Use of the HCP5 single nucleotide polymorphism to predict hypersensitivity reactions to abacavir: correlation with HLA-B*5701

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Objectives: To study the correlation between the HLA-B*5701 allele and the single nucleotide polymorphism in HCP5 (rs2395029).

Patients and methods: All HIV patients naive for abacavir seen at our institution between September 2007 and December 2008 were prospectively screened for HLA-B*5701. HCP5 rs2395029 genotyping was carried out by allelic discrimination using the TaqMan 5′-nuclease assay. High-resolution HLA class I typing was undertaken using sequence-specific primers.

Results: A total of 245 HIV patients were included in the study. A good correlation between HLA-B*5701 and HCP5 was observed (negative and positive predictive values of 100% and 93%, respectively).

Conclusions: The use of HCP5 rs2395029 testing could be as useful as HLA-B*5701 typing to prevent the abacavir hypersensitivity reaction. Given that HCP5 testing is cheaper, less time-consuming and easier to perform than HLA typing, it may confidently replace the latter in clinical settings.

Keywords: abacavir hypersensitivity reaction, SNPs, NRTIs

Introduction

Abacavir is a potent nucleoside analogue reverse transcriptase inhibitor used as part of HIV therapy. About 5%–8% of HIV-infected individuals who initiate abacavir therapy develop a hypersensitivity reaction (HSR) within the first 4–6 weeks of treatment. It generally improves within 24 h following abacavir discontinuation. However, rechallenge with abacavir may result in severe recurrence of symptoms, with increased risk of life-threatening complications and death. A specific allele of the major histocompatibility complex, HLA-B*5701, has been associated with the development of abacavir HSR.1,2 Studies such as PREDICT-1 have demonstrated the benefit of HLA-B*5701 testing prior to considering treatment with abacavir.3 Accordingly, current guidelines recommend the screening of HLA-B*5701 before prescribing abacavir, to minimize the risk of HSR.

Several methodologies are available for HLA-B*5701 testing. The gold standard in HLA typing is the high-resolution sequence-based typing method. The use of this method, however, is limited, given that it requires specialized laboratories, is expensive and is time consuming. An alternative methodology is based on high-resolution genetic testing, which uses a sequence-specific primer (SSP) assay. All of these techniques for HLA genotyping, however, are quite complex and have prompted researchers to consider other strategies to identify patients at risk for developing the abacavir HSR. In this regard, some authors have shown a good correlation between a polymorphism at codon 245 of the HIV-1 reverse transcriptase enzyme and the presence of HLA-B*5701, suggesting that assessment of this polymorphic site may be used as a surrogate for HLA-B*5701.4 However, a recent study has highlighted that this approach does not seem to prevent the abacavir HSR, arguing against its wide use in the clinic.5 Another genetic marker proposed as surrogate of the HLA-B*5701 allele is a polymorphism located within the HLA complex P5 gene, HCP5 rs2395029. This polymorphism was originally found to be in high linkage disequilibrium with HLA-B*5701.6 Few studies so far have explored the potential of HCP5 testing to predict the abacavir HSR. The objective of our study was to examine the correlation between HLA-B*5701 and HCP5 rs2395029 in a relatively large HIV population.

Patients and methods

A total of 245 HIV patients naive for abacavir, seen at our institution between September 2007 and December 2008, were prospectively screened for HLA-B*5701. All gave informed consent for genetic
testing. DNA was extracted from whole blood using the QIAamp DNA Mini kit (Qiagen, Munich, Germany). HCP5 rs2395029 genotyping was carried out by allelic discrimination using the TaqMan 5′-nuclease assay (Applied Biosystems, Foster City, CA, USA). Patients were classified as positive or negative carriers for the HCP5 rs2395029. High-resolution HLA class I typing was undertaken using SSP (SSP HLA DNA typing. One Lambda Inc., Palo Alto, CA, USA). Patients were classified as positive or negative carriers for the HLA-B*5701 allele. The clinical criteria to consider a patient to have abacavir HSR is the development of at least two of fever, rash or diarrhoea within 6 weeks after starting abacavir. Immuno-logical methods to verify abacavir HSR were not used.

