Letter to the Editor

Immune Response to a Refrigerator-Stable Zoster Vaccine

We wish to correct some errors made by Gilderman et al. in their article entitled “A Double-Blind, Randomized, Controlled, Multicenter Safety and Immunogenicity Study of a Refrigerator-Stable Formulation of Zostavax,” published in Clinical and Vaccine Immunology (1).

(i) They cite reference 19 as demonstrating that Zostavax decreased the frequency of herpes zoster (HZ) and postherpetic neuralgia. The study cited did not utilize Zostavax and did not have efficacy as an endpoint (2).

(ii) In Materials and Methods, they cite reference 23 in their article as a source for statements about “assays correlated with vaccine-induced protection.” Such studies were not undertaken in the study referenced (4). The authors likely meant to reference the 2008 article in The Journal of Infectious Diseases (JID) by Levin et al. (3).

(iii) If the authors meant to cite the Levin et al. JID 2008 reference, we do not believe it is possible for the authors to conclude from that publication that “the immune response measured by gpELISA [glycoprotein enzyme-linked immunosorbent assay], in terms of postvaccination geometric mean titer (GMT) and the geometric mean rise (GMR) in the VZV [varicella-zoster virus] antibody titer from the baseline to the period postvaccination, correlated best with protection against HZ.” The information pertinent to this issue in the JID 2008 article (3) is in Table 3, which lists many correlations between immune responses and the occurrence of HZ in the large pivotal trial of an HZ vaccine. The data provided in that table do not identify VZV-specific antibody as the “best correlate” for immunity postvaccination, and the JID 2008 paper clearly states that a surrogate marker of threshold for immunity was not identified. Furthermore, data on the relationship of GMR to HZ, referred to by Gilderman et al., are not provided in this paper.

We believe that these corrections are important because the Gilderman et al. article concluded that the two zoster vaccine formulations tested were comparable in immunogenicity (and by implication in clinical efficacy) solely on the basis of gpELISA results, whereas there is strong clinical evidence that VZV cell-mediated immunity (CMI) is necessary and sufficient for the prevention of herpes zoster, and immunologic assessments in several studies, including the Levin et al. JID 2008 article, document that levels of antibody to VZV (e.g., measured by gpELISA) are not correlated with levels of VZV CMI (3).

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Myron J. Levin*
Pediatric Infectious Diseases
University of Colorado—Denver
Building 401
1784 Racine Street
Aurora, Colorado 80045

Michael N. Oxman
Department of Veterans Affairs
San Diego Healthcare System
San Diego, California

Gary R. Johnson
Jane H. Zhang
Anthony R. Hayward
Adriana Weinberg

Department of Veterans Affairs
Cooperative Studies Program Coordinating Center
West Haven, Connecticut
National Institute of Allergy and Infectious Diseases
Bethesda, Maryland
Departments of Pediatrics, Medicine, and Pathology
University of Colorado—Denver
Aurora, Colorado

*Phone: (303) 724-2451
Fax: (303) 724-2409
E-mail: myron.levin@ucdenver.edu

Authors’ Reply

Thank you for sharing with us the letter submitted by Dr. Levin and colleagues, written in response to the above-mentioned article. In August 2008, we submitted an erratum letter to correct errors in referencing and to remove statements regarding GMR that cited Levin et al. (3) in error, based on an earlier draft of the manuscript. Here, we respond to additional questions raised by Levin et al. concerning the choice of immunologic assay in our study and to provide the rationale for using the gpELISA as a serological marker for immune response to Zostavax, based upon the Shingles Prevention Study (SPS) CMI substudy (3, 5).

As shown in Table 3 of Levin’s article (3), VZV antibody titer measured by gpELISA at 6 weeks postvaccination correlated well with protection from HZ conferred by Zostavax. Additional analyses performed on SPS CMI substudy data, not provided in reference 3 but included in Table 1 below, provide...
further support for use of gpELISA to measure vaccine response.

