REGULAR ARTICLE

blood advances

Tandem high-dose influenza vaccination is associated with more durable serologic immunity in patients with plasma cell dyscrasias

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Key Points

- PCD patients have an increased risk of influenza infections and poor serologic response to standard influenza vaccination.
- Tandem high-dose influenza vaccination leads to more robust as well as more durable seroprotection in patients with PCDs.

Patients with plasma cell dyscrasias (PCDs) experience an increased burden of influenza, and current practice of single-dose annual influenza vaccination yields suboptimal protective immunity in these patients. Strategies to improve immunity to influenza in these patients are clearly needed. We performed a randomized, double-blind, placebo-controlled clinical trial comparing tandem Fluzone High-Dose influenza vaccination with standard-of-care influenza vaccination. Standard-of-care vaccination was single-dose age-based vaccination (standard dose, <65 years; high dose, ≥65 years), and patients in this arm received a saline placebo injection at 30 days. A total of 122 PCD patients were enrolled; 47 received single-dose standard-of-care vaccination, and 75 received 2 doses of Fluzone High-Dose vaccine. Rates of hemagglutinin inhibition (HAI) titer seroprotection against all 3 strains (H1N1, H3N2, and influenza B) were significantly higher for patients after tandem high-dose vaccination vs control (87.3% vs 63.2%; $P = .003$) and led to higher seroprotection at the end of flu season (60.0% vs 31.6%; $P = .04$). These data demonstrate that tandem high-dose influenza vaccination separated by 30 days leads to higher serologic HAI titer responses and more durable influenza-specific immunity in PCD patients. Similar vaccine strategies may also be essential to achieve protective immunity against other emerging pathogens such as novel coronavirus in these patients. This trial was registered at www.clinicaltrials.gov as #NCT02566265.

Introduction

Plasma cell dyscrasias (PCDs) are hematologic disorders characterized by clonal plasma cells that secrete clonal immunoglubulins and manifest as conditions such as multiple myeloma or its precursor, monoclonal gammopathy of undetermined significance. PCDs are associated with alterations in both innate and adaptive immunities, which begin in the precursor stages.[1,2] Humoral deficits in PCDs often involve persistent hypogammaglobulinemia, and antimyeloma therapy may worsen immune deficiency and reduce the efficacy of vaccines.[3,4]

Current Centers for Disease Control and Prevention guidelines recommend yearly influenza vaccination to everyone age >6 months, prioritizing those at higher risk, including adults age >50 years or the immunocompromised.[5] Inactivated influenza vaccines consist of hemagglutinin (HA) antigen from recent H1N1, H3N2, and influenza B (FluB) virus strains. The vaccine induces antibodies against HA, inhibiting

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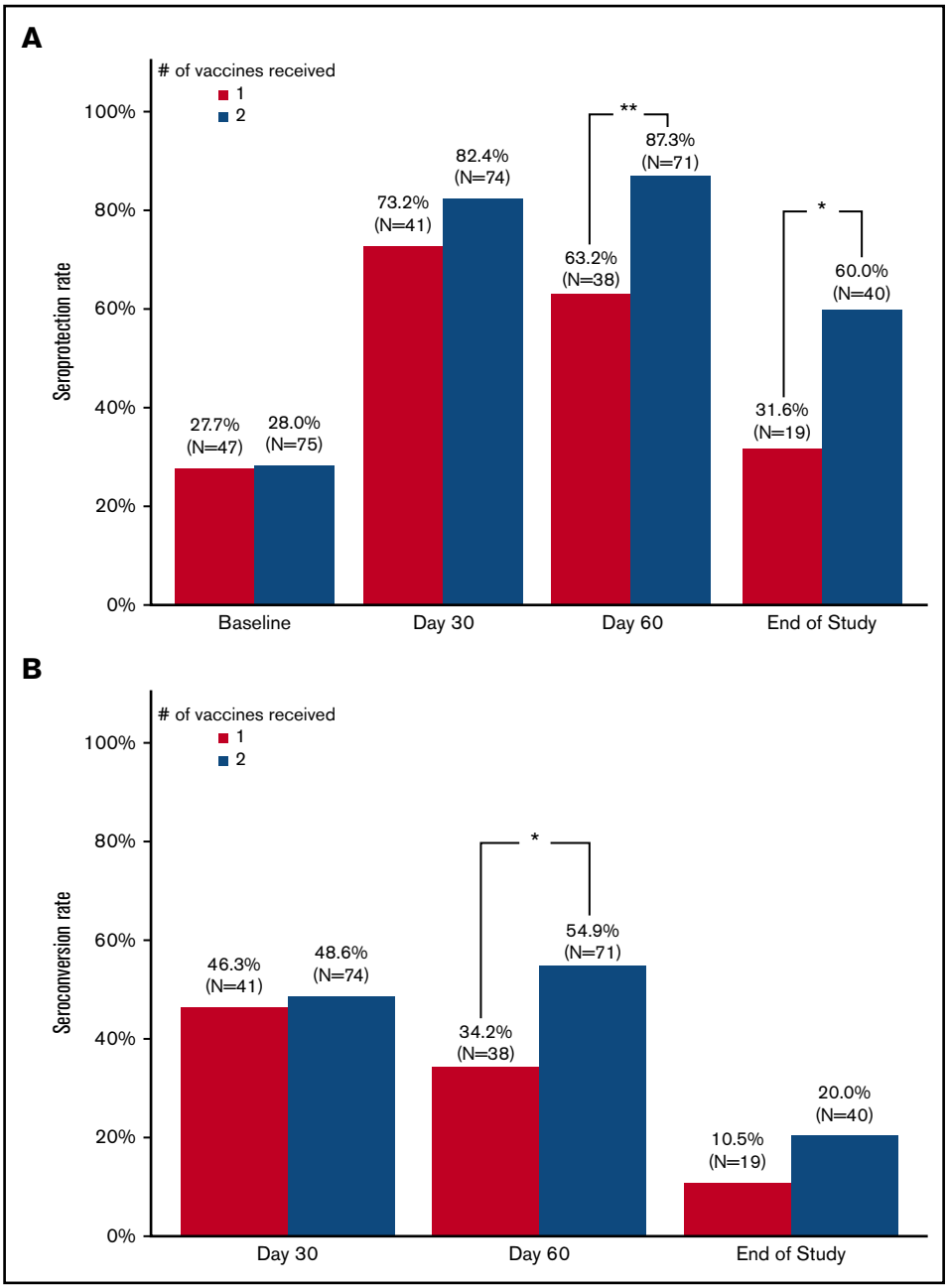

