

Letter to the Editor

Immune response to varicella vaccine in children with atopic dermatitis compared with nonatopic controls

To the Editor:

Patients with atopic dermatitis (AD) are predisposed to severe cutaneous viral infections including herpes (eczema herpeticum [EH]) and vaccinia (eczema vaccinatum).¹ A recent study in the Journal reported that EH was seen primarily in children with severe AD who are highly atopic.² This is consistent with reports demonstrating that EH is associated with filaggrin mutations and thymic stromal lymphopoietin gene variants.^{3,4} To understand better the systemic viral immune response in young children with AD, we studied their immune response to varicella-zoster virus (VZV) vaccine, which is routinely administered to this age group. Peripheral blood T cells in AD are polarized to a T_H2 phenotype. T_H1 responses are critical for an effective antiviral response, whereas T_H2 cells may hinder an effective response. Protection against infection is mediated both by neutralizing antibodies and by cytotoxic T cells. We hypothesized that this T_H2 skewing in patients with severe AD might impair their ability to mount effective responses to VZV immunization. Although previous studies found the VZV vaccine to be effective in mild AD, the effectiveness of VZV vaccine in a moderate and severe population has not been studied.⁵

Subjects age 1 to 3 years with moderate to severe AD or with no history of atopy, who had received the VZV vaccine, were seen for 1 visit at Children's Hospital Boston or National Jewish Health in Denver. Exclusion criteria included previous varicella infection, recent systemic steroid use, and use of antiviral agents within 7 days before immunization. Immunization records were obtained for all subjects. The nonatopic control subjects had no personal or family history of food allergy or AD. Rajka-Langeland severity scores were determined for the subjects with AD. Immune responses were assessed at 1 time point between 2 to 8 weeks after VZV vaccination. Although the original intent was to obtain immune assessments 3 weeks postvaccination, the postvaccination window was extended (2-16 weeks) to enhance recruitment. Laboratory studies included complete blood count, specific IgE testing (ImmunoCAP; Phadia AB, Portage, Mich), and assessments of VZV-specific responses. Because of quantity of blood or technical issues, not all studies were performed on all subjects. This study was approved by the Children's Hospital Boston Committee on Clinical Investigation and by the National Jewish Health Institutional Review Board. Data related to side effects from naturally occurring chicken pox and varicella vaccination were extracted from the Atopic Dermatitis Vaccinia Network Registry.²

ELISPOT assays were used to measure the frequency of VZV-specific IFN- γ -producing PBMCs expressed as spot-forming cells (SFCs) per 10⁶ PBMCs.⁶ PBMCs were stimulated with VZV, mock-infected control antigen, or phytohemagglutinin in microtiter plates precoated with anti-IFN- γ mAbs. SFCs were counted with an ImmunoSpot Analyzer (Cellular Technology Limited, Cleveland, Ohio). T-cell subset studies have shown that this assay detects primarily VZV-specific CD4⁺ T cells, which is consistent with the stimulant being an inactivated antigen that is preferentially processed for MHC class II presentation.⁶ Levels of class-specific VZV-specific antibodies and total antibody levels were measured by using an ELISA.

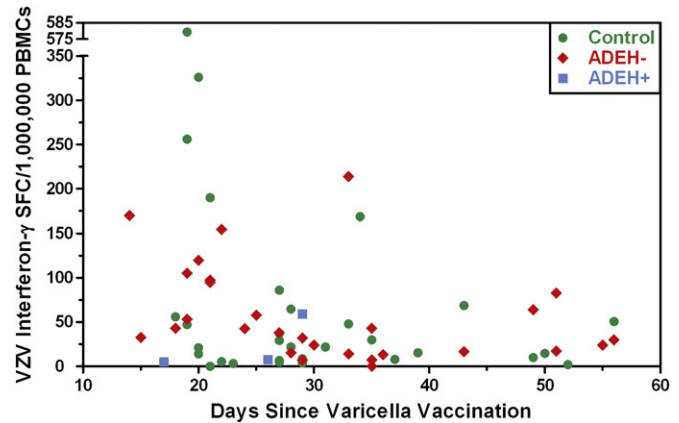


FIG 1. IFN- γ SFCs after VZV stimulation as measured by ELISPOT in controls versus subjects with AD.

