mococcal isolates from patients with IPD were sent to the National Microbiology Center for serotyping. In the 2000–2002 seasons, when PCV7 was initially not available, and later, when it was available only to a limited extent, PCV7 serotypes caused only 43% of IPD cases in children aged <5 years [3].

The observation that vaccine effectiveness against PCV7-serotype IPD was higher among partially vaccinated children than among fully vaccinated children was not statistically significant and is explained by a single vaccine failure.

We did separate analyses for 2 periods: the 2001–2003 and 2003–2005 epidemiological seasons. The matched OR for occurrence of IPD from all serotypes with at least 1 dose of vaccine was 0.46 (95% CI, 0.13–1.58) in the 2001–2003 seasons and 0.81 (95% CI, 0.39–1.70) in 2003–2005. The matched OR for IPD from non-PCV7 serogroups was 5.58 (95% CI, 0.48–65.0) in 2001–2003 and 6.41 (95% CI, 1.30–31.5) in 2003–2005. These results rule out the confounding effect of temporal changes and suggest a loss of PCV7 effectiveness over time.

Performance of blood cultures for sick children increased in Spain. If more cases of IPD were detected as a result, it is reasonable that these would have been primarily less severe forms. In Navarre, the percentage of cases of occult bacteremia has remained stable, with no significant changes between 2000 and 2005 [3]. In any case, this circumstance has little relevance to the validity of our case-control study [2].

Aristegui et al. [5] analyzed cases from several hospitals in the Basque County and Navarre. Theirs was a hospital-based study that was independent of the active population-based surveillance in Navarre. The IPD incidence among children aged <5 years found in the active population-based surveillance [3] was systematically higher than that estimated by Aristegui and colleagues. We were able to determine the serotype of all cases, with the exception of one strain that could not be revived and another nontypable case [2].

Our conclusion is correct as applied to Navarre and may be of value for other places with similar conditions. We included all cases of IPD detected by active surveillance. The preventive effect of PCV7 against vaccine serotypes is partially neutralized by the risk of IPD from non-PCV7 serogroups, in both relative and absolute terms.

Acknowledgment

Potential conflicts of interest. All authors: no conflicts.

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Clinical Infectious Diseases 2007; 45:1242–3 © 2007 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2007/4509-0022S15.00 DOI: 10.1086/529518

Polymorphisms at Position 245 of HIV Reverse Transcriptase Do Not Accurately Predict the Presence of Human Leukocyte Antigen B*5701

To the Editor—We read with interest the article by Chui et al. [1] supporting the use of screening for polymorphisms at position 245 of HIV reverse transcriptase. The authors propose that this relatively cheap and simple test could be used as an alternative to screening for the HLA-B*5701 polymorphism to ascertain the risk of developing the abacavir hypersensitivity reaction. Following the initial presentation of this data at the 2006 International Conference on Antimicrobial Agents and Chemotherapy, we tested the association between the presence of a polymorphism at position 245 and the presence of the HLA-B*5701 allele in 2 London-based clinic cohorts.

We have used prospective HLA-B*5701 screening prior to commencing abacavir therapy since September 2005 at Chelsea and Westminster Hospital (London, UK) and since April 2006 at St. Mary’s Hospital (London, UK). At both centers, the incidence of abacavir hypersensitivity reaction has decreased since the introduction of this test [2, 3]. As outlined by Chui et al. [1], the HLA class I plays a key role both in immune-mediated hypersensitivity reaction and in exerting selective pressures that shape HIV sequence evolution; codon 245 lies within an HLA-B*5701–restricted epitope, and non–wild-type (i.e., valine) identity was deemed to be an alternative to HLA screening to estimate abacavir hypersensitivity reaction risk.

