Protease, gag and gp41 mutations associated with virological response to PI regimen

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\textsuperscript{1} We enrolled 154 HIV-1 infected antiviral-naive patients initiating a first cART including 2 NRTI associated with DRV(\textsuperscript{N} = 129) or ATV(\textsuperscript{N} = 25).

\textsuperscript{2} 36 patients experienced VF as two consecutive plasma viral load (VL) >50 c/ml following VL <50 c/ml as defined by the absence of reaching VL <50 c/ml six months after cART initiation.

\textsuperscript{3} PR, gag and gp41 regions were amplified (Figure 1) and ultra-deep sequencing (UDS) was performed using Illuma\textsuperscript{®} technology.

\textsuperscript{4} The aim of this study was to assess, in ARV-naive patients, the impact of baseline determinates in PR, gag and gp41 regions on virological response to a first-line PI-based regimen.

\textsuperscript{5} Viral load failure (VF) in patients receiving protease inhibitors (PI)-based regimens is rarely associated with selection of resistance mutations in the protease (PR) region.

\textsuperscript{6} The mechanisms are not well understood. It could be due to a combination of erratic adherence, high genotypic barrier and PI pharmacokinetics or a possible emergence of unknown resistance mutations outside the protease region.

\textsuperscript{7} Alternative mechanisms of resistance to PI have been recently described, showing mutations in the envelope region (gp120) and in the Gag proteasomes (outside cleavage sites) associated with VF (Loi et al., 2015; Coutier et al., 2017).

\textsuperscript{8} We performed Ultra High Resolution Mass Spectrometry and FoldX -1 proteases were modelled using FoldX software.

Background

Patients and methods

Results

Table 1. Patient’s characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Darunavir (\textsuperscript{N} = 128)</th>
<th>Atazanavir (\textsuperscript{N} = 25)</th>
<th>Total (\textsuperscript{N} = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n(%)</td>
<td>54 (42)</td>
<td>14 (56)</td>
<td>58 (38)</td>
</tr>
<tr>
<td>HIV-1 subtype, n(%)</td>
<td>42 (33)</td>
<td>5 (20)</td>
<td>47 (31)</td>
</tr>
<tr>
<td>C315F AG</td>
<td>49 (36)</td>
<td>10 (40)</td>
<td>59 (38)</td>
</tr>
<tr>
<td>Other</td>
<td>38 (29)</td>
<td>10 (40)</td>
<td>48 (31)</td>
</tr>
<tr>
<td>Median HIV-1 viral load, ln\textsubscript{10} c/ml (SQR)</td>
<td>5.03 (4.73-5.43)</td>
<td>4.93 (3.80-5.26)</td>
<td>5.02 (4.55-5.43)</td>
</tr>
<tr>
<td>Median CD4 cell count, \textsubscript{1000} (SQR)</td>
<td>317 (156-423)</td>
<td>340 (192-394)</td>
<td>320 (160-416)</td>
</tr>
</tbody>
</table>

\textbf{Protease}:

- Protease U50 was successful in 138 samples

\textbf{Gag}:

- Gag U50 was successful in 138 samples

\textbf{gp41}:

- gp41 U50 was successful in 134 samples

\textbf{In conclusion}:

- This study, based on patients initiating a first-line DRV on an ATV-based regimen, we identified baseline mutations associated with virological response as well as inside outside as PR, in gag and gp41 regions.

- Mutation I270F of gp41 is localized in cytoplasmic tail, a region playing a role in inhibitory potential of PI's (Rabe et al., 2013).

- Further in vitro studies are needed to better characterize the impact of these new mutations on PI pharmacokinetics susceptibility.

Figure 1. Primer’s localization and size of amplified fragments

Figure 2. 3D structure of mutated HIV-1 protease

Figure 3. Localization of identified gag mutations

Figure 4. Localization of identified gp41 mutations

Conclusion

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