Efficacy of Ofatumumab on Microglia in Patients with Relapsing forms of Multiple Sclerosis: Study Design

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#EPR-225

Introduction

- Microglia are innate immune cells of CNS and their overactivation has been implicated in the pathogenesis of MS[1]
- B-cell depletion using anti-CD20 antibodies led to reduced microglial activation and lesion formation in animal models[2]
- An 18-kilodalton translocator protein (TSPO) is over expressed on the outer mitochondrial membrane of activated microglia.
  A quantitative TSPO positron emission tomography (PET) with a second-generation 18F-PBR06 ligand has been used to assess the microglial activation in patients with MS[3]
- Ofatumumab is a fully human anti-CD20 monoclonal antibody approved for the treatment of RMS in adults in the US, Europe and other countries*
- The potential impact of ofatumumab on microglial activation in MS is currently unknown

Objective

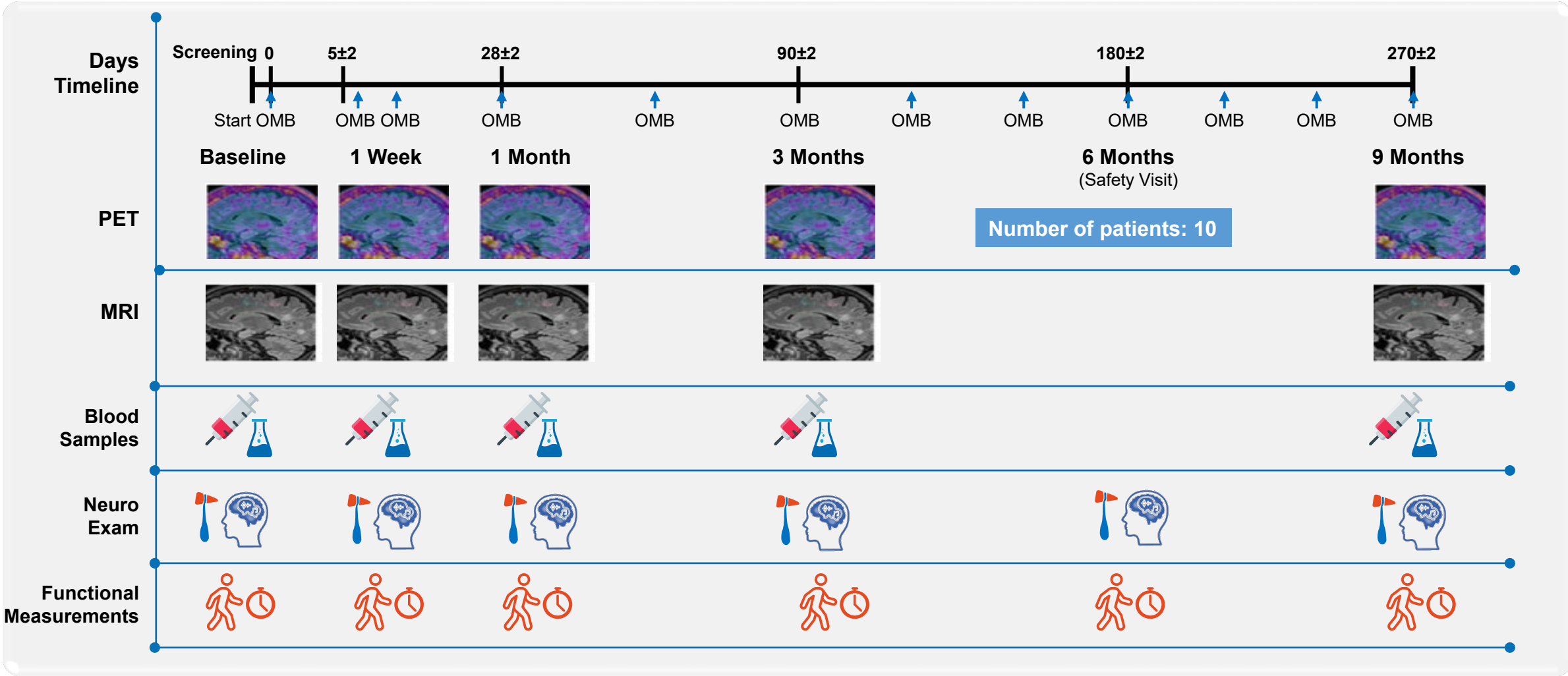
To determine the effect of ofatumumab on microglial activation in relation to changes in serum markers, MRI abnormalities and clinical impairment longitudinally over 9 months using [F-18]PBR06-PET in RMS patients

*Australia, Canada, Singapore, Switzerland, UAE, Albania, Argentina, India, Japan, Great Britain and Brazil. CNS, central nervous system; MS, multiple sclerosis;; RMS, relapsing multiple sclerosis.

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. Singhal T, et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e587.

Study design

An open-label, single center, observational, prospective, 9-month study in RMS patients



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

Study Eligibility criteria

Key inclusion criteria

- RMS patients aged 18 to 60 years
- Diagnosed with *active[a], relapsing MS course*[1]
- EDSS 0 to 5.5
- Normal CD19 (>110/µL), WBC (>4000/µL), lymphocytes (>1000/µL) and IgG level (>700mg/dL)
- Variable transition time from other DMTs

Key exclusion criteria

- Subjects suspected of not being able or willing to cooperate or comply with study protocol requirements in the opinion of the investigator
- Subjects with primary progressive MS[2] or SPMS without disease activity[1]
- Disease duration of more than 10 years in patients with an EDSS score of 2 or less
- Subjects with low TSPO binding affinity

[a]at least 1 relapse during the previous 1 year or 2 relapses during the previous 2 years or a positive gadolinium-enhancing MRI scan or MRI scan with new or unequivocally enlarging T2 lesions in previous year
DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; Ig, immunoglobulin; RMS, relapsing multiple sclerosis; SPMS, secondary progressive multiple sclerosis

1. Lublin FD, et al. *Neurology*. 2014;83(3):278-286. Polman CH, et al. *Annals of neurology*. 2011;69:292-302.

Study objectives and endpoints

Primary

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

Secondary

- To determine the time course of effect of ofatumumab on microglial activation and its relationship at Days 5, 28, 90 and 273 with:
  - Peripheral B-cell depletion
  - Serum neurofilament light chain
  - Glial-fibrillary acid protein levels
  - Other serum biomarkers (IP-10, ITAC, MCP-1 and MIP-3b)
- To determine the relationship of PET changes following ofatumumab initiation with 3T MRI changes (including QSM) and clinical parameters (EDSS, T25FW, MFIS, relapses)

EDSS, Expanded Disability Status Scale; MFIS, modified form of the Fatigue Impact Scale; MRI, magnetic resonance imaging; PET, positron emission tomography; RMS, relapsing multiple sclerosis; T25FW, Timed 25-Foot Walk

Conclusions

- ✓ This is the first study to evaluate the effect of ofatumumab on microglial activation and its relationship with serum markers of neurodegeneration
- ✓ This study will also assess the relationship between peripheral B-cell depletion and changes in microglial activation following ofatumumab administration
- ✓ Patient enrollment is expected to complete by the end of 2021

Disclosures

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