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Ofatumumab Attenuates Cortical Microglial Activity in Patients With Relapsing Forms of Multiple Sclerosis Following B-cell Depletion: Results From a 9-Month Study

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Abstract:
Background: Overactivation of microglia, the innate immune cells of the central nervous system, has been implicated in the pathogenesis of multiple sclerosis (MS). Histopathologically, chronic active lesions are also characterized by progressive tissue matrix damage, driven by a rim of iron laden activated microglia at the lesion edge. In the interim analysis, ofatumumab treatment significantly decreased microglial activation in cortical grey matter (CoGM) and brain iron levels.
Objectives: To further evaluate the effect of ofatumumab on microglial activation and brain iron, in relation to peripheral B-cell depletion, brain atrophy, serum biomarker concentrations, and changes in clinical impairment, longitudinally over 9 months.
Methods: An open label, single-center, observational study was conducted in 10 patients with active relapsing MS (RMS). The following evaluations were performed at baseline, and at Week 1, and Months 1, 3, and 9 after ofatumumab initiation in the first 5 patients (mean age, 40.2±12 years, median Expanded Disability Status Scale [EDSS], 3.0): [F-18]PBR06 positron emission tomography (PET) scans, peripheral CD19 counts, magnetic resonance imaging (including whole brain and deep grey volumes and quantitative susceptibility mapping [QSM]), clinical evaluations (EDSS, timed 25 foot walk [T25FW], anxiety and depression scores and 9 hole peg test [(9HPT]), serum neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), CXCL10 and CCL19 levels. Statistical parametric mapping (SPM) analysis was performed to assess the reduction in PET and QSM signal, analyzed at Month 9 versus baseline. Normal-appearing white matter (NAWM), CoGM, and thalamic (Th) regions of interest (ROI) in standard atlas space were interrogated for peak cluster T-values corresponding to $p<0.05$.
Results: At 3 and 9 months following ofatumumab initiation, voxel-clusters with significantly decreased PET uptake were observed in the CoGM ($P<0.01$) versus baseline. Clusters of decreased QSM signal, representing decreased brain iron, were seen in CoGM and NAWM ($p<0.01$). Whole brain and deep grey volumes remained stable over 9 months. Serum NfL, CXCL10, and CCL19 but not serum GFAP, were significantly lower at 9 months ($p<0.05$). $CD19^+$ cells and serum CCL19 were reduced significantly after 1 week and 1 month, respectively. EDSS and T25FW remained stable but hospital anxiety and depression scores and 9HPT in the dominant