Figure 1. Cumulative HAI serologic response rates against all influenza strains. (A) Bar graph showing proportion of patients analyzed by actual number of vaccine doses received who achieved total seroprotection (against FluB, H1N1, and H3N2) at baseline, day 30 (after initial vaccine dose), day 60 (after second vaccine dose/placebo), and end of study. (B) Bar graph showing proportion of patients analyzed by actual number of vaccine doses received who achieved seroconversion against FluB, H1N1, and H3N2 at baseline, day 30 (after initial vaccine dose), day 60 (after second vaccine dose/placebo), and end of study. $^{*}P < .05$, $^{**}P < .01$.

viral entry and neutralizing virus.[6] Serum HA inhibition (HAI) antibody titers are correlated with clinical protection against influenza.[7] Fluzone High-Dose contains 4 times more HA antigen vs standard vaccine; lower rates of influenza infection have been demonstrated with Fluzone High-Dose vs standard vaccine in adults age ≥65 years,[8] and it has been US Food and Drug Administration approved since 2009 for this population. However, recent studies have shown that current vaccines lead to suboptimal induction of long-lived plasma cells, which limits durable immunity.[9]

Patients with PCDs including myeloma have an increased risk of influenza infections[10] and demonstrate poor serologic response to influenza vaccinations, with studies suggesting <20% seroprotection rates after standard influenza vaccination.[4,11-13] Previously, we reported a pilot study using tandem high-dose influenza vaccine (separated by 30 days) in PCD patients. This trial demonstrated the attainability of high seroprotection rates in PCD patients: 49% after 1 high-dose and 76% after a second high-dose influenza vaccine dose.[14] In the present study, we analyze serologic data from a randomized clinical trial comparing tandem high-dose vaccination with single-dose age-based influenza vaccination.

Methods

We conducted a randomized, double-blind, placebo-controlled clinical trial during the 2015 to 2016 flu season, SHIVERING 2 (Study of High-Dose Influenza Vaccine Efficacy by Repeated Dosing in Gammopathy Patients: A 2 Arm Trial). Tandem Fluzone

