Phenotypic evaluation of resistance to tipranavir (TPV) in non B subtypes possibly resistant according to genotype interpretation rules

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Background

A higher prevalence of mutations involved in resistance to antiretroviral drugs (ARV) in B subtypes has been described in naive non B subtypes. Several resistance algorithms have been developed to predict resistance to the protease inhibitor (PI) TPV, most of them based on data from clinical studies including a majority of subtype B infected patients, and possibly leading to discordant interpretations. The prevalence of some mutations involved in resistance to TPV in B subtypes is known to be high in naive non-B subtypes, leading to frequent genotypic possible resistance.

Objectives

The number of patients infected with a non B subtype of HIV-1 and under antiretroviral therapy is constantly increasing in France. Such patients experiencing a treatment failure and who could benefit of a salvage therapy including TPV are not uncommon. In order to find an alternative way of testing susceptibility to TPV in PIs experienced patients with a non B subtype, this preliminary study was designed to evaluate the feasibility of a phenotypic measurement of the susceptibility to TPV with PHENOSCRIPT® and to compare genotypic and phenotypic data obtained from PIs naive patients considered as possibly resistant to TPV by genotypic evaluation.

Material and Methods

Between January 2006 and march 2007, 156 samples were received at Laboratoire Pasteur for HIV resistance genotyping. Genotyping and subtyping were performed by RT-PCR and sequencing using the Bayer/Siemens Tugene HIV reagents and software according to the manufacturer’s recommendations. Final mutation profile interpretation was done according to the ANRS 2005 (upgraded in 2006) algorithm including the rules available at that time for TPV. A patient was then considered as resistant to TPV if at least 8 mutations among L10I, L10V, K20M/R/V, L33F, E35D/G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D and I84V were present, and possibly resistant if only 4 to 7 of these mutations were present. 32 successive patients infected by a non B subtype, PI naive and considered as possibly resistant to TPV according to the mutations were present.

Results

Table 1: Impact of HIV-1 diversity on boosted protease inhibitors resistance scores.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>CRF-01_AE</th>
<th>CRF-15_BI</th>
<th>CRF-01_BI</th>
<th>CRF-02_BI</th>
<th>CRF-02_VI</th>
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<th>CRF-01_VI</th>
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<tbody>
<tr>
<td>Mean viral load</td>
<td>4.56 log (3.07 – 5.94)</td>
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<td>4.56 log (3.07 – 5.94)</td>
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<tr>
<td>Mean CD4 count</td>
<td>205 (41-472)</td>
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<tr>
<td>Previous history of ARV therapy</td>
<td>PI naive: 32 (100%)</td>
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<td>ARV naive: 19 (59.4%)</td>
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<td>NNRTI experienced: 13 (40.6%)</td>
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<td>NNRTI experienced: 7 (21.9%)</td>
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Discussion

Dissonance between TPV possible resistance genotype interpretation performed with the initial (2005/2006) algorithm and phenotypic susceptibility obtained with PHENOSCRIPT® is consistent with an excess of sensitivity of rules defined mostly on subtype B to predict susceptibility or resistance in non B subtypes. A comparable study with genotypic and phenotypic results on 57 naive B and non B subtypes demonstrated a 100% agreement of subtype adapted rules for predicting response or resistance for B and non B subtypes, and to evaluate the role of polymorphism mutations in a possible degree of sensitivity to current and new PIs, as well as in possible different ways and kinetics of acquisition of resistance to PIs under therapy.

Conclusions

This small study demonstrates that the absence of subtype-specific genotypic interpretation rules, testing for TPV resistance with phenotypic tests as PHENOSCRIPT® can be an helpful alternative when needed for PIs experienced patients with non-B subtypes. More in vivo and clinical studies are needed with ARV naive non B subtypes infected patients to achieve a comparable level of accuracy and sensitivity in the interpretation of resistance to TPV in B subtypes and non B subtypes, and possibly leading to discordant interpretations.

References


[3] Eurofins-Viralliance - Paris - France

[4] ANRS 2007 interpretation rules (2)(3)(4) defined on a population of more than 80% of B subtypes are not valid for testing non-B subtypes.