Published in final edited form as:

J Allergy Clin Immunol. 2010 December ; 126(6): 1306–1307.e2. doi:10.1016/j.jaci.2010.08.010.

Immune response to Varicella vaccine in children with atopic dermatitis compared to non-atopic controls

Lynda Schneider, MD¹, Adriana Weinberg, MD², Mark Boguniewicz, MD^{2,3}, Patricia Taylor, NP³, Hans Oettgen, MD, PhD¹, Lisa Heughan, BS¹, Daniel Zaccaro, MS⁴, Brian Armstrong, MPH⁴, Aaron Holliday, BS⁴, and Donald Y M Leung, MD, PhD^{2,3}

¹Children's Hospital, Boston, Massachusetts

²University of Colorado, Denver, Colorado

³National Jewish Health, Denver, Colorado

⁴Rho Inc, Chapel Hill, North Carolina

Abstract

Atopic dermatitis subjects and controls had similar cellular immune responses to Varicella vaccine. Atopic dermatitis subjects with a history of eczema herpeticum made high levels of Varicella specific IgE.

Keywords

Atopic dermatitis; IgE; Varicella specific IgE; Varicella vaccination; eczema herpeticum

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} In order to better understand 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 Th2 phenotype. Th1 responses are critical for effective anti-viral response while Th2 cells may hinder an effective response. Protection against infection is mediated both by neutralizing antibodies and by cytotoxic T cells. We hypothesized that this Th2 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

© 2010 American Academy of Allergy, Asthma and Immunology. Published by Mosby, Inc. All rights reserved.

Corresponding Author: Lynda Schneider, MD, Children's Hospital Boston Division of Immunology, 300 Longwood Avenue, Boston, MA 02115, Phone: 617-355-6180, Fax: 617-730-0310, lynda.schneider@childrens.harvard.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 one visit at Children's Hospital Boston (CHB) or National Jewish Health (NJH) in Denver. Exclusion criteria included previous varicella infection, recent systemic steroid use, and use of anti-viral agents within 7 days prior to 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 one time point between 2 to 8 weeks after VZV vaccination. Although the original intent was to obtain immune assessments 3 weeks post-vaccination, the post-vaccination window was extended (2 – 16 weeks) to enhance recruitment. Laboratory studies included CBC, specific IgE testing (Phadia ImmunoCAP), and assessments of VZV-specific responses. Due to quantity of blood or technical issues, not all studies were performed on all subjects. This study was approved by the CHB Committee on Clinical Investigation and by the NJH Institutional Review Board. Data related to side effects from naturally occurring chicken pox and varicella vaccination were extracted from the Atopic Dermatitis Vaccinia Network (ADVNI) Registry.² ELISPOT assays were used to measure the frequency of VZV-specific interferon- γ (IFN- γ) producing peripheral blood mononuclear cells (PBMCs) expressed as spot forming cells (SFCs) per 10^6 PBMCs. PBMCs were stimulated with VZV, mock-infected control antigen, or phytohemagglutinin (PHA) in microtiter plates pre-coated with anti-IFN- γ monoclonal antibodies. SFCs were counted with an ImmunoSpot Analyzer (Cellular Technology). 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 major histocompatibility complex (MHC) class II presentation.⁶ Levels of class specific VZV-specific antibodies and total antibody levels were measured using an enzyme-linked immunosorbent assay (ELISA).

All immune response values were $\log_{10}$ transformed to satisfy statistical assumptions. ELISPOT values were compared among groups with analysis of covariance (ANCOVA) models adjusting for background levels and time (in days) since vaccination. ELISA values were compared among groups with analysis of variance (ANOVA) techniques with pairwise comparisons employed when appropriate. As this study was exploratory and the results descriptive, no adjustments for multiple testing were employed. All analyses were performed with SAS[®] version 9.1.3.

Thirty-seven AD and 31 control subjects were enrolled. Gender, race and ethnicity of the subjects were similar between groups (See Table E1 in this article's Online Repository). Of the AD subjects, 30 had moderate AD and 7 had severe AD as defined by Rajka-Langeland. Four subjects had a history of eczema herpeticum (ADEH+).

VZV-stimulated IFN- γ SFCs values were lower as time since vaccination increased (Figure 1). Maximum responses were observed between 2 – 4 weeks post-immunization where geometric mean IFN- γ SFCs were similar between AD versus control subjects (54.3 versus 37.8, respectively). Two of the three ADEH+ subjects assessed had low levels (6.0 and 10.6 SFC/ 10^6 PBMCs). Mean ($\pm$ SD) days post-vaccination was similar for AD (31.7 ± 14.20) versus control (30.0 ± 10.66) subjects. Geometric mean PHA-stimulated IFN- γ production (ELISPOT) was lower in AD subjects than controls (340 versus 542 SFC/ 10^6 PBMCs; Figure E1, $p=0.018$).

