Characteristics of Abacavir Hypersensitivity Diagnoses According to HLA-B*5701 Status and Subsequent Abacavir Patch Test Result

E Phillips1, S Staszewski2, J Arritza3, N Fitch3, N Given2 on behalf of the PREDICT-1 Study Team
1Monash University, Perth, Australia; 2Johannes Wolfgang Goethe-Universität, Frankfurt, Germany; 3La Paz Hospital, Madrid, Spain; GlasserSmithKline at Birmingham and Greenford, UK

Introduction

- Hyperkaryocyte (HLA-B) to abacavir (ABC) occurs in approximately 50% of patients, usually within the first weeks of treatment, and necessitates immediate and permanent ABC discontinuation.1
- Clinical presentation is non-specific and includes combinations of symptoms from several categories of organ involvement (fever, skin rash, gastrointestinal [GI], constitutional, respiratory, etc).
- Clinical HSR is defined as the occurrence of rash, constitutional symptoms from several categories of organ involvement (fever, skin rash, gastrointestinal [GI], respiratory, etc) within 6–10 weeks after drug discontinuation.
- All subjects with a positive EPT result were clinically diagnosed with a HSR phenotype.
- Subjects with a positive EPT result were those who developed a presentation consistent with ABC hypersensitivity within 6–10 weeks after drug discontinuation.6

Methods

- PREDICT-1 (ClinicalTrials.gov Identifier NCT00529807) was a large, multi-centred multi-country study that was designed to be able to include at least 7,000 infection-naive patients in order to complete prospective analysis of HLA-B*5701 screening (screening arm) or to a control arm with retrospective HLA-B*5701 screening at enrollment.
- HLAs of HLA-B*5701-positive subjects in the screening arm did not receive ABC in the study. All subjects were screened on an ongoing basis for the development of a HSR phenotype.
- Subjects with a clinical diagnosis of ABC HSR underwent for positive HLA-B*5701 status, as determined by a positive EPT result.
- Clinically diagnosed HSR during the observation period and clinically diagnosed HSR during the observation period were the two co-primary endpoints of the study.
- Post-hoc exploratory analyses were undertaken to assess the relationship between HSR symptoms and HLA-B*5701 status, EPT finding, introduction of a new NNRTI and use of a concomitant PI using a fisher’s exact test.

Results

Table 1: HLA-B*5701 Status and EPT Results in Subjects with Clinically Diagnosed ABC HSR

<table>
<thead>
<tr>
<th>Subjects with clinical HSR diagnosis</th>
<th>HLA-B*5701-positive</th>
<th>HLA-B*5701-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with clinical HSR diagnosis</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with clinical HSR diagnoses</td>
<td>61</td>
<td>26</td>
</tr>
<tr>
<td>Subjects with a positive EPT result</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

- Of patients who had a clinical diagnosis of HSR, 30% (61/203) were HLA-B*5701-positive. All but one of these were EPT-negative.
- Positive results were obtained in 20% (25/123) of cases tested.
- Six HLA-B*5701-positive subjects with a clinical HSR diagnosis gave a positive EPT result.
- All subjects with a positive EPT result were HLA-B*5701-positive.

Figures 1 and 2: Days to Onset of Symptoms for Clinically Diagnosed ABC HSR According to Subsequent EPT Result

- The median time to onset of symptoms was 10 days (IQR 7–15) for HLA-B*5701-positive subjects and 4 days (IQR 1–11) for HLA-B*5701-negative subjects.
- HLA-B*5701-positive subjects had a median time to onset of symptoms of 10 days (IQR 7–15) and HLA-B*5701-negative subjects had a median time to onset of symptoms of 4 days (IQR 1–11).
- HLA-B*5701-positive subjects were more likely to present with a rash and constitutional symptoms, while HLA-B*5701-negative subjects were more likely to present with fever and GI symptoms.

Figures 3 and 4: Combinations of HSR Symptom Categories by Subsequent EPT Result

- For HSR diagnoses that gave negative EPT results, rash and respiratory symptoms were significantly more common in those who acquired a new NNRTI during the study compared with those who did not (fever: 80% [21/26] vs 57% [26/46]; P = 0.0195; respiratory: 77% [20/26] vs 41% [21/51]; P = 0.0045).
- Subjects with clinical HSR diagnoses with a positive EPT result versus only 39% (25/64) of diagnoses that gave a negative EPT result (P = 0.0048).
- Similar, but less compelling results were observed for HSR diagnoses in subjects who were extensively co-infected (P = 0.0392).

Conclusions

- These clinical data from the PREDICT-1 study suggest that patients with immunologically mediated abacavir HSR, as evidenced by carriage of HLA-B*5701 and a positive EPT result:
  - develop symptomatic HSR whereas median onset occurs earlier (though not significantly so) and which presents with a shorter time period (within 3 weeks of abacavir initiation)
  - develop a presentation that is significantly more likely to involve fever and symptoms from at least 3 categories of organ involvement
- However, overlap still exists between HSR symptom categories and time of onset for diagnoses between subjects with positive and negative EPT results, suggesting that ordering the clinical manifestations of HSR can help in identifying HLA-B*5701-positive individuals who might reduce clinical overt-diagnosis but would not eliminate it.

References