Original Study

Clinical and Serologic Responses After a Two-dose Series of High-dose Influenza Vaccine in Plasma Cell Disorders: A Prospective, Single-arm Trial

Andrew R. Branagan,[1,2] Eamon Duffy,[2] Randy A. Albrecht,[3] Dennis L. Cooper,[1,2] Stuart Seropian,[1,2] Terri L. Parker,[1,2] Geliang Gan,[4] Fangyong Li,[4] Daniel Zelterman,[4] Chandra Sekhar Boddupalli,[1,2] Lin Zhang,[1,2] Rakesh Verma,[1,2] Thomas M. Ferencz,[1] Madhav V. Dhodapkar[1,2]

Abstract

The goal of the present study was to evaluate a novel prospective influenza vaccination strategy for patients with plasma cell disorders. Fifty-one patients were treated with a 2-dose series of high-dose inactivated trivalent influenza vaccine. This vaccination strategy was well tolerated and led to very high rates of seroprotection against influenza.

Background: Patients with multiple myeloma (MM) and other plasma cell disorders are highly susceptible to influenza infections, which are major causes of morbidity in this population, despite the routine administration of a seasonal influenza vaccination. Existing data are limited by small and retrospective studies, which suggest poor seroprotection rates of $< 20\%$ after standard influenza vaccination in patients with MM. **Patients and Methods:** Patients with plasma cell dyscrasia ($n = 51$) were treated with a 2-dose series of high-dose inactivated trivalent influenza vaccine during the 2014 to 2015 influenza season. Laboratory-confirmed influenza infections were identified through seasonal surveillance, sera were collected for influenza hemagglutination antibody inhibition (HAI) titer assays, and logistic regression models were used to identify the clinical correlates to the HAI serologic responses. **Results:** Influenza vaccine was well tolerated, without any vaccine-related grade ≥ 2 adverse events. Only 3 patients (6%) experienced laboratory-confirmed influenza. The rates of HAI seroprotection against all 3 vaccine strains (A/California/7/2009 [H1N1] pdm09-like virus; A/Texas/50/2012 [H3N2]-like virus; and a B/Massachusetts/2/2012-like virus) increased from 4% at baseline to 49% and 65% after 1 and 2 doses, respectively. The risk factors associated with a lower likelihood of HAI serologic response included plasma cell disorder requiring therapy, less than a partial response found on disease response assessment, and active conventional chemotherapy. Alternatively, active therapy with an immunomodulatory drug alone or with a proteasome inhibitor was associated with a greater likelihood of an HAI serologic response. **Conclusion:** These data have demonstrated that, in contrast to the historically poor results with standard influenza vaccination, this novel high-dose booster vaccination strategy leads to high rates of seroprotection. Randomized controlled studies are needed to compare this novel strategy to the standard vaccination strategy.

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Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder (PCD), marked by neoplastic plasma cells in bone marrow that secrete monoclonal immunoglobulins.[1] Infections are a significant cause of morbidity and a leading cause of death for patients with MM.[2] Influenza is a major cause of morbidity and in the United

[1]Yale Cancer Center, New Haven, CT
[2]Yale School of Medicine, New Haven, CT
[3]Icahn School of Medicine at Mount Sinai, New York, NY
[4]Yale School of Public Health, New Haven, CT

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Address for correspondence: Andrew R. Branagan, MD, Yale University, 333 Cedar Street, PO Box 208032, New Haven, CT 06520-8028
E-mail contact: Andrew.branagan@yale.edu

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States is responsible for > 40,000 deaths annually.[3] Despite the routine administration of a seasonal influenza vaccination to patients with MM, the risk of influenza infection remains high. A Swedish study of > 9000 myeloma patients demonstrated that myeloma was associated with a 10-fold increased risk of viral infections, including a 6.1-fold risk of influenza, relative to healthy controls.[4]

Patients with MM have multiple factors that contribute to immunosuppression, including suppression of normal uninvolved immunoglobulins and alteration in T-cell immunity.[5,6] Anticancer therapies can further affect the immune system, and chemotherapy has been associated with diminished protection from influenza vaccination.[7,8] Finally, immunity in patients with PCDs is also affected by the age-related decline in immune function.