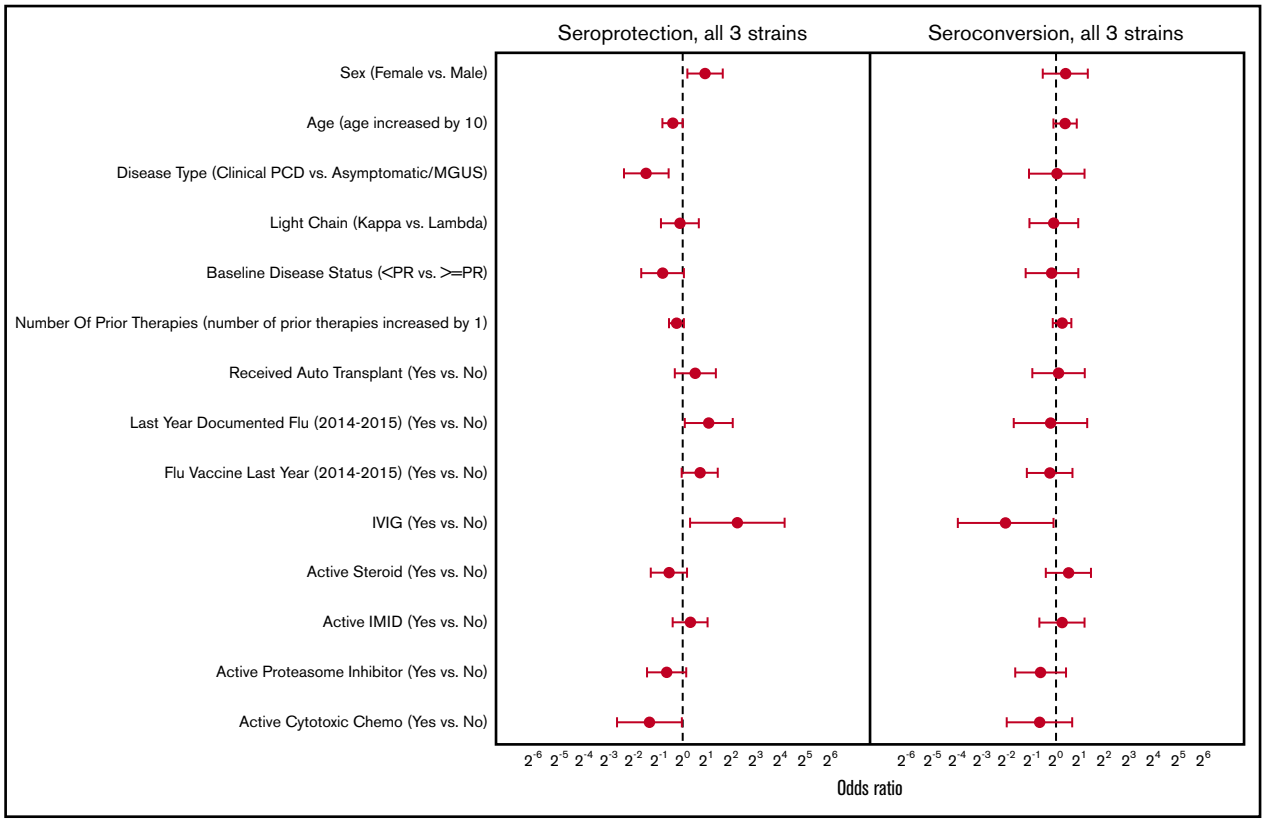

Figure 2. Correlates of serologic response. Forest plot illustrating effect of a group of risk factors on achieving seroprotection and seroconversion among all study participants. The x-axis is on log scale with base at 2. Filled black dots represent estimates of odds ratios regarding relevant risk factors. 95% confidence intervals are represented by horizontal lines with short vertical lines at both ends. Odds ratios with *P* value for each variable calculated for seroprotection and seroconversion against each individual influenza vaccine strain are detailed in supplemental Table 1. IMID, immunomodulatory drug; IVIG, IV immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance; PR, partial response.

High-Dose influenza vaccination (separated by 30 days) was compared with standard-of-care influenza vaccination. Standard-of-care influenza vaccination was single-dose age-based vaccination (standard dose, <65 years; high dose, ≥65 years), and patients in this arm received a saline placebo injection at 30 days. The study was approved by the institutional review board at Yale University.

A validated HAI assay was used to quantify antibody titers based on standard protocol.[15] As defined elsewhere,[16,17] seroprotection after the influenza virus vaccine is based on achieving an antibody titer ≥1:40, and seroconversion to the influenza virus vaccine is based on a fourfold increase in antibody titers.

χ^2 or Fisher's exact test was used to compare rates of seroprotection and seroconversion between treatment arms. Generalized estimating equations were used to assess the effect of individual risk factors (ie, clinical correlates) on seroprotection and seroconversion. For all statistical tests, the significance level was set at $P < .05$. All analytics were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

Results and discussion

A total of 122 PCD patients were enrolled (active multiple myeloma, Waldenstrom's macrogobulinemia, or amyloid light-chain amyloidosis, n = 97; asymptomatic gammopathy, n = 25). Forty-one patients were randomly assigned the to control arm, and 81 were randomly assigned to the tandem high-dose vaccination arm, of whom 75 received both doses of high-dose vaccine (supplemental Figure 1). Median age was 68 years (range, 37-90 years). Both arms were balanced for major clinical characteristics (supplemental Table 1).

