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Influenza Vaccines in Maintenance Hemodialysis Patients: Does Seroresponse Vary With Different Vaccine Formulations?

Tarek Barbar, Sri Lekha Tummalapalli, and Jeffrey Silberzweig

The COVID-19 pandemic has further highlighted the major role of respiratory illnesses as vaccine-preventable sources of morbidity and mortality for patients on dialysis. Influenza-like illnesses contribute to more than 1,000 excess deaths per year among patients with kidney failure, resulting in a seasonal pattern of mortality.[1] Influenza can cause viral pneumonia, secondary bacterial pneumonias, and multisystem extrapulmonary complications, including heart failure exacerbation.[2] Optimal formulation and timing of influenza vaccinations could decrease the burden of influenza-associated illnesses. Among older adults (>65 years) in the general population, randomized trials have compared a high-dose, trivalent, inactivated influenza vaccine (HD-IIV3; 60 μg of hemagglutinin per strain) to a standard-dose, trivalent, inactivated influenza vaccine (SD-IIV3; 15 μg of hemagglutinin per strain). In a 2014 trial, HD-IIV3 elicited a stronger seroresponse than SD-IIV3, as measured by hemagglutination inhibition (HI) titers, and prevented approximately 1 in 4 influenza illnesses.[3] Serious adverse events were fewer in the HD-IIV3 recipients compared with the SD-IIV3 recipients.[4] This evidence has been extrapolated to the dialysis population. The Advisory Committee on Immunization Practices (ACIP) recommends yearly inactivated or recombinant quadrivalent influenza vaccine (RIV4) for individuals receiving maintenance dialysis.[5] High-dose vaccines are recommended for those receiving maintenance dialysis who are 65 years of age or older.[6] Medicare costs range from ~$20 for standard-dose influenza vaccines to ~$65 for high-dose and recombinant vaccines.[7]

Related Article, p. 309

Although randomized clinical trial evidence comparing influenza vaccine formulations is lacking in the maintenance hemodialysis population, numerous observational studies have sought to address this question.[8] Miskulin et al[9] compared hospitalization and mortality among greater than 9,000 patients at 230 Dialysis Clinic, Inc (DCI) clinics who received different influenza vaccine formulations. During the 2015-2016 season, there were no significant differences in adjusted rates of hospitalizations and mortality in patients receiving HD-IIV3, SD-IIV3, or standard-dose quadrivalent influenza vaccine (SD-IIV4). During the 2016-2017 season, HD-IIV3 was associated with a significant reduction in hospitalization compared with SD-IIV4 (adjusted hazard ratio, 0.93 [95% CI, 0.86-1.00]; $P = 0.04$) but no significant difference in death.[9] Another study, by Butler et al,[10] compared influenza-like illnesses, hospitalizations, and mortality in 2010-2015 US Renal Data System data among patients who received HD-IIV3 versus SD-IIV3 or SD-IIV4. In addition to adjusting for demographics and comorbidities, the authors accounted for frailty and the receipt of other preventive health services as potential confounders. In contrast to the findings of Miskulin et al, no significant differences in illnesses, hospitalizations, and mortality were observed in the high-dose versus standard-dose groups. Only 2.6% of the study population received HD-IIV3, and it is unknown whether patients deemed at higher risk of adverse influenza-associated outcomes in unobserved ways were more likely to receive it, thereby potentially underestimating its benefits. Research studying the seroresponse to different influenza vaccine formulations in maintenance hemodialysis patients could provide biological plausibility for future studies examining clinical outcomes.

In this issue of *AJKD*, Manley et al[11] study the seroresponse to HD-IIV3, SD-IIV4, or RIV4 in patients receiving maintenance hemodialysis. The authors present a prospective, observational study of 254 patients receiving maintenance hemodialysis during the 2017-2018 influenza season. The study leveraged a natural experiment where different vaccines were used in 4 DCI clinics. Vaccine acceptance was high (98%). One clinic administered HD-IIV3 to all patients, another clinic provided SD-IIV4 to all patients, a third clinic provided RIV4 to all patients, and the fourth clinic provided SD-IIV4 to patients under age 65 and HD-IIV3 to patients age 65 and older.

