Efficacy of Ofatumumab on Microglial Activity in Patients with Relapsing forms of Multiple Sclerosis: Interim Analysis

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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 formation[2]
- Upon activation, human microglia cells form clusters in active lesion rims and in normal tissue. These clusters are detectable via targeting the glial marker 18-kilodalton 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 MS[4]
- 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 MS is currently unknown

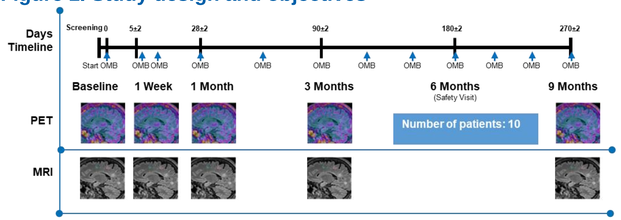
Objective

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-centre, 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, 28 and 90 after initiating OMB)
- Peripheral CD19 counts and clinical evaluations were also performed
- 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 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



MRI, magnetic resonance imaging; OMB, ofatumumab; PET, positron emission tomography

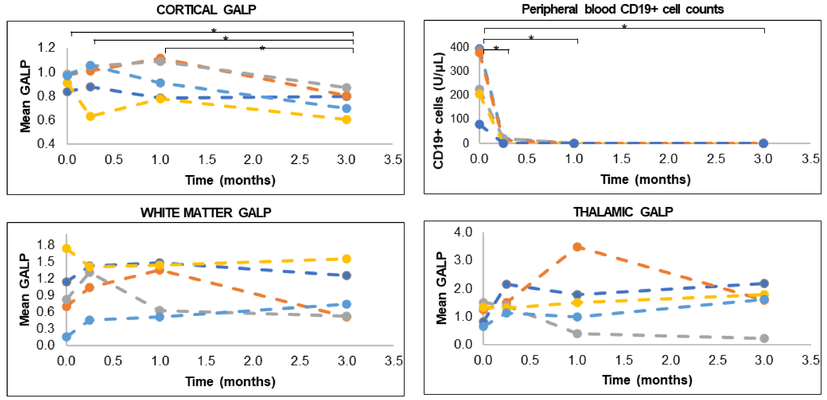
Primary objective

- To determine the effect of OMB on microglial activation over 9 months in patients with RMS

Secondary objectives

- To determine the time course of effect of OMB on microglial activation and its relationship at Days 5, 28, 90 and 273 with peripheral B-cell depletion, serum NfL chain, GFAP levels, and other serum biomarkers (IP-10, ITAC, MCP-1 and MIP-3b)
- To determine the relationship of PET changes following OMB initiation with 3T MRI changes (including QSM) and clinical parameters (EDSS, T25FW, MFIS, relapses)

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

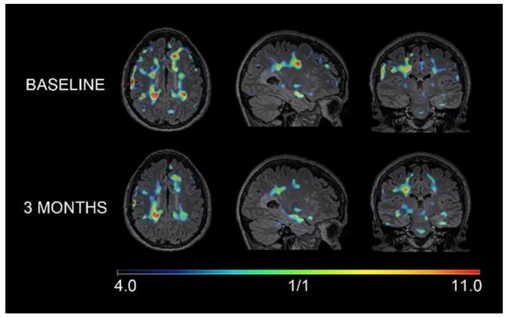


*p<0.05. GALP, glial activity load on PET; MO, month

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 initiation, the mean CGM-GALP decreased significantly versus baseline at Day 90 (0.75±0.09 vs. 0.93±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±0.98% vs. 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 3. Individualized z-score mapping of the TSPO-PET signal in RMS



Fused PET/MRI maps showing a reduced TSPO signal in an RMS patient at 3 months after starting OMB

Conclusions

- This is the first study to evaluate the effect of OMB on microglial activation and its relationship with serum markers of neurodegeneration
- 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

References

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Disclosures

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