As expected, AD subjects without EH (ADEH-) had higher total IgE levels than controls ($p < 0.001$) and ADEH+ subjects had the highest IgE levels (Figure 2, A, $p=0.005$ compared to ADEH-). Of note, ADEH+ subjects had higher levels of VZV-specific IgE than controls ($p=0.006$) or ADEH- subjects ($p=0.002$) (Figure 2, B). Similar levels of VZV-specific IgG were found in all groups (Figure 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 Th2 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 high affinity IgE receptor on lung dendritic cells by virus-specific IgE resulted in a Th2 response. We postulate that a similar mechanism could occur in cutaneous dendritic cells in AD patients. Post-vaccination specific IgE responses to tetanus and diphtheria toxoids have been previously reported and in one 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 ADVN Registry, ADEH+ subjects reported more adverse effects from primary VZV infection or vaccination than non-atopic subjects. (unpublished data)

AD subjects have an increased susceptibility to viral skin infections, and we anticipated that cell-mediated immunity to VZV vaccine would be reduced in moderate – severe AD subjects. However, we found that the control and AD subjects 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 AD subjects 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.

Acknowledgments

This project was funded with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services under Contract Numbers- N01 AI40029 and N01 AI40033 as well as the Clinical Translational Scientific Award UL1 RR025780 (National Jewish) and UL1 RR025758-01 from the National Center for Research Resources, National Institutes of Health, to the Harvard Catalyst Clinical & Translational Science Center (Harvard Catalyst).

We thank the supervising study coordinator Irene Borrás-Coughlin and administrative assistant, Jeanne Testa at Children's Hospital Boston, and the pediatric offices, who referred subjects including Longwood Pediatrics and the Children's Hospital Primary Care Center in Boston, MA.

Abbreviations

AD	atopic dermatitis
EH	eczema herpeticum
VZV	Varicella Zoster virus
CHB	Children's Hospital Boston
NJH	National Jewish Health
ADVN	Atopic Dermatitis Vaccinia Network
IFN	interferon
PBMCs	peripheral blood mononuclear cells
PHA	phytohemagglutinin
SFCs	spot forming cells

References

1. Boguniewicz M, Leung DYM. Recent insights into atopic dermatitis and implications for management of infectious complications. *J Allergy Clin Immunol* 2010;125(1):4–13. PMID: 20109729. [PubMed: 20109729]
2. Beck LA, Boguniewicz M, Hata T, Schneider LC, Hanifin J, Gallo R, et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. *J Allergy Clin Immunol* 2009;124(2):260–269. [PubMed: 19541356]
3. Gao PS, Rafaels NM, Hand T, Murray T, Boguniewicz M, Hata T, et al. Filaggrin mutations that confer risk of atopic dermatitis confer greater risk for eczema herpeticum. *J Allergy Clin Immunol* 2009;124(3):507–513. [PubMed: 19733298]
4. Gao PS, Rafaels NM, Mu D, Hand T, Murrau T, Boguniewicz M, et al. Genetic variants in thymic stromal lymphopoietin are associated with atopic dermatitis and eczema herpeticum. *J Allergy Clin Immunol*. 2010 May 13; (10.1016/j.jaci.2010.03.016).
5. Kreth HW, Hoeger PH. Members of the VZV-AD study group. Safety, reactogenicity and immunogenicity of the live attenuated varicella vaccine in children between 1 and 9 years of age with atopic dermatitis. *European J of Pediatrics* 2006;165:677–683.
6. Smith JG, Liu X, Kaufhold RM, Clair J, Caulfield MJ. Development and validation of a gamma interferon ELISPOT assay for quantitation of cellular immune responses to varicella-zoster virus. *Clin Diagn Lab Immunol* 2001;8(5):871–879. [PubMed: 11527795]
7. Kumar A, Grayson MH. The role of viruses in the development and exacerbation of atopic disease. *Ann Allergy Asthma Immunol* 2009;103(3):181–186. [PubMed: 19788013]
8. Nagel JE, Whie C, Lin MS, Fireman P. IgE synthesis in Man II. Comparison of tetanus and diphtheria igE antibody in allergic and nonallergic children 1979;63(5):308–314.
9. Mark A, Bjorksten B, Granstrom M. Immunoglobulin IgE responses to diphtheria and tetanus toxoids after booster with aluminium-adsorbed and fluid DT-vaccines. *Vaccine* 1995;13:669–673. [PubMed: 7668036]

Figure 1. Interferon- γ Spot Forming Cells after VZV stimulation as measured by ELISPOT in controls versus atopic dermatitis subjects

Figure 2. Total IgE level (A), VZV-specific IgE (B) and VZV-specific IgG (C) in control and atopic dermatitis subjects without a history of eczema herpeticum (ADEH-) and with a history of eczema herpeticum (ADEH+)