Rates of total seroprotection (against all 3 influenza vaccine strains) were significantly higher after second vaccine dose/placebo for patients randomly assigned to tandem high-dose vaccination (86.3% vs 63.9%; $P = .007$). At the end of flu season, rates of total seroprotection trended toward significance for those randomly assigned to tandem high-dose vaccination (58.5% vs 33.3%; $P = .07$) but were significantly higher when analyzed by patients who received 2 high-dose vaccine doses vs single-dose vaccination (60.0% vs 31.6%; $P = .04$; Figure 1A). Rates of seroconversion against all 3 influenza vaccine strains after second vaccine dose/placebo trended higher for patients randomly assigned to tandem high-dose vaccination (53.4% vs 36.1%; $P = .09$) but were significantly higher when analyzed by patients who received 2 high-dose vaccine doses vs single-dose vaccination (54.9% vs 34.2%; $P = .04$; Figure 1B).

Considering individual virus strains, H1N1 seroprotection rates were significantly higher for patients randomly assigned to tandem high-dose vaccination (90.4% vs 69.4%; $P = .006$) and trended

toward significance against FluB (94.5% vs 88.3%; $P = .08$). At the end of flu season, H1N1 seroprotection rates were significantly higher for patients randomly assigned to tandem high-dose vaccination (78.1% vs 44.4%; $P = .01$) and trended toward significance against H3N2 (75.6% vs 50%; $P = .05$; supplemental Figure 2). After the second vaccine dose/placebo, FluB seroconversion rates were significantly higher for patients randomly assigned to tandem high-dose vaccination (69.9% vs 47.2%; $P = .02$) and trended toward significance against H3N2 (90.4% vs 77.8%; $P = .08$; supplemental Figure 3).

Generalized estimating equation logistic regression modeling[18] was used to identify potential variables associated with total seroprotection and seroconversion (Figure 2). Female sex, receiving active IV immunoglobulin treatment, and influenza infection in the previous flu season were associated with higher odds of total seroprotection ($P < .05$ for each). Receiving a flu vaccine in the prior year trended toward higher likelihood of total seroprotection ($P = .07$). In contrast, increasing age, having a diagnosis of PCD requiring therapy (as opposed to asymptomatic disease/monoclonal gammopathy of undetermined significance), and active therapy with alkylating agent chemotherapy ($P < .05$ for each) were associated with lower odds of seroprotection. Two other variables trended toward lower likelihood of total seroprotection: disease response status lower than partial response at study entry ($P = .06$) and greater number of prior cancer therapies ($P = .07$). Conversely, receiving active immunomodulatory drug therapy was associated with higher likelihood of seroprotection against H3N2 ($P < .05$; supplemental Table 2). Receiving active IV immunoglobulin treatment was associated with significantly lower likelihood of achieving seroconversion against all 3 vaccine strains ($P < .05$). Conversely, receiving active immunomodulatory drug therapy was associated with higher likelihood of H3N2 seroconversion ($P < .005$; supplemental Table 2).

These data, to our knowledge, provide the first controlled evidence that tandem high-dose influenza vaccination is associated with higher rates of seroconversion and total seroprotection, as well as more durable seroprotection at the end of flu season. This maintenance of seroprotection was most pronounced for seroprotection against H1N1 (the predominate pathogenic strain for the studied 2015-2016 flu season), occurring in 77.5% of patients after 2 high-dose vaccine doses compared with 47.4% of those receiving single-dose vaccination. The low protective titers in the control arm at the end of flu season suggest that most PCD patients lose serologic protection within a given flu season. Strengths of this study are the randomized trial design and systematic evaluation of immunity, including at end of flu season, coupled with formal influenza surveillance. Furthermore, it is notable that HAI seroprotection as studied here is considered by the US Food and Drug Administration to be the best currently available correlate of protection from natural infection and therefore used for regulatory approval of influenza vaccines.[19]

Infections such as influenza continue to cause significant morbidity in patients with PCDs. Our findings support a change in current vaccination strategy practice against influenza in PCD patients. Indeed, on the basis of our data, this recommendation is now being incorporated into the International Myeloma Working Group guidelines (Noopur Raje, MGH Cancer Center, personal communication, 4 January 2021). The current SARS-CoV-2 pandemic highlights the importance of developing effective vaccines, particularly for populations at greatest risk.[20] Newer vaccine strategies as described here may be needed to improve protection against other infections, including SARS-CoV-2, for patients with PCDs.

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Authorship

Contribution: A.R.B. and M.V.D. designed the study; A.R.B. wrote the initial draft of the manuscript; A.R.B., T.L.P., S.S., D.B., J.K., D.W., and M.V.D. enrolled patients in the study; E.D., C.F., R.V., and L.Z. collected and processed patient samples; G.G. and F.L. performed the statistical analysis; T.M.F. maintained the randomization table and distribution of study drugs from pharmacy; and all authors were involved in interpreting the data, reviewing and revising the manuscript, and providing final approval.

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