Seroresponse was examined across 2 dimensions: strength and durability. HI titers were measured from sera collected at 5 different time points: 1 prevaccination (baseline) and 4 postvaccination (months 1, 2, 3, and 4). As the primary outcome, a HI titer of 1:40 or greater was used as a measure of protective seroresponse. A higher threshold of seroprotection, a titer of 1:160 or greater, was assessed as a secondary outcome. Generalized linear models accounted for within-participant correlation and potential confounders including demographics, prior influenza vaccinations, and other measures of dialysis quality.

The results from Manley et al indicate that durability may be the greatest benefit of HD-IIV3. At month 1, patients receiving HD-IIV3 and RIV4 developed robust HI

titers against influenza A strains (H1N1 and H3N2), which were higher than SD-IIV4 HI titers (illustrated in Figures 1-2 of Manley et al). HD-IIV3–induced titers had longer durability and were higher than those elicited by SD-IIV4 and RIV4 at months 3 and 4. Patients receiving HD-IIV3 were more likely to have seroprotection at an HI titer threshold of ≥1:160 at months 3 and 4, compared with those receiving SD-IIV4 and RIV4 (depicted in Figures 3-4 of Manley et al). There was no significant difference in likelihood of HI titers ≥1:40 between the vaccine types. Seroprotection was noted to be higher against influenza A strains (H1N1 and H3N2) than against B strains ($P < 0.001$).

When comparing seroprotection between different age groups (age <65 versus ≥65), the younger group demonstrated higher rates of seroprotection at an HI titer of ≥1:160 compared to the older group against H1N1 (odds ratio, 2.39 [95% CI, 1.44-3.96]; $P < 0.001$) and B strains. There was no significant difference in seroprotection rate against H3N2 across age groups. Assessing whether there was an interaction between age group and vaccine type was limited by the small number of patients receiving SD-IIV4 who were younger than 65 years. Further analyses could also account for presence of immune-modulating medications, which have been associated with lower likelihood of seroresponse to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA vaccines in maintenance dialysis patients.[12]

This study by Manley et al adds a further dimension to this literature by demonstrating the strength and durability of seroprotection elicited by HD-IIV3 compared with SD-IIV4 and RIV4 in the maintenance dialysis population. Patients with kidney failure have impaired immune function related to uremia-associated changes in the innate and adaptive immune system, oxidative stress, intestinal dysbiosis, and premature immunological aging.[13] During the influenza A(H1N1) pandemic in 2009, a study found that patients receiving hemodialysis had a diminished seroresponse to an adjuvanted H1N1 vaccine compared with healthy individuals.[14] Namely, approximately 64% of hemodialysis patients showed a positive response, versus 98% of healthy patients. Nonetheless, the seroresponse improved upon administration of a second dose. This prior work highlights the need for dedicated studies in the hemodialysis population of influenza vaccine immunogenicity and efficacy.

In addition to these promising clinical data in support of HD-IIV3, Manley et al illustrate how dialysis facility protocols can be used as a source of exogenous variation, creating a quasi-experiment that may reduce unmeasured confounding. Ultimately, the infrastructure of large dialysis organizations could be used to conduct a pragmatic cluster-randomized clinical trial comparing high-dose, standard-dose, and recombinant influenza vaccines and their impact on influenza-like illnesses, hospitalizations, and influenza-associated deaths. Given the waning seroprotection seen with SD-IIV4 and RIV4, the timing of vaccine administration could also be evaluated. Embedded pragmatic trials in a dialysis population have been shown to be feasible,[15] although adequate power and data capture of clinical outcomes remain a challenge. Generating additional high-quality evidence of the efficacy and cost-effectiveness of influenza vaccine formulations is a worthwhile goal to decrease influenza-associated morbidity among maintenance hemodialysis patients.

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