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

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Disclosures

Author Name	Disclosures
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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 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 abnormalities, and clinical impairment longitudinally over 9 months using [F-18]PBR06-PET in patients with RMS**

MRI, magnetic resonance imaging; PET, positron emission tomography.

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.

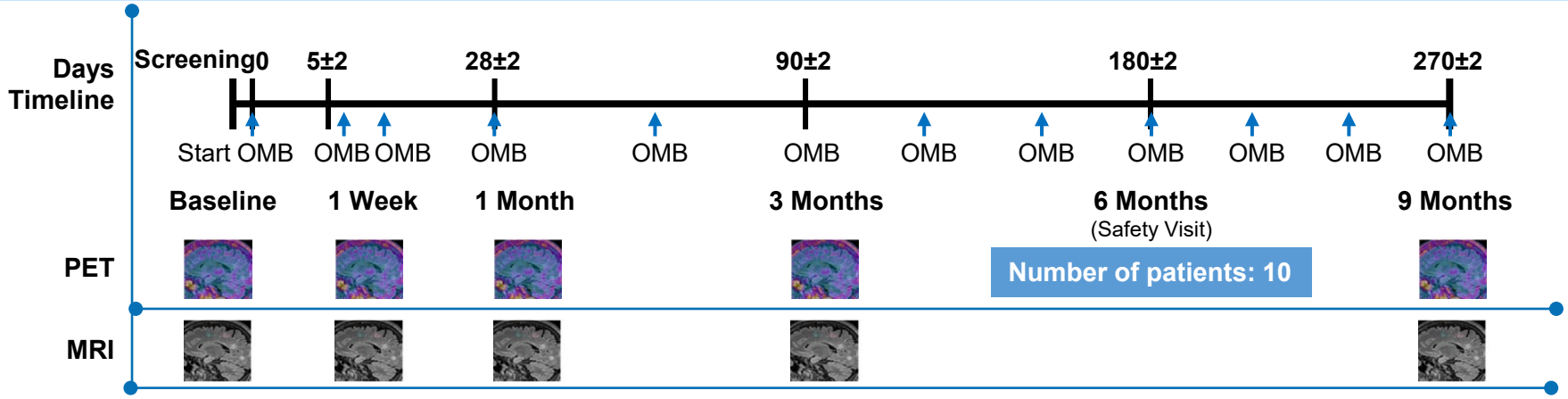
Study Design, Objectives, & Methods

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)



