD has not been reported. In the Department of Veterans Affairs (VA) Cooperative Study, 448 patients aged ≥ 50 years who had COPD received IM trivalent inactivated influenza virus vaccine (TIV). They were also randomized to receive intranasal trivalent, live attenuated, cold-adapted influenza virus vaccine (LAIV) [TC group] or intranasal placebo (TP group) in a double-blind manner.[15] The purpose of this report is to compare changes in lung function, performance status, and health-related quality of life among these older, vaccinated individuals who had laboratory-documented influenza (LDI)-caused illness, other acute respiratory illnesses not documented to be influenza (non-LDI-caused illnesses), or no acute respiratory illness.

Materials and Methods

Volunteers aged ≥ 50 years who met spirometric criteria for COPD were recruited at 20 VA Medical Centers, as described.[15] All study subjects gave written informed consent. The study was approved by the institutional review boards at the participating sites, and followed procedures in accordance with the recommendations found in the Helsinki Declaration of 1975.

Pulmonary function tests performed included FEV_1, percentage of predicted FEV_1 ($PPFEV_1$), and FEV_1/FVC ratio.[37,38] COPD was defined as $FEV_1 \leq 80\%$ of the predicted value and FEV_1/FVC ratio < 0.70. The study required spirometry within 4 weeks prior to immunization. Spirometric criteria were not met in 11 subjects who had a baseline FEV_1/FVC ratio ≥ 0.70, and in 1 subject who had a baseline $PPFEV_1$ of 91%. The analysis included these 12 subjects because of their history of chronic lung disease.

Immunizations occurred in October 1998 through January 1999. All subjects received TIV for the 1998 to 1999 influenza season. Subjects were randomly assigned in a 1:1 ratio to receive intranasally either LAIV (MedImmune Vaccines, Inc, formerly Aviron; Mountain View, CA) [TC group] or placebo (TP group).[15] Subjects underwent clinical evaluation, spirometry, and serum collection for antibody 3 to 4 weeks after immunization. From November 1998 through April 1999, the subjects were evaluated when they had either three symptoms of acute respiratory illness (new-onset or increased chronic cough, new-onset or increased sputum production, increased dyspnea, chills, headache, myalgias, widespread aches and pains, malaise, sore throat, and nasal congestion) or fever accompanied by two symptoms of acute respiratory illness.

Nasopharyngeal swab specimens and serum samples were obtained for viral culture and antibody, respectively, to detect influenza virus infection. If the subjects could not come to the clinic, information regarding the acute respiratory illness was gathered by telephone. Three to 4 weeks after the onset of acute respiratory illness, the subjects were asked to return to clinic to provide a second serum sample for antibody testing. LDI was defined as the sudden onset of respiratory illness plus the following: (1) a nasal swab culture positive for wild-type influenza virus A or B; and/or (2) a fourfold increase in the end point titer of serum hemagglutination inhibition antibodies to influenza A or B.[15,39,40] A final study visit consisting of a clinical evaluation and spirometry was scheduled for each subject between April and July 1999.

Severity of illness was assessed using the symptom-based, chronic lung disease severity index (CLDSI) that was developed as part of the Veteran's Health Study[41–43] to evaluate functional status and well-being and the effects of chronic lung disease on general health-related quality of life. The chronic lung disease questionnaire is a self-reported rating of the severity of six symptoms: frequency of dyspnea, severity of dyspnea on exertion, frequency of wheezing, severity of wheezing on exertion, frequency of cough, and quantity of sputum production in the preceding three months. The CLDSI combines the unweighted raw scores from the scales used to quantify the rating of each of the six symptoms. The raw CLDSI score ranges from 6 (best) to 27 (most severe).[41]

The statistical analysis included the first episode of acute respiratory illness for each subject that occurred > 7 days after vaccination, and that met the study definition of acute respiratory illness. The analysis included only the first episode of illness, not later episodes in the same subject, because the earlier illness could affect the characteristics of the later illness and the number of later illnesses was small. The study population was divided into three "illness groups": those whose first respiratory illness was an LDI-caused illness, those whose first respiratory illness was a non-LDI-caused illness, and those who did not have a respiratory illness.

We compared changes in mean FEV_1, $PPFEV_1$, and CLDSI score between study visits. A 15% change in FEV_1 between study visits was considered clinically significant, as described.[38,44] A 15% change in CLDSI score between study visits was an arbitrary change chosen to categorize study subjects.

The χ^2 test or Fisher exact test were used to compare categorical characteristics of the three illness groups, and the Wilcoxon rank-sum test was used to compare continuous char-

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This study was performed at 20 VA clinical study sites: Ann Arbor, MI; Bay Pines, FL; Birmingham, AL; Boston, MA; Cleveland, OH; Dallas, TX; Dayton, OH; Durham, NC; Gainesville, FL; Houston, TX; Long Beach, CA; Minneapolis, MN; North Chicago, IL; Palo Alto, CA; Richmond, VA; Salt Lake City, UT; San Juan, Puerto Rico; Sepulveda, CA; St. Louis, MO; and Tucson, AZ. The biostatistical center site was the VA Cooperative Studies Program Coordinating Center, West Haven, CT.
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