We analyzed data from 2 groups of patients who had undergone HLA-B*5701 screening and full reverse transcriptase sequencing as part of baseline drug-resistance testing. Of 117 individuals, 64 tested HLA-B*5701 positive, and 53 tested HLA-B*5701 negative. Overall, 37 (57.8%) of 64 HLA-B*5701–negative isolates and 49 (90.7%) of 54 HLA-B*5701–positive isolates had a polymorphism at position 245. Of the clade B samples, 22 (50%) of 44
HLA-B*5701–negative isolates and 35 (89.7%) of 39 HLA-B*5701–positive isolates had a polymorphism at position 245; of the non–clade B viruses, 5 (25%) of 20 HLA-B*5701–negative isolates and 14 (100%) of 14 HLA-B*5701–positive isolates had a polymorphism at position 245. The sensitivity, specificity, and positive and negative predictive values for a polymorphism at position 245 as a marker of the presence of HLA-B*5701 are presented in table 1 for all isolates and for clade B and non–clade B viruses separately. The higher rate of position 245 polymorphisms in HLA-B*5701–positive isolates, compared with HLA-B*5701–negative isolates, was statistically significant by the χ² test (P < .001).

We believe that, particularly for patients with infection due to clade B virus, the sensitivity and specificity of a polymorphism at position 245 is insufficient as a marker for the presence of HLA-B*5701. The low specificity rates would necessitate an HLA-B*5701 test for up to 50% of individuals to avoid their being denied abacavir treatment unnecessarily. Among subjects with infection due to clade B virus, >10% of those individuals with isolates with the HLA-B*5701 allele have wild-type 245 virus; again, in our opinion, this is unacceptably high. The higher sensitivity rates among patients with non–clade B virus may warrant further investigation, because the number of such subjects in our analyses was small. We do not feel that, at present, screening for polymorphisms at position 245 should replace HLA screening.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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References


Reply to Waters et al.

To the Editor—We agree that HIV reverse-transcriptase (RT) codon 245 polymorphisms should not be used to deny abacavir therapy to patients [1]. As has been emphasized, the positive predictive value of the codon 245 test is low [1, 2]; ideally, persons with codon 245 polymorphisms should be screened for HLA-B*5701 prior to abacavir use. Instead, the high negative predictive value of the codon 245 test indicates that persons with wildtype RT 245V are at a substantially reduced risk for the abacavir hypersensitivity reaction. Given the ready availability of HIV RT sequence data (collected during routine drug-resistance testing) examining virus variation at codon 245 could be useful in situations in which HLA testing is limited or cost-prohibitive.

HLA-B*5701 allele prevalence is typically highest among white individuals (∼5%) [3]. However, the prevalence of HLA-B*5701 in the population tested by Waters et al. [1] was ∼10-fold higher (54.7%), which is unprecedented in any unselected population. Waters et al. [1] specifically selected HLA-B*5701–positive individuals, with a random control group of HLA-B*5701–negative individuals for comparison (A. Pozniak, personal communication). Because negative predictive value depends on the characteristics of the population tested [4], the negative predictive value calculated by Waters et al. [1] is accurate only for this highly selected population and is irrelevant for the general population of HIV-infected individuals receiving antiviral drugs. The 2 large, prospective cohorts from which the study subset used in Waters et al. [1] was drawn exhibit a typical HLA-B*5701 allele prevalence of ∼7% [5, 6]. With this HLA-B*5701 prevalence, the negative predictive value in their population, using their reported 92.5% sensitivity, would actually be 99%, broadly similar to that given in our original report [2], and with overlapping confidence intervals.

The proportion of HLA-B*5701–negative individuals with codon 245 polymorphisms is substantially higher than the ∼29% and ∼35% amino acid variability at this codon observed among clade B virus–infected, antiretroviral-naive individuals.

Table 1. Sensitivity, specificity, and positive and negative predictive values for a polymorphism at position 245 as a marker of the presence of HLA-B*5701.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All isolates (n = 117)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>92.5 (81.8–97.9)</td>
</tr>
<tr>
<td>Specificity</td>
<td>42.2 (29.9–55.2)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>57.0 (45.9–67.6)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>87.1 (70.2–96.4)</td>
</tr>
</tbody>
</table>

Clade B virus may warrant further investigation, because the number of such subjects in our analyses was small. We do not feel that, at present, screening for polymorphisms at position 245 should replace HLA screening.

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