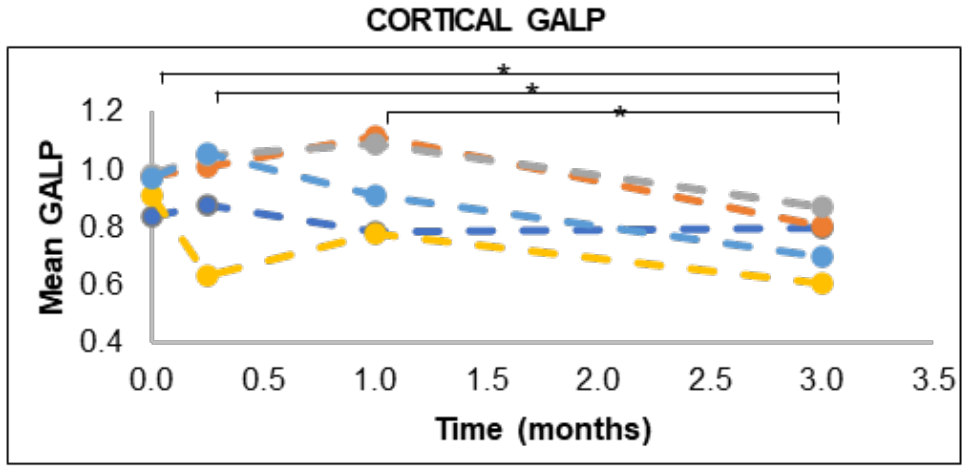
Study Methods

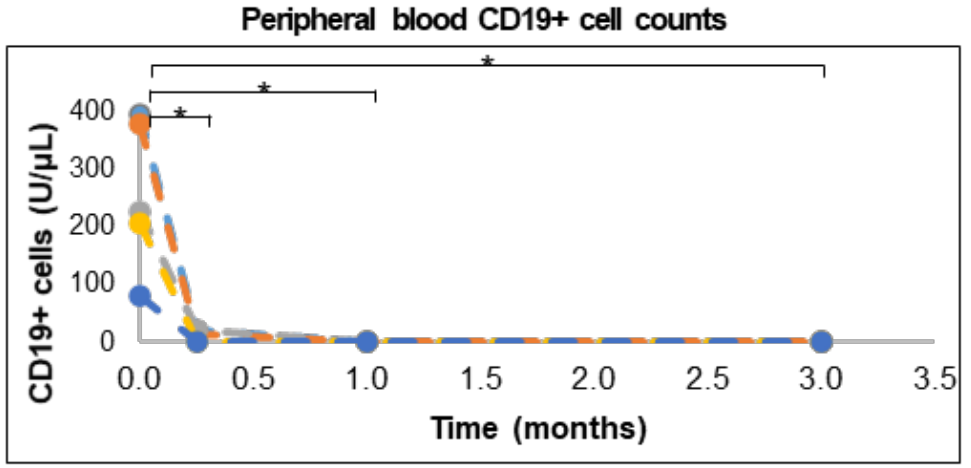
- **This is an interim analysis of an open-label, single-center, observational, prospective, 9-month study in 10 patients with active RMS**
- [F-18]PBR06-PET scans were performed in RMS patients (prior to and at Days 5, 28 and 90 after initiating OMB)
- Peripheral CD19 counts and clinical evaluations were also performed
- Individualized 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 and thalamic regions of interest in the standard atlas space
- All parameters assessed over 90 days were compared with baseline values

EDSS, Expanded Disability Status Scale; GFAP, glial fibrillary acid protein; MRI, magnetic resonance imaging; NfL, neurofilament light; OMB, ofatumumab; PET, positron emission tomography; RMS, relapsing multiple sclerosis.

Results: Early effect on microglia: Cortical PET is reduced at 3 months

- 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 enrollment has been completed as of March, 2022
- 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)



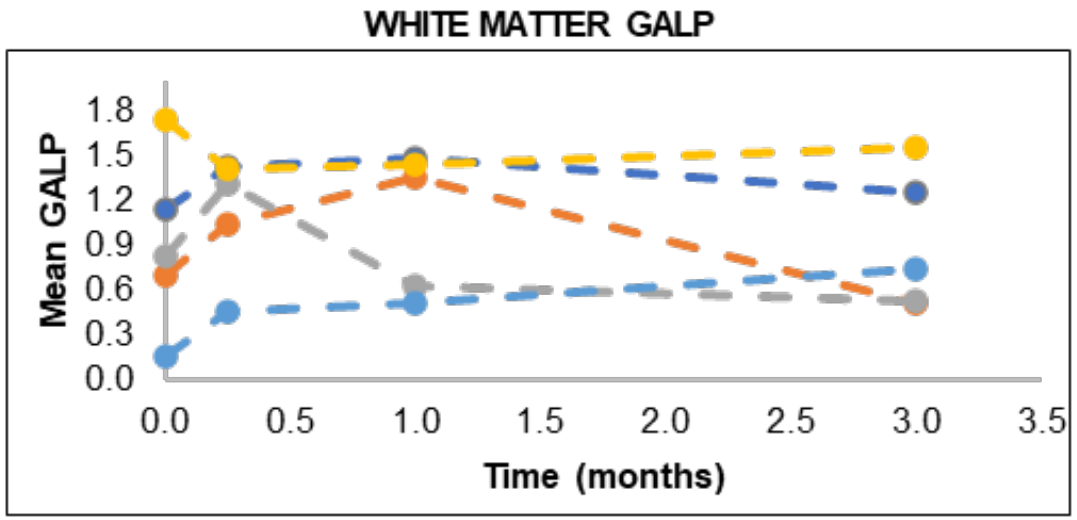


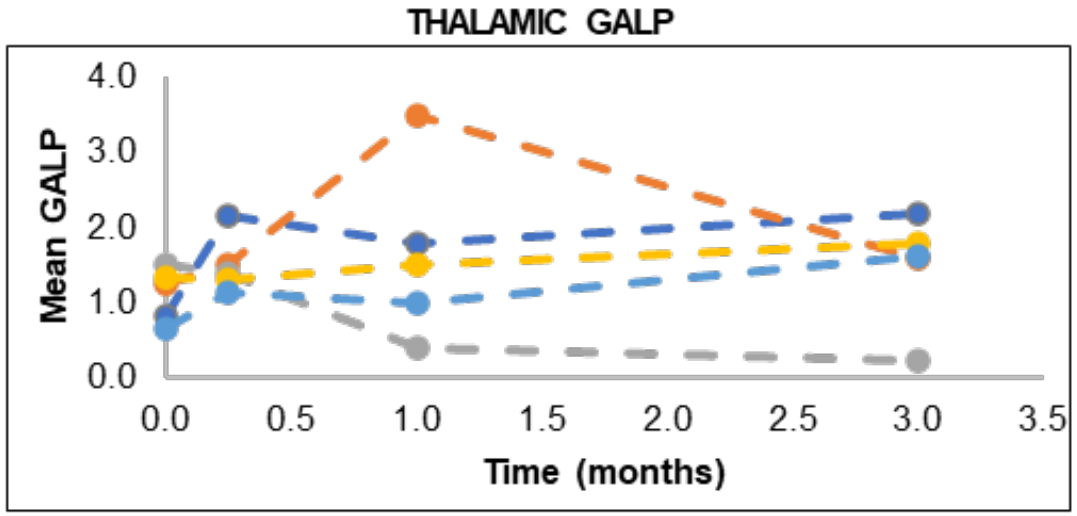
*p<0.05

CGM, cortical grey matter; EDSS, Expanded Disability Status Scale; GALP, glial activity load on PET; OMB, ofatumumab; PET, positron emission tomography; RMS, relapsing multiple sclerosis; SD, standard deviation.