The US Advisory Committee on Immunization Practices has recommended that all adults aged ≥ 50 years and immunocompromised individuals, such as those with MM, receive a single annual dose of inactivated influenza vaccine.[9] Inactivated influenza vaccination is associated with a robust primary serologic antibody response against hemagglutinin surface protein of each viral subtype within the vaccine, which can be measured by the hemagglutination antibody inhibition (HAI) titer levels. Seroconversion refers to a fourfold or greater increase in HAI titers, and seroprotection refers to an HAI titer level of ≥ 1:40. HAI seroprotection corresponds to an estimated 50% clinical protection from influenza infections according to the results of studies of young, healthy adults.[10,11] HAI titers are the most widely accepted serologic correlates and form the basis for the approval of new influenza vaccines.[12]

The existing data on influenza vaccine responses in MM patients are limited but suggest that low HAI titers with seroprotection rates of < 20% after standard influenza vaccination.[8,13-15] One potential approach to enhancing the immune efficacy of a vaccine is the administration of a booster dose. Two studies previously investigated the benefit of a 4-week booster dose of a standard-dose influenza vaccine in MM patients. Ljungman et al[15] randomly assigned a mix of patients with all hematologic malignancies (including 10 with MM and 4 with Waldenström macroglobulinemia) to vaccination with 1 versus 2 doses of influenza vaccine and found no overall increase in serologic protection in the cohort receiving 2 vaccines. However, their study included patients with diverse hematologic malignancies that differed in their capacity to respond to vaccines. Hahn et al[14] reported the findings from a retrospective analysis of 48 MM patients during the 2013 to 2014 influenza season at their institution. Seroprotection after 1 vaccine was detected in only 7 patients (14%). Of the remaining 41 patients, 24 received a second vaccine, and 33% of these patients achieved seroprotection. Because of the retrospective nature of the study, the effects on influenza infection were not systematically evaluated. An unmet need remains for prospective data evaluating the clinical and serologic efficacy of the influenza vaccination specifically in PCD patients because the existing data suggest that only a few patients respond to the current vaccination strategy.

One potential approach to enhance vaccine efficacy is to administer a higher dose of antigen. Based on studies reporting increased serologic protection, Fluzone High-Dose inactivated influenza vaccine (Sanofi Pasteur, Swiftwater, PA) was approved in the United States for adults aged ≥ 65 years (60 μg HAI vs. 15 μg standard dose). Safdar et al[16] observed an improvement in vaccine-induced HAI titer responses by increasing the hemagglutinin antigen level in a dose-dependent fashion of ≤ 135 μg without increased toxicity. Previous studies have not specifically evaluated a booster strategy with a high-dose influenza vaccine for MM patients.

Therefore, we designed a novel influenza strategy for MM patients combining the use of a high-dose inactivated influenza vaccine and a 2-dose series in the present study.

Patients and Methods

Clinical Trial Design

We evaluated a novel influenza vaccine strategy in the SHIVERING trial (study of high-dose influenza vaccine efficacy by repeated dosing in gammopathy patients) during the 2014 to 2015 influenza season. This pilot clinical trial was conducted at a single, US academic hospital (Yale Smilow Cancer Hospital). The eligibility criteria allowed inclusion of any patient with a diagnosis of MM or another PCD without any known contraindication to trivalent inactivated influenza vaccine. All participants received the study intervention of 2 doses of trivalent Fluzone High-Dose influenza vaccination 30 days apart, regardless of age. The participants were stratified into 2 broad cohorts: those with PCD requiring therapy and those with asymptomatic gammopathy. The present analysis focused on the changes in the HAI titer serologic response rates. Other endpoints included safety and the laboratory-confirmed influenza infection rates.

Study Oversight

The trial was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and appropriate regulatory requirements. The local ethics committees or institutional review boards approved the protocol. All patients provided written informed consent. The trial was registered before patient enrollment at Clinicaltrials.gov (ClinicalTrials.gov identifier, NCT02267733).

Study Influenza Vaccine

Fluzone High-Dose is a trivalent inactivated vaccine administered intramuscularly. The vaccine contains influenza split virus antigens that are formulated to contain a total of 180 μg of influenza virus hemagglutinin (60 μg each from the 3 current influenza virus strains). During the 2014 to 2015 influenza season, the vaccine contained an A/California/7/2009 (H1N1) pdm09-like virus; A/Texas/50/2012 (H3N2)-like virus; and a B/Massachusetts/2/2012-like virus.

HAI Titer Measurements

HAI assays were performed using the following standardized protocol.[17] In brief, sera were treated with a receptor destroying enzyme, *Vibrio cholera* filtrate (Sigma-Aldrich, St. Louis, MO), which eliminates nonspecific inhibitors that could confound the assay results. Working stocks for each of the 3 current influenza virus strains included in the clinical trial influenza vaccine were prepared by diluting the virus stock to a final HA titer of 8 HA units per 50 μL. Twofold dilutions of the receptor-destroying enzyme-treated sera in buffer were then mixed with the working stock of