Cox regression analysis demonstrated that at 6 weeks post-vaccination, both GMT (3) and GMR from baseline (data on file), as measured by gpELISA, correlated well with protection from HZ. Immune responses to vaccination by both VZV-specific gamma interferon enzyme-linked immunospot assay and gpELISA have been shown to increase on a population level (2, 5), with less assay variability in gpELISA. However, these analyses were limited by small numbers of data points in HZ cases, which is not unexpected in a vaccine trial, in which immunogenicity data among cases following vaccination are limited.

We agree with Levin that there is ample evidence that VZV CMI is necessary for prevention of HZ. The correlation between VZV antibody titer as determined by gpELISA and efficacy is presumed to be due to the fact that gpELISA measures T-cell-dependent antibody responses (i.e., CD4+ memory T cells stimulated by vaccination, triggering B-cell antibody production, in addition to expanding the pool of activated T cells). Therefore, gpELISA may reflect a “downstream” measure of the CMI response to Zostavax. We agree, of course, that VZV antibody does not appear to have a direct role in prevention of HZ, and although antibody may not be protective, titers can still be predictive. Antibody may also be a surrogate for a different effector response (i.e., something other than T-cell expansion) that protects against HZ. Additional investigations to advance understanding of VZV memory T-cell, effector T-cell, and antibody responses and protection against HZ would be welcomed.

We also agree that a surrogate marker of a specific threshold for protection against HZ was not identified in the SPS CMI substudy. Pivotal vaccine efficacy trials often have not demonstrated such surrogate markers of vaccine protection. However, when surrogacy is lacking, correlates of protection may serve as the foundation for subsequent immunogenicity studies. For clinical trials evaluating the comparability of vaccine formulations, concomitant administration with other vaccines, and use in certain subgroup populations, gpELISA is an attractive and appropriate assay for measurement of Zostavax response. There is a strong correlation with vaccine efficacy against HZ; this assay is practical for use in a variety of clinical trial settings (testing performed on serum and not peripheral blood mononuclear cells), and the magnitude of postvaccination response, combined with low assay variability, allows for discrimination of responses between study populations with a high degree of confidence, despite the fact that populations have high baseline titers (1–4). Therefore, we stand by the utility and relevance of gpELISA as reported in our article.

Thank you once again for your time and consideration.

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Larry I. Gilderman
University Clinical Research
1150 N. University Dr.
Pembroke Pines, Florida 33024

Ivan S. F. Chan
Clinical Biostatistics
Merck Research Laboratories
Malisuto UG1CD-38
P.O. Box 1080
North Wales, Pennsylvania 19454

Jeffrey Silber*
Infectious Disease & Vaccine Clinical Research
Merck & Co., Inc.
P.O. Box 1000, Mailstop UG1CD-38
North Wales, Pennsylvania 19454

*Phone: (267) 305-7963
Fax: (267) 305-6431
E-mail: jeffrey_silber@merck.com

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TABLE 1. Summary of VZV antibody titers determined by gpELISA at 6 weeks postvaccination in the SPS CMI substudy

| Endpoint | Outcome | VZV group (n = 691) | Placebo group (n = 704) |
|----------|---------|---------------------|------------------------|
|          | No. of patients | Value* (95% CI) | No. of patients | Value* (95% CI) |
| GMT      | Developed HZ | 9 | 271.9 (161.9–456.7) | 23 | 181.6 (133.5–246.9) |
|          | Did not develop HZ | 658 | 478.4 (444.6–514.7) | 661 | 296.2 (273.3–321.1) |
| GMR      | Developed HZ | 9 | 1.1 (0.9–1.4) | 23 | 0.9 (0.8–1.1) |
|          | Did not develop HZ | 646 | 1.7 (1.6–1.8) | 650 | 1.0 (1.0–1.0) |

* GMT or GMR, in accordance with the indicated endpoint.