Early Efficacy of Ofatumumab on Microglia in Patients With Relapsing Forms of MS: Interim Analysis of a 9-month Study

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Introduction
• Microglia are innate immune cells of the central nervous system and overactivation of microglia has been implicated in the pathogenesis of multiple sclerosis (MS)1
• In animal models, B-cell depletion using anti-CD20 antibodies led to reduced microglial activation and lesion formation2
• Upon activation, human microglia cells form clusters in active lesion rims and in normal tissue. These clusters are detectable via targeting the gial marker 18-kidolaton translocator protein (TSPO)3
• A quantitative TSPO positron emission tomography (PET) scan with a second-generation 18F-PBR06 ligand has been used to assess the microglial activation in patients with MS4
• Ofatumumab (OMB) is a fully human anti-CD20 monoclonal antibody approved for the treatment of relapsing forms of MS (RMS) in adults
• The potential impact of OMB on microglial activation in people with MS is currently unknown

Objective
• To determine the effect of OMB on microglial activation in relation to changes in serum markers, MRI (magnetic resonance imaging) abnormalities, and clinical impairment longitudinally over 9 months using [F-18]PBR06-PET in patients with RMS

Methods
• This is an interim analysis of an open-label, single-center, observational, prospective, 9-month study in 10 patients with active RMS (Figure 1)
• [F-18]PBR06-PET scans were performed in RMS patients (prior to and at Days 5, 25 and 90 after initiating OMB)
• Individualised z-score maps of brain parenchymal microglial activation were generated by a voxel-by-voxel comparison between each subject’s PET standardized uptake value ratio images and a control dataset of nine healthy individuals
• Glial activity load on PET (GALP) was calculated as the sum of voxel-by-voxel z-scores ≥4 in the lesional and perilesional normal-appearing white matter, cortical grey matter (CGM) and thalamic regions of interest in the standard atlas space
• All parameters assessed over 90 days were compared with baseline values

Figure 1. Study design and objectives

<table>
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<th>Days</th>
<th>Timeline</th>
<th>PET</th>
<th>MRI</th>
</tr>
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<tbody>
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<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>7</td>
<td>Day 5</td>
<td>1 Week</td>
<td>1 Week</td>
</tr>
<tr>
<td>21</td>
<td>Day 25</td>
<td>1 Month</td>
<td>1 Month</td>
</tr>
<tr>
<td>90</td>
<td>Day 90</td>
<td>9 Months</td>
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</table>

Results
• Twenty (F-18]PBR06 PET scans were performed in 5 RMS patients (mean: SD age, 40.2±12 years; 4 females; median EDSS score, 3.0). Patient enrolment is expected to be completed by the end of 2021
• After OMB treatment initiation, the mean CGM-GALP decreased significantly versus baseline at Day 90 (0.75±0.09 vs. 0.95±0.06, −19.4%, p<0.05), but not at Days 5 or 28
• Absolute and percentage CD19 counts were significantly decreased at Day 5 versus baseline (11.5±9.1 vs. 256.6±117.4 cells/µL, −96%, p<0.01 and 0.98±0.96%, 14.7±8.7%, -93%, p=0.02, respectively), which persisted at Day 90 (data not shown)
• There was no statistically significant difference in mean GALP scores in thalamic, lesional, and perilesional, or in clinical measurements over 90 days (all p>0.05) (Figure 2)

Figure 2. Early effect on microglia: Cortical PET is reduced at 3 months

CORTICAL GALP

<table>
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<th>0.5</th>
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<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
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</tr>
<tr>
<td>9 Months</td>
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</tbody>
</table>

Figure 3. Individualised z-score mapping of the TSPO-PET signal in RMS

Conclusions
• In this interim analysis, OMB treatment was associated with decreased CGM microglial activation at 3 months and was preceded by peripheral CD19+ cell depletion at Day 5, which may suggest an indirect, downstream effect of B-cell depletion on microglial activity in RMS patients
• This is the first study to evaluate the effect of OMB on microglial activation and its relationship with serum biomarkers of neurodegeneration

References

Disclosures
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