A clinical trial of intradermal and intramuscular seasonal influenza vaccination in patients with atopic dermatitis

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Background: Antibody responses to the inactivated seasonal influenza vaccine in patients with atopic dermatitis (AD) have not been carefully characterized.

Objective: The primary objective of this study was to compare antibody responses to intradermal vaccination in participants with moderate/severe AD with those in nonatopic participants. Secondary objectives were to evaluate the effect of route of administration, *Staphylococcus aureus* skin colonization, and disease severity on vaccine response.

Methods: This was an open-label study conducted in the 2012-2013 influenza season at 5 US clinical sites. A total of 360 participants with moderate/severe AD or nonatopic subjects were assessed for eligibility, 347 of whom received intradermal or intramuscular vaccination per label and were followed for 28 days after vaccination. The primary outcome was the difference in the proportion of participants achieving seroprotection (hemagglutination-inhibition antibody titer ≥1:40 on day 28 after vaccination).

Results: Seroprotection rates for influenza B, H1N1, and H3N2 were not different (1) between participants with AD and nonatopic participants receiving intradermal vaccination and (2) between AD participants receiving intradermal and intramuscular vaccination. After intradermal, but not intramuscular, vaccination, participants with AD with *S aureus* colonization experienced (1) lower seroprotection and seroconversion rates and lower hemagglutination-inhibition antibody titer geometric mean fold increase against influenza B and (2) lower seroconversion rates against influenza H1N1 than noncolonized participants with AD.

Conclusion: Participants with AD colonized with *S aureus* exhibited a reduced immune response to influenza vaccination compared with noncolonized participants after intradermal but not intramuscular vaccination. Because most patients with AD are colonized with *S aureus*, intramuscular influenza vaccination should be given preference in these patients. (J Allergy Clin Immunol 2017;139:1575-82.)

Key words: *Atopic dermatitis,* Staphylococcus aureus*, eczema, influenza, vaccination, skin, antibody*

Atopic dermatitis (AD) is the most common chronic skin disease, affecting more than 15% of children and persisting into adulthood in half of these patients.[1,2] Patients with AD have a unique predisposition to infection by *Staphylococcus aureus* and herpes simplex virus.[3-6] The National Institutes of Health/National Institute of Allergy and Infectious Diseases–funded Atopic Dermatitis Research Network (ADRN) aims to elucidate mechanisms underlying cutaneous and systemic immunity in patients with AD and to identify biomarkers that characterize groups of patients with AD with and without a history of staphylococcal colonization, history of eczema herpeticum, or both.

Intradermal vaccination in normal skin is more immunogenic than intramuscular vaccination.[7-9] The current knowledge of

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Abbreviations used
AD: Atopic dermatitis
ADRN: Atopic Dermatitis Research Network
GMFI: Geometric mean fold increase
GMR: Geometric mean ratio
HAI: Hemagglutination-inhibition
NJH: National Jewish Health
OR: Odds ratio
SASC: *Staphylococcus aureus* skin colonization
SEB: Staphylococcal enterotoxin B
TSST-1: Toxic shock staph glococol 1

antibody responses to intradermal administration of antigens in patients with AD is unknown, but more than 6 million doses of intradermal seasonal influenza vaccine (personal communication, Dr M. Decker, Sanofi Pasteur) have been administered since it was licensed in the United States in 2011.[10]

In the current study the primary analysis compared the antibody responses to intradermal vaccination against influenza strains B, H1N1, and H3N2 in patients with AD compared with those in nonatopic participants. As secondary analyses, we also compared the antibody responses of participants with moderate/severe AD receiving intradermal versus intramuscular vaccination, antibody responses in participants with AD with and without *Staphylococcus aureus* skin colonization (SASC), sex, and race.

METHODS

Participants aged 18 to 64 years received open-label vaccination at 5 centers (National Jewish Health [NJH], University of Rochester, Oregon Health & Science University, Boston Children's Hospital, and Northwestern University) on approval from their institutional review boards. Participants with AD had active moderate/severe skin lesions per the Rajka-Langeland Severity Score.[11] Nonatopic participants had no personal or first-degree family history of AD, asthma, allergic rhinitis, or food allergy. See the Methods section and Table E1 in this article's Online Repository at www.jacionline.org for inclusion/exclusion criteria and classification method of race and ethnicity.

Participants with moderate/severe AD (hereafter referred to as AD) were randomized 1:1 to receive intradermal or intramuscular administration of the 2012-2013 seasonal influenza vaccine.[12] At NJH, nonatopic participants were randomized 3:2 to intradermal or intramuscular vaccination until 23 participants received intramuscular vaccination. Thereafter, the remaining nonatopic participants at NJH received intradermal vaccination. All nonatopic participants at the remaining centers received intradermal vaccination. The 23 nonatopic participants receiving intramuscular vaccination served as a reference group for exploratory analyses (Fig 1). Stratified block randomization was used to balance sex and AD severity between vaccination routes by clinical site.

