Clinical validation of a genotypic tropism algorithm to guide the therapeutic use of CCR5 antagonists

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Background

- Viral tropism determination is required before considering MVC use.

- The phenotypic determination of tropism is considered the gold standard. This assay was used for screening HIV patients enrolled into MVC registrational trials.

- Phenotypic assays for determining HIV-1 display logistic and technical limitations.

- Genotypic methods based on the analysis of the V3 region may represent a more feasible alternative in the clinical practice.
Genotypic assays and Trofile predict similar MVC response

Virologic response at week 8 in MOTIVATE and A4001029

<table>
<thead>
<tr>
<th>Assay</th>
<th>Tropism</th>
<th>Response (n)</th>
<th>No response (n)</th>
<th>R5 success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trofile</td>
<td>R5</td>
<td>522</td>
<td>273</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>Non R5</td>
<td>48</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td>R5</td>
<td>503</td>
<td>263</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>Non R5</td>
<td>67</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

*McGovern et al., AIDS 2010*

- Clinical experience regarding the accuracy of genotypic tools to guide MVC use is limited.
Objective

Evaluation of the clinical outcome of HIV patients that initiate MVC based on the exclusion of X4 variants using genotypic tools
Patients and Methods

- HIV patients who underwent genotypic tropism assessment at Hospital Carlos III and subsequently initiated MVC at several Spanish clinics.

- Viral tropism was genotypically interpreted as a consensus prediction among geno2pheno\textsubscript{FPR=10\%}, WebPSSM\textsubscript{XR-8} and WebPSSM\textsubscript{SN-6.4} in plasma and PBMC samples.

  \textit{Poveda et al., JAC 2009}

- Viral load, CD4 counts, backbone GSS (genotypic sensitivity score) and treatment strategy were recorded at MVC initiation.

- Virologic (FDA snapshot) and immunological outcomes were evaluated after 6 and 12 months of MVC therapy.
Results

- A total of 62 HIV patients infected with R5 tropic viruses initiated MVC as:

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salvage</strong></td>
<td>n=23</td>
<td>n=19</td>
<td>n=11</td>
</tr>
<tr>
<td><strong>Intensification</strong></td>
<td>n=23</td>
<td>n=18</td>
<td>n=16</td>
</tr>
<tr>
<td><strong>Simplification</strong></td>
<td>n=16</td>
<td>n=14</td>
<td>n=13</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>n=62</td>
<td>n=51</td>
<td>n=40</td>
</tr>
</tbody>
</table>

- Most patients (97%) were infected with clade B viruses.
1. Salvage therapy cohort

- 23 patients

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VL (log HIV-RNA copies/mL)</td>
<td>3.30 [2.46-4.03]</td>
</tr>
<tr>
<td>CD4 counts (cells/mm³)</td>
<td>396 [286-658]</td>
</tr>
</tbody>
</table>

Concomitant Therapy

Backbone GSS

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High virologic response at months 6 and 12

Patients with VL < 50 copies/mL (%)

Baseline (n=23)  Month 6 (n=19)  Month 12 (n=10)

- Virologic failure
  - Baseline: 0%
  - Month 6: 1%
  - Month 12: 0%

- Virological success
  - Baseline: 100%
  - Month 6: 89%
  - Month 12: 90%

*: Another patient discontinued MVC due to intolerance at month 11 and was excluded from this analysis.

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Significant CD4 gain at months 6 and 12

Baseline (n=23)  Month 6 (n=18*)  Month 12 (n=9*)

<table>
<thead>
<tr>
<th>CD4 counts (cells/mm³)</th>
<th>Baseline</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
</table>

*: One patient did not have available CD4 count data.

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2. Intensification cohort

- 23 patients

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with VL&lt;50 copies/mL (%)</td>
<td>74% (17/23)</td>
</tr>
<tr>
<td>VL of remaining 6 patients (log HIV-RNA copies/mL)</td>
<td>2.2 [2.0-2.8]</td>
</tr>
<tr>
<td>CD4 counts (cells/mm³)</td>
<td>145 [103-190]</td>
</tr>
</tbody>
</table>

**Concomitant Therapy**

- RAL: 30
- DRV: 35
- ETR: 9
- Any: 57

**Backbone GSS**

- <2: 4
- ≥2: 96
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Most patients kept or achieved suppressed viremia at months 6 and 12

* Discontinuations:  
- Two patients due to intolerance at month 6.  
- One patient due to voluntary withdrawal after 10 months of therapy.  
- Two patients due to lack of significant CD4 gain after 6 months of therapy
2. Intensification Therapy

Significant CD4 gain at month 6 of therapy

Discontinuations:
- Two patients due to intolerance at month 6 (CD4 gain at month 6: 32 and 78 cells/mm³).
- One patient due to voluntary withdrawal after 10 months of therapy (CD4 gain at month 6: 131 cells/mm³).
- Two patients due to lack of significant CD4 gain after 6 months of therapy (CD4 gain: 1 and -4 cells/mm³).
3. Simplification therapy cohort

- 16 patients

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with VL &lt; 50 copies/mL</td>
<td>81% (13/16)</td>
</tr>
<tr>
<td>VL in the remaining 3 patients (log HIV-RNA cop/mL)</td>
<td>2.5 [1.8-3.5]</td>
</tr>
<tr>
<td>CD4 counts (cells/mm³)</td>
<td>532 [244-681]</td>
</tr>
</tbody>
</table>

MVC replaced:

- NRTI: 63%
- PI: 25%
- NNRTI: 6%
- INI: 6%

Concomitant Therapy

- RAL: 31
- DRV: 63
- ETR: 13
- Any: 88

Backbone GSS

- <2: 31
- ≥2: 69

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
Most patients achieved or kept suppressed viremia at months 6 and 12:

- 4 virologic failures:
  - 1 Non adherence
  - 2 functional bitherapy (RAL+MVC and TDF+MVC)
  - 1 unknown

*: One patient discontinued due to intolerance after 3 months of MVC therapy and was excluded from this analysis.

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No significant CD4 gain

p=NS

Baseline (n=16)

Month 6 (n=12)

Month 12 (n=9)

CD4 counts (cells/mm³)

3. Simplification Therapy

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## Summary

### Virologic response

<table>
<thead>
<tr>
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<th>Month 6</th>
<th>Month 12</th>
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</thead>
<tbody>
<tr>
<td>Salvage</td>
<td>89%</td>
<td>90%</td>
</tr>
<tr>
<td>Intensification</td>
<td>89%</td>
<td>91%</td>
</tr>
<tr>
<td>Simplification</td>
<td>69%</td>
<td>67%</td>
</tr>
</tbody>
</table>

### CD4 gain

<table>
<thead>
<tr>
<th></th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvage</td>
<td>p=0.004</td>
<td>p=0.038</td>
</tr>
<tr>
<td>Intensification</td>
<td>p=0.003</td>
<td>p=NS</td>
</tr>
<tr>
<td>Simplification</td>
<td>p=NS</td>
<td>p=NS</td>
</tr>
</tbody>
</table>

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Conclusions

- In this clinical setting, viral response in HIV patients treated with MVC seems to be good regardless treatment strategy when exclusion of X4 variants is made based on genotypic tools.

- Significant CD4 gains are seen in HIV patients treated with MVC as part of salvage or intensification strategies but not when used as simplification therapy.

- These results support the usefulness of the genotypic assessment of HIV tropism to guide MVC use in different treatment scenarios outside clinical trials.
Acknowledgments

- Hospital La Princesa, Madrid
- Complejo Hospitalario, Toledo
- Hospital Universitario Príncipe de Asturias, Alcalá

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