Results

- 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)

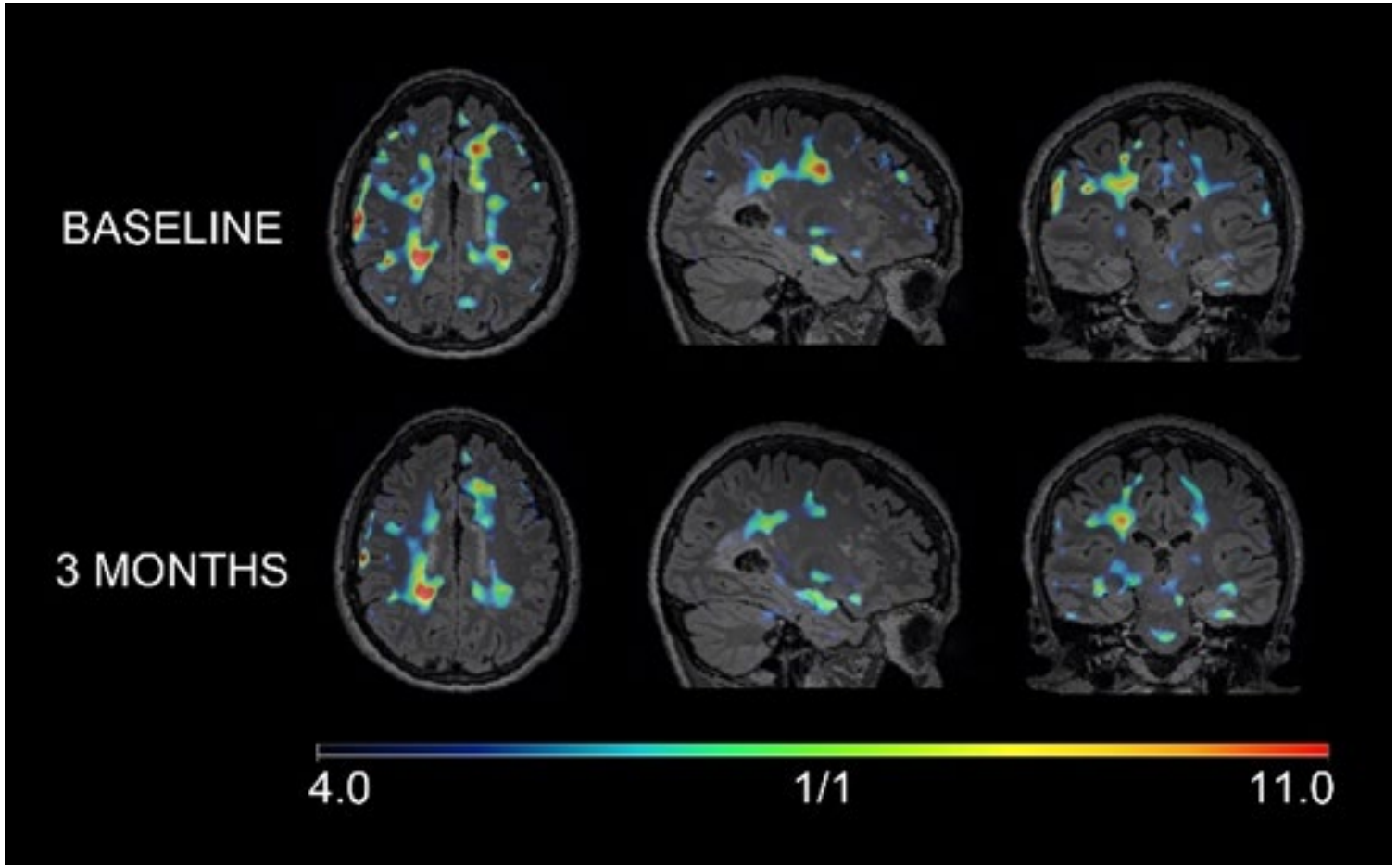




GALP, glial activity load on PET.

Results: 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



MRI, magnetic resonance imaging; OMB, ofatumumab; PET, positron emission tomography; RMS, relapsing multiple sclerosis; TSPO, translocator protein.

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

CGM, cortical grey matter; OMB, ofatumumab; RMS, relapsing multiple sclerosis.