### Results

Overall, paired examination of HLA-B*5701 and HCP5 was performed in 245 HIV patients. Eighty percent were male, 72% Caucasian, 12% African and 16% Hispanic. The median age was 40 years (interquartile range: 33–48 years). Fifteen patients carried the HCP5 rs2395029 allele and 14 of them were HLA-B*5701 positive. The sensitivity of the HCP5 rsnp for carrying the HLA-B*5701 allele was 100% (95% confidence interval (CI): 73%–100%) and its specificity was 99% (95% CI: 97%–99%). The negative predictive value was 100% (95% CI: 97%–100%) and the positive predictive value was 93% (95% CI: 66%–99%). All individuals testing negative for HCP5 were HLA-B*5701 negative (Figure 1).

All 14 patients who carried the HLA-B*5701 allele did not start abacavir treatment. Of the remaining 231 patients who were HLA-B*5701 negative, 52 started abacavir treatment. Three subjects discontinued the drug prematurely; none of them fulfilled our criteria for abacavir HSR. Only one of these patients developed a rash 2 months after beginning abacavir therapy, a symptom potentially associated with the abacavir HSR. This patient was HCP5 negative. The only patient positive for HCP5 but negative for HLA-B*5701 was of African origin and carried the *58 allele, which is closely related to the *5701 allele. This patient started abacavir treatment and tolerated the medication well.

### Discussion

The use of abacavir as part of antiretroviral therapy has expanded within the last few years, given its advantageous prescription in co-formulation with zidovudine plus lamivudine (Trizivir®) or lamivudine (Kivexa® or Epzicom®). The major short-term adverse effect associated with abacavir use is the HSR, which may be largely avoided by excluding from therapy patients positive for HLA-B*5701. Due to the complexity of standard methods used for HLA typing, other simpler tests are being eagerly sought. In agreement with preliminary findings from others, our results support that testing of HCP5 rs2395029, which is strongly linked to HLA-B*5701, may provide strong negative and positive predictive values (100% and 93%, respectively). We did not identify any patient negative for HCP5 but positive for HLA-B*5701, a discordance that could result in a risk for developing the abacavir HSR. However, the possibility of discordance between both genetic markers may exist, since the linkage disequilibrium between these two markers is incomplete. Therefore, genetic testing must not replace careful clinical vigilance. The high negative predictive value found for HCP5 rs2395029 in our study (100%) is reassuring and allows us to predict a role for this marker as a tool to avoid the abacavir HSR in clinical settings.

With regard to the possibility of an HSR among patients negative for HCP5, the clinical diagnosis of the abacavir HSR requires the presence of at least two of fever, rash or diarrhoea within 6 weeks after starting abacavir. Only three of our patients negative for HCP5 stopped abacavir treatment prematurely and only one of them developed symptoms potentially attributable to the abacavir HSR. It should be noted, however, that the rash noticed in this patient developed 2 months after beginning abacavir therapy, making it very unlikely that this was a true abacavir HSR. In any case, the patient was advised to stop abacavir due to the rash, which resolved within a few days after stopping abacavir.

In our study, only one discrepancy was found comparing HCP5 and HLA-B*5701 testing. The single patient who was HCP5 positive and HLA-B*5701 negative was of African origin, and he carried the HLA-B*58 allele, which is closely related to allele *5701. Interestingly, this patient tolerated abacavir therapy well. The prevalence of the allele *5701 is lower in Africans than in Caucasians, but those Africans who carry HLA-B*5701 have the same risk of developing abacavir HSR as Caucasians. In our opinion, the negative predictive value of HCP5 testing in Africans may be as good as in Caucasians, but the predictive positive value might be lower due to the higher prevalence of alleles closely related to B*5701, such as B*5702, B*5703 and B*5801. In Caucasians, however, the prevalence of these alleles is very low, and therefore discrepancies between HCP5 and HLA-B*5701 testing must be expected to be low.

In conclusion, HCP5 genotyping showed a good correlation with HLA-B*5701 typing, at least in Caucasian patients. Therefore, the easier and cheaper HCP5 testing could replace HLA-B*5701 testing to prevent the abacavir HSR. Although further confirmation will be useful, in settings where molecular HLA testing is not possible, or not reliable, this simple test would have value. As with all such tests (including HLA testing), its use as a screening tool does not obviate the need for clinical watchfulness and immediate identification of individuals who might be experiencing the abacavir HSR.

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Transparency declarations
None to declare.

References