The CNS Effects of Maraviroc: A Study to Assess CSF Exposure and Cerebral Metabolites

Background

• Factors including low protein-binding, high reported genital tract exposure and predominance of CCR5-tropic HIV in the CNS suggest MVC may have CNS antiviral activity

• Data describing MVC CSF exposure from cohort studies in varied clinical scenarios with confounding factors eg different ARV regimens and CNS disease

• No data assessing in vivo cerebral effects

Study design

Stable patients VL<50 Asymptomatic Truvada +Kaletra

Baseline MR-spectroscopy

Pre-dose plasma sample (C_{t\text{rough}})

CSF and plasma sample at C4-6h post dose

- CSF/PLASMA MVC%
Results

Number of subjects, n 12
Age (years), mean (SD) 42 (8)
Male, n (%) 9 (75)
CD4 count, mean (SD) 503 (199)
HIV VL <50 copies/mL, n(%) 12 (100)

<table>
<thead>
<tr>
<th>MVC CSF:plasma ratio (%)</th>
<th>Mean</th>
<th>SD</th>
<th>CV(%)</th>
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<tr>
<td></td>
<td>1.01</td>
<td>0.29</td>
<td>28.92</td>
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Results- MRS

- Increase in basal ganglia NAA was significantly associated with higher MVC plasma C_{trough} (p=0.047, r=0.61)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frontal grey matter</th>
<th>Frontal white matter</th>
<th>Right basal ganglia</th>
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<tbody>
<tr>
<td></td>
<td>NAA/Cr Cho/Cr ml/Cr</td>
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<tr>
<td>Absolute change</td>
<td>[0.02 [0.14] [0.01 [0.63] [0.00 [0.19] [0.00 [0.23] [0.17 [0.65] [0.27 [0.61] [0.14 [0.23] [0.24 [0.60]</td>
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NAA = marker of neuronal integrity
Summary

• MVC detected in CSF of all subjects (>5x median protein-free IC$_{90}$) with MVC CSF:plasma ratio of 1.01% and changes in neuronal (NAA/Cr) metabolites associated with MVC plasma exposure.

• This is the first study to describe a cerebral effect of MVC and a relationship to exposure.

• Future work needed to investigate whether changes associated with cognitive function and assess these effects over longer periods, in both neuro-symptomatic and asymptomatic subjects.