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

P966

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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 people with MS is currently unknown

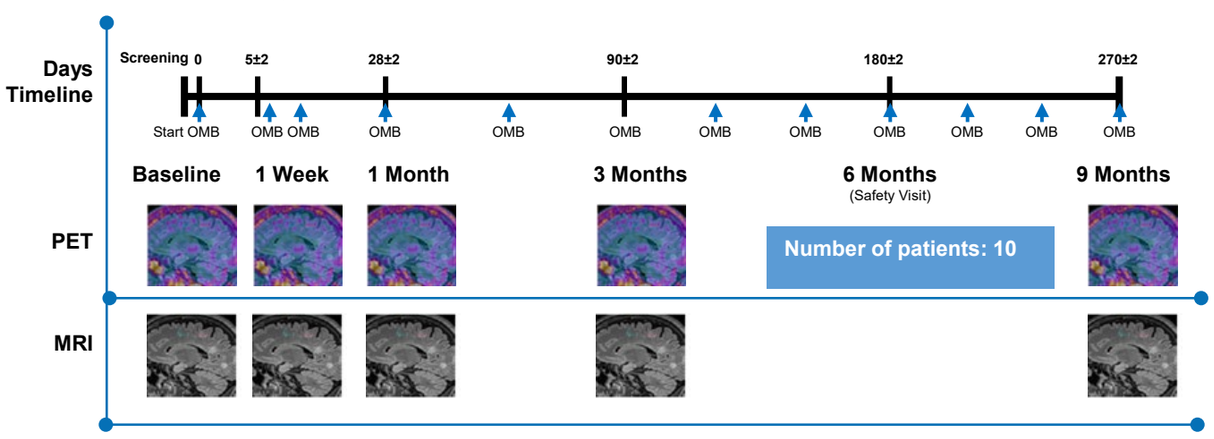
Objective

- 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, 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, 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 in patients with RMS over 9 months

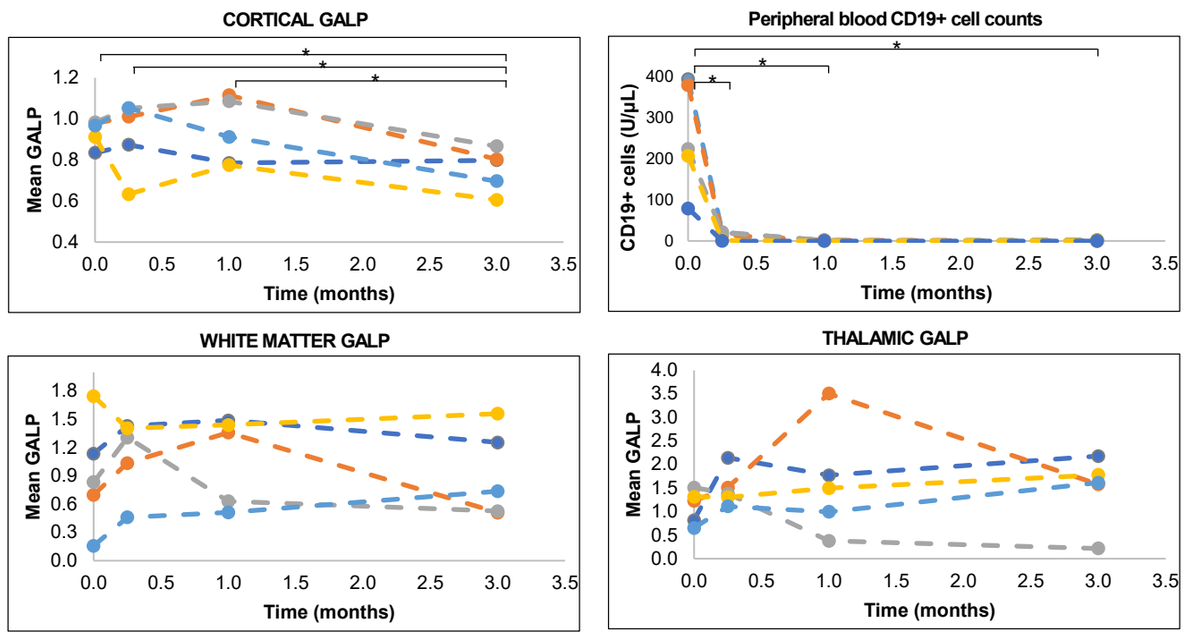
Secondary objectives

- To determine the time course of effect of OMB on microglial activation and its relationship at Days 5, 28, 90 and 270 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)

Results

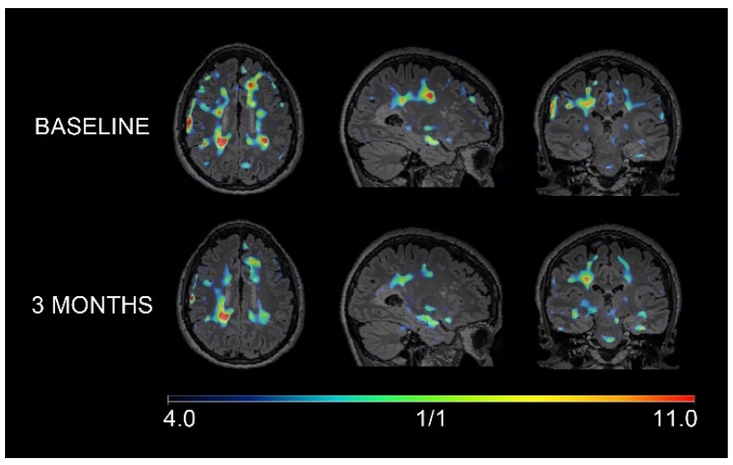
- Twenty [F-18]PBR06 PET scans were performed in 5 RMS patients (mean±SD age, 40.2±12 years; 4 females; median EDSS score, 3.0). Patient enrolment is expected to be completed by the end of 2021
- After OMB treatment initiation, the mean CGM-GALP decreased significantly versus baseline at Day 90 (0.75±0.09 vs. 0.93±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 2. Early effect on microglia: Cortical PET is reduced at 3 months



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

Figure 3. Individualised 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

- 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

1. Olcum M, et al. *Adv Protein Chem Struct Biol*. 2020;119:247-308.
2. Anthony DC, et al. *Ann Clin Transl Neurol*. 2014;1:659–669.
3. Nutma E, et al. *Glia*. 2021;69(10):2447-2458.
4. Singhal T, et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e587.

Disclosures

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