Hemagglutination-inhibition (HAI) antibody titers and influenza B–specific IgG_1, IgG_2, IgG_3, and IgA by means of ELISA were measured before vaccination and 28 ± 7 days after vaccination. IgE and IgG antibodies specific for toxic shock staph glococol 1 (TSST-1) and staphylococcal enterotoxin B (SEB), total IgE levels, and complete blood counts were measured before vaccination. Prior measurements of total IgE levels and complete blood counts obtained within 30 days of vaccination were used, if available.

S aureus cultures of skin swabs had been obtained previously in nonatopic participants and participants with AD as part of the ADRN Registry. In participants with AD, skin swabs were collected from the participant's most severe AD lesion and also from adjacent nonlesional skin. Methodologies of *S aureus* culture and laboratory assays are presented in the Methods section in this article's Online Repository. Sensitivity analyses involving SASC were also performed for 2 subgroups: (1) including only participants who had an *S aureus* culture within 30 days of the vaccination date or (2) including only participants with moderate disease.

For each of the 3 influenza strains, the primary outcome was the proportion of participants achieving seroprotection (HAI antibody titer ≥ 1:40 on day 28 after vaccination). Secondary outcomes included the geometric mean fold increase (GMFI) in HAI antibody titers from baseline to day 28 after vaccination and the proportion of participants experiencing seroconversion (≥4-fold increase in baseline HAI antibody titers on day 28 after vaccination). Participants with baseline HAI titers of 1:40 or greater for a particular strain were excluded from the analyses for that particular strain, and counts of those not seroprotected at baseline per strain are included in Fig 1.

Demographics and baseline characteristics were compared by using the Fisher exact test for categorical measures and the Wilcoxon 2-sample test for continuous measures. Binary rates are presented as proportions and exact 95% CIs, and comparisons are summarized by using odds ratios (ORs) and the Fisher exact test. Continuous variables were summarized with unadjusted geometric means and 95% CIs. Robust regression models using M-estimation were used to analyze continuous outcomes of $\log_2$ HAI titer fold increase and $\log_{10}$ influenza B-specific IgG_1, IgG_2, IgG_3, and IgA levels. Geometric mean ratios (GMRs) were defined as the ratio of geometric means of one group to the other. Multiple imputation methodology was used for influenza B–specific IgG_1, IgG_2, IgG_3, and IgA levels outside the limits of quantification. Baseline $\log_{10}$ IgE and IgG antibodies specific for TSST-1 and SEB were analyzed by using left-censored Tobit regression models. All continuous models adjust for age and sex. The individual effects of SASC and disease severity were analyzed by using an R_n^2 test[13] from a similar robust regression model, as described above, that included both SASC and disease severity as covariates.

Sample size calculations were based on H3N2 data from our previous ADRN Influenza Vaccine Pilot Study (NCT01518478)[14] with the intradermal 2011-2012 seasonal influenza vaccine,[15] in which 57% and 85% of participants with AD and nonatopic participants, respectively, achieved seroprotection after vaccination. Because no adjustments were made for multiple comparisons among groups or endpoints, all *P* values reported are descriptive/hypothesis generating except for the (inferential) *P* value testing H3N2 seroprotection of participants with AD vs nonatopic participants among those given intradermal vaccination.

By using the Fisher exact test and assuming a 2-sided significance level of .05, a sample size of at least 62 nonatopic participants and 62 participants with AD who were not seroprotected at baseline was necessary to detect a 28% difference in seroprotection rates between participants with AD and nonatopic participants receiving intradermal vaccination with at least 90% power. For secondary objective analyses, we similarly chose a sample size of at least 62 participants with AD without seroprotection at baseline to receive intramuscular vaccination.

RESULTS

Demographics and baseline characteristics

Of 360 candidates screened, 347 were enrolled and vaccinated, and 336 were evaluable in the per-protocol analysis (participants with AD receiving intradermal vaccine, 100; participants with AD receiving intramuscular vaccine, 102; nonatopic participants receiving intradermal vaccine, 111; and nonatopic participants receiving intramuscular vaccine, 23; Fig 1). A total of 136 (43%) of the 313 participants in the 3 main study groups (participants with AD receiving intradermal vaccine, participants with AD receiving intramuscular vaccine, and nonatopic participants receiving intradermal vaccine) were enrolled and vaccinated at NJH. The proportions of the 3 main study groups enrolled at each site were similar across all sites, except Boston Children's Hospital, where nonatopic participants given intradermal vaccination comprised 65% of its enrollment. Among participants receiving intradermal vaccination, the age of the nonatopic group was higher than that of the AD group (Table I). The AD group