CORRESPONDENCE

Antibody Production in Response to Hepatitis B Surface Antigen in a Combination Hepatitis A/Hepatitis B Vaccine

To the Editor—It was with interest that we read the study by Frey et al. [1], which describes a randomized trial in which 3 manufacturing consistency lots of a combined hepatitis A and B vaccine were compared with the corresponding monovalent vaccines. The authors observed a nonsatisfactory response to the hepatitis B component in the combined vaccine. We are concerned that this report may be misleading, because SmithKline Beecham is mentioned on 2 occasions in the report in either misleading or inaccurate statements. The first instance is in the last paragraph of the introduction [1, page 2019]. As it is written, the reader may incorrectly infer that the vaccine used in this trial was Twinrix (hepatitis A inactivated and hepatitis B [recombinant], SmithKline Beecham Biologicals, Rixensart, Belgium). In fact, the product under discussion in the article was an unnamed combination hepatitis A and B vaccine, developed by Merck & Co. and tested in a 2-dose schedule. In the Materials and Methods section, it is incorrectly stated that RECOMBIVAX HB/H-B-VAXII is manufactured by SmithKline Beecham [1, page 2019], whereas, in fact, it is manufactured and distributed by Merck & Co.; SmithKline Beecham Biologicals manufactures Engerix-B (hepatitis B vaccine [recombinant]).

The above statements might lead to the misconception that interference with the hepatitis B response may occur after administration of any combined hepatitis A and B vaccine. However, there are sufficient published data to demonstrate that SmithKline Beecham Biologicals’ combined hepatitis A and B vaccine, Twinrix, administered on a 0-, 1-, 6-month schedule, induces a strong immune response to both vaccine components. Pooled data from 6 pivotal clinical trials [2] carried out in young adults demonstrated high seroprotection rates and geometric mean titers (GMTs) against hepatitis B after vaccination with Twinrix (on a 0-, 1-, and 6-month schedule), as is shown in table 1.

Additionally, in a US study conducted in adults (more than half were >40 years old), the immunogenicity of Twinrix (administered as a 3-dose series) was compared with separate injections of the corresponding monovalent products. A better immune response to the hepatitis B component was demonstrated in the combined vaccine than in the monovalent vaccine [3]. After the third dose, 95.1% of subjects receiving Twinrix and 92.2% of subjects receiving Engerix-B had protective titers. GMTs were 2099 mIU/mL and 1871 mIU/mL for Twinrix and Engerix-B, respectively.

In conclusion, although Frey et al. [1] did show interference with the hepatitis B response after administration of the combination hepatitis A and B vaccine developed by Merck & Co., SmithKline Beecham Biologicals’ combination hepatitis A and B vaccine, Twinrix, shows no evidence of interference with either component.

Betsy Abraham and Dennis Parenti
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Table 1. Seroprotection rates and geometric mean titers (GMTs) against hepatitis B after vaccination with Twinrix on a 0-, 1-, and 6-month schedule.

<table>
<thead>
<tr>
<th>Time</th>
<th>No. of subjects tested</th>
<th>Seroprotection, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>GMT, mIU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>768</td>
<td>33.7</td>
<td>10</td>
</tr>
<tr>
<td>Month 2</td>
<td>759</td>
<td>83.9</td>
<td>62</td>
</tr>
<tr>
<td>Month 6</td>
<td>755</td>
<td>96.7</td>
<td>236</td>
</tr>
<tr>
<td>Month 7</td>
<td>741</td>
<td>99.3</td>
<td>4814</td>
</tr>
</tbody>
</table>

NOTE. Twinrix is a hepatitis A inactivated and hepatitis B (recombinant) vaccine manufactured by SmithKline Beecham Biologicals, Rixensart, Belgium. <sup>a</sup> Percentage of subjects with anti-hepatitis B surface antigen titers >10 mIU/mL.

References

Reply

To the Editor—The following clarification is in response to the letter by Abraham and Parenti [1], from SmithKline Beecham (Collegeville, PA) in regard to our December 1999 article in the Journal [2].