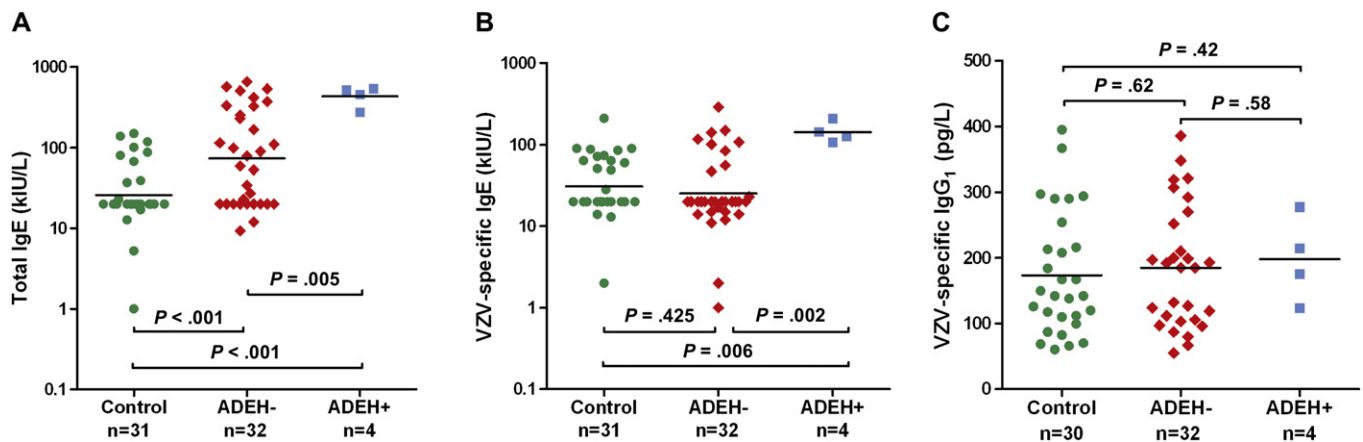
All immune response values were log₁₀-transformed to satisfy statistical assumptions. ELISPOT values were compared among groups with analysis of covariance models, adjusting for background levels and time (in days) since vaccination. ELISA values were compared among groups with ANOVA techniques with pairwise comparisons used when appropriate. Because this study was exploratory and the results descriptive, no adjustments for multiple testing were used. All analyses were performed with SAS version 9.1.3. (SAS Institute, Inc, Cary, NC)

Thirty-seven subjects with AD and 31 control subjects were enrolled. Sex, race, and ethnicity of the subjects were similar between groups (see this article's Table E1 in the Online Repository at www.jacionline.org). Of the subjects with AD, 30 had moderate AD and 7 had severe AD as defined by Rajka-Langeland. Four subjects had a history of EH (ADEH+).

VZV-stimulated IFN- γ SFCs values were lower as time since vaccination increased (Fig 1). Maximum responses were observed between 2 and 4 weeks postimmunization where geometric mean IFN- γ SFCs were similar between subjects with AD and control subjects (54.3 vs 37.8, respectively). Two of the 3 ADEH+ subjects assessed had low levels (6.0 and 10.6 SFC/10⁶ PBMCs). Mean $\pm$ SD days postvaccination were similar for subjects with AD (31.7 $\pm$ 14.20) versus control subjects (30.0 $\pm$ 10.66). Geometric mean phytohemagglutinin-stimulated IFN- γ production (ELISPOT) was lower in subjects with AD than controls (340 vs 542 SFC/10⁶ PBMCs; see this article's Fig E1 in the Online Repository at www.jacionline.org; $P = .018$).

As expected, subjects with AD without EH (ADEH-) had higher total IgE levels than controls ($P < .001$), and ADEH+ subjects had the highest IgE levels (Fig 2, A; $P = .005$ compared with ADEH-). Of note, ADEH+ subjects had higher levels of VZV-specific IgE than controls ($P = .006$) or ADEH- subjects ($P = .002$; Fig 2, B). Similar levels of VZV-specific IgG were found in all groups (Fig 2, C).

