CEREBROSPINAL FLUID MARKERS IN LONG-TERM ATAZANAVIR/RITONAVIR MONOTHERAPY

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Disclosures

MODAt study

- is registered at United States National Institutes of Health [NCT01511809]
- is sponsored by San Raffaele Scientific Institute and Bristol Meyer Squibb
Ritonavir boosted protease inhibitors monotherapy (mono PI/r)

- Lower virological efficacy compared to standard treatment
- Prompt reintensification usually sufficient for re-suppression
- Virological failure usually not associated with:
  - Resistance mutations
  - Loss of future therapeutic options
- Concerns about efficacy in the CNS compartment

Methods

CSF biomarker pilot substudy of the RCT MODAt

**Primary Objective:**

- virological efficacy of ATV/r monotherapy in CSF

**Secondary objectives:**

- presence of neurological symptoms
- presence of morphological MRI abnormalities
- levels of CSF immune activation biomarkers

Study design

**MODAt**

- **Arm A**: Mono-ATV/r (N=50)
- **Arm B**: ATV/r+2N(t)RTI (N=51)

**Neuro-MODAt**

- **Arm A**: Mono-ATV/r (N=11)
- **Arm B**: ATV/r+2N(t)RTI (N=12)

**Study design**

- **Baseline Randomization**: 1:1
- **48 weeks**
- **96 weeks**

**ATV/r+2N(t)RTI (48 w)**

- HIV-RNA<50 cp/mL (24 w)

**CVR resuppression within 12 w**

## Pts characteristics at randomization

<table>
<thead>
<tr>
<th></th>
<th>Arm A (mono-ATV/r)</th>
<th>Arm B (ATV/r + 2N(t)RTIs)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=11</td>
<td>N=12</td>
<td>N=23</td>
</tr>
<tr>
<td>Age</td>
<td>42 (37-50)</td>
<td>43 (41-47)</td>
<td>43 (38-47)</td>
</tr>
<tr>
<td>Male gender (nr, %)</td>
<td>11 (100%)</td>
<td>11 (92%)</td>
<td>22 (95%)</td>
</tr>
<tr>
<td>Years from HIV diagnosis</td>
<td>6 (4-8)</td>
<td>4.5 (3-6.5)</td>
<td>5 (4-7)</td>
</tr>
<tr>
<td>Nadir CD4+ (cells/μL)</td>
<td>282 (228-363)</td>
<td>347 (315-419)</td>
<td>334 (268-366)</td>
</tr>
<tr>
<td>Nadir CD8+ (cells/ μL)</td>
<td>908 (665-133)</td>
<td>694 (529-912)</td>
<td>814 (551-1256)</td>
</tr>
<tr>
<td>Pre ART HIV-RNA (log10 c/mL)</td>
<td>4.76 (4.05-5.60)</td>
<td>4.88 (4.58-5.32)</td>
<td>4.86 (4.49-5.43)</td>
</tr>
<tr>
<td>Current CD4+ (cells/μL)</td>
<td>641 (464-812)</td>
<td>586 (485-673)</td>
<td>599 (467-699)</td>
</tr>
<tr>
<td>AIDS</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>HCV infection (nr, %)</td>
<td>1 (9%)</td>
<td>3 (25%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Duration of current ART (months)</td>
<td>26.3 (19.5-70.5)</td>
<td>25 (17.9-45)</td>
<td>25.2 (19.5-54.0)</td>
</tr>
<tr>
<td>Duration of HIV-RNA &lt;50 c/mL (months)</td>
<td>20.7 (13.7-65.5)</td>
<td>19.3 (12.1-39.6)</td>
<td>19.5 (13.7-48.7)</td>
</tr>
</tbody>
</table>

Median (interquartile range IQR) are reported. P values were calculated with Wilcoxon rank sum or Fisher exact test, as appropriate. HIV-RNA determined by Versant k PCR (limit of detection 37 c/mL).
Results

<table>
<thead>
<tr>
<th></th>
<th>Arm A (mono-ATV/r)</th>
<th>Arm B (ATV/r + 2N(t)RTIs)</th>
<th>p</th>
<th>All (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=11 Study week</td>
<td>123 (109-138)</td>
<td>124 (115-133)</td>
<td>0.758</td>
<td>123 (110-134)</td>
</tr>
<tr>
<td>CD4+ (cells/µL)</td>
<td>691 (544-836)</td>
<td>680 (580-813)</td>
<td>0.975</td>
<td>691 (544-836)</td>
</tr>
<tr>
<td>Plasma HIV-RNA &lt;50 c/mL</td>
<td>11 (100%)</td>
<td>12 (100%)</td>
<td>-</td>
<td>23 (100%)</td>
</tr>
<tr>
<td>CSF HIV-RNA &gt;50 c/mL</td>
<td>1 (9%, 114 c/mL)</td>
<td>0</td>
<td>-</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>CSF cells (cells/µL)</td>
<td>2 (1-4)</td>
<td>1 (1-2)</td>
<td>0.056</td>
<td>1.5 (1-3)</td>
</tr>
<tr>
<td>CSF glucose (mg/dL)</td>
<td>63 (62-68)</td>
<td>61 (59-64)</td>
<td>0.156</td>
<td>63 (60-64)</td>
</tr>
<tr>
<td>CSF protein (mg/dL)</td>
<td>36 (27-49)</td>
<td>34 (30-39)</td>
<td>0.669</td>
<td>35 (30-45)</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>MRI microvascular changes</td>
<td>4 (36%)</td>
<td>4 (33%)</td>
<td>0.998</td>
<td>8 (38%)</td>
</tr>
</tbody>
</table>

Median (interquartile range IQR) are reported. P values were calculated with Wilcoxon rank sum or Fisher exact test, as appropriate. HIV-RNA determined by Versant k PCR (limit of detection 37 c/mL).
CSF viral escape case

**Characteristics**
- ATV/r monotherapy for 120 weeks
- 2 non consecutive HIV-RNA blips in plasma (94, 99 c/mL)
- CD4+ nadir: 311 cells/μL
- Neuroasymptomatic
- No MRI abnormalities
- CSF: unremarkable protein and cell levels

**Intervention**
- re-intensification (TDF FTC)

**Outcome**
- Plasma and CSF HIV-RNA undetectable after 20 w
Biomarkers of immune activation

**CSF**

- **CCL2**
  - Log 10 pg/mL
  - A, B, All

- **IL6**
  - Log 10 pg/mL
  - A, B, All

- **sCD14**
  - Log 10 pg/mL
  - A, B, All

- **sCD163**
  - Log 10 pg/mL
  - A, B, All

**Plasma**

- **CCL2**
  - Log 10 pg/mL
  - A, B, All

- **IL6**
  - Log 10 pg/mL
  - A, B, All

- **sCD14**
  - Log 10 pg/mL
  - A, B, All

- **CXCL10**
  - Log 10 pg/mL
  - A, B, All

*Wilcoxon rank sum test*

- **CCL2**
  - $p = 0.063$

- **sCD14**
  - $p = 0.047$
Conclusions

- Asymptomatic CSF viral escape uncommon in selected pts on ATV/r monotherapy
- Re-intensification sufficient for CSF re-suppression
- CSF biomarkers of immune activation not increased in patients receiving monotherapy compared to patients receiving standard treatment
Aknowledgments

Patients
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Valeria Longo
Laura Galli
Laura Passeri
Simonetta Gerevini
Vincenzo Spagnuolo
Adriano Lazzarin
Paola Cinque
Antonella Castagna

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