In the last paragraph of the introduction, Twinrix (SmithKline Beecham Biologicals, Rixensart, Belgium) was mentioned as a positive example, indicating that hepatitis A and hepatitis B vaccines could be given in one injection. It was not the authors’ intention to make the reader think that this study was undertaken using Twinrix. This would have been clarified in the Materials and Methods section, under Vaccines, but, unfortunately, SmithKline Beecham was listed after we mentioned the RECOMBIVAX HB/H-B-VaxII vaccine product. This in-
formation was published in an erratum in the February issue of the Journal [2]. This is an obvious error, because the study, funded by Merck & Co., used the Merck & Co. product RECOMBIVAX HB/H-B-VaxII. The Discussion section discussed only the use of RECOMBIVAX HB/H-B-VaxII as a 2-dose regimen. It was not our intent to suggest that the Twinrix product did not stimulate a good immunologic response. We regret any confusion that this may have caused for the reader, and we certainly regret the concerns that it has caused for SmithKline Beecham and Merck & Co.

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Lack of Evidence of *Borrelia* Involvement in Alzheimer’s Disease

To the Editor—The etiology of Alzheimer’s disease (AD), the most prevalent cause of dementia in the elderly, is unknown. Various published reports have either supported or contradicted the possibility that *Borrelia* organisms have a role in the etiology of AD [1–5]. Here we present the results of our investigation, using polymerase chain reaction (PCR) analysis, of evidence of *Borrelia* infection among patients with AD.

Brain specimens from 15 patients with AD and 15 age- and sex-matched controls were obtained from the Johns Hopkins University Alzheimer’s Disease Research Center (Baltimore; National Institutes of Health grant AG 05146). The pathological diagnosis of AD followed the recommendations of the Consortium to Establish a Registry for Alzheimer’s Disease [6]. The mean ages of patients with AD and controls were 79 years (range, 56–93 years) and 79 years (range, 59–93), respectively. Autopsies were performed ≈19 h after death. Specimens were stored at −80°C.

DNA was extracted from a 50-mg piece of tissue from each specimen using the QIAamp Tissue Kit (Qiagen, Valencia, California). For amplification of *Borrelia* DNA, 1 pair of oligonucleotide primers was selected (5’-biotin)-GGCGGCCACCTTAAACA-CTTAGCTT-3’ and 5’-GGGAAAGCAGAATCCTGCTGGTC- AA-3’) that produces a 153-bp product from the 16S ribosomal gene from the *Borrelia* genus. The 16S gene primers are able to amplify *B. burgdorferi sensu stricto*, *B. garinii*, *B. afzelii*, *B. andersonii*, *B. turdi*, *B. hermsii*, and *B. anserina*. An internal control (IC), constructed by using the *Borrelia* primers extended on their 3’ ends to amplify a section of the pBR322 vector, was included in each amplification reaction tube. An IC probe binding sequence was selected, and the length of the amplified product was designed to be ≈50 bp longer than the *Borrelia* amplicon.

The PCR analysis was performed in a mixture of 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 3.0 mM MgCl₂, 200 μM deoxynucleoside triphosphates, 2.5 U Taq polymerase, 0.4 μM of each *Borrelia* primer, 500 copies of IC, 25 μg/mL isosporalen-10, 2.5 mg/mL bovine serum albumin, and 10% glycerol in a total volume of 50 μL. After adding 5 μL of the extracted sample, the reaction tubes were incubated in a thermal cycler. An initial denaturation period of 4 min at 95°C was followed by 35 cycles of 95°C for 30 s, 69°C for 30 s, and 72°C for 1 min. Incubation concluded with a final extension period of 5 min at 72°C.

*Borrelia* PCR analysis was performed in triplicate on the extracted DNA from the frontal, temporal, and occipital lobes of 10 patients with AD and 14 controls and was performed in sextuplicate on extracted DNA from 5 patients with AD and 1 control. We inoculated 18 samples, from guinea pig brains, with *B. burgdorferi* strain LP3 as positive controls, and we used

References


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