This is the first report that ADEH+ subjects make high levels of VZV-specific IgE after VZV vaccination. The high total IgE production (stronger T_H2 skewing) of ADEH+ subjects may contribute to the high VZV-specific IgE. Recent studies have emphasized the role of virus-specific IgE in the development and exacerbation of asthma.⁷ In these studies, cross-linking of the



Note: Horizontal lines in dot plots represent geometric means (A and B) and mean values (C).

FIG 2. Total IgE level (A), VZV-specific IgE (B), and VZV-specific IgG (C) in control subjects and subjects with AD without a history of EH (ADEH-) and with a history of EH (ADEH+).

high-affinity IgE receptor on lung dendritic cells by virus-specific IgE resulted in a T_H2 response. We postulate that a similar mechanism could occur in cutaneous dendritic cells in patients with AD. Postvaccination specific IgE responses to tetanus and diphtheria toxoids have been previously reported, and in 1 study, high rates of local side effects were found.^{8,9} Our current data raise the possibility that virus-specific IgE could result in adverse responses to future vaccinations or exposures. Of note, in the Atopic Dermatitis Vaccinia Network Registry, ADEH+ subjects reported more adverse effects from primary VZV infection or vaccination than nonatopic subjects (unpublished data, Zaccaro, Atopic Dermatitis Vaccinia Network, May 2010).

Subjects with AD have an increased susceptibility to viral skin infections, and we anticipated that cell-mediated immunity to VZV vaccine would be reduced in subjects with moderate to severe AD. However, we found that the control subjects and subjects with AD had similar cellular responses. Future studies of varicella may yield larger differences by enrolling more ADEH+ patients. We were surprised to see the wide variation in cellular responses in both groups and the effect of the timing of the blood draw after VZV vaccination.

In summary, controls and subjects with AD had similar cell-mediated responses to the VZV vaccine. However, ADEH+ subjects demonstrated higher VZV-specific IgE, a possible risk factor for adverse effects to booster doses of vaccine or to wild-type VZV exposure.

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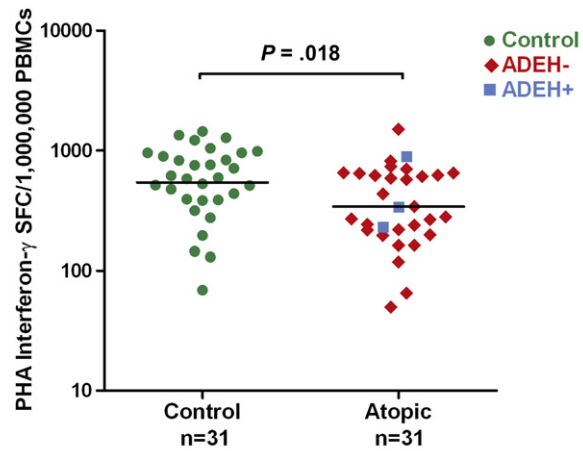
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Note: Horizontal lines in dot plot represent geometric means.

FIG E1. IFN- γ SFCs after PHA stimulation as measured by ELISPOT in controls versus subjects with AD.

TABLE E1. Overall demographics, completed subjects only

	Control, N = 31	AD, N = 37
Clinical site, n (%)		
Children's Hospital Boston	13 (41.9)	25 (67.6)
National Jewish Health	18 (58.1)	12 (32.4)
Age (mo)		
Mean (SD)	13.7 (0.83)	15.4 (3.23)
Median (minimum, maximum)	13.5 (12.5, 16.6)	13.7 (12.3, 25.1)
Sex, n (%)		
Male	19 (61.3)	27 (73.0)
Ethnicity, n (%)		
Hispanic or Latino	11 (35.5)	8 (21.6)
Race, n (%)		
Black	11 (35.5)	11 (29.7)
White	16 (51.6)	17 (46.0)
Other	4 (12.9)	9 (24.3)
Time since vaccination (d)		
Mean (SD)	30.0 (10.66)	31.7 (14.20)
Median (minimum, maximum)	27.0 (18.0, 56.0)	29.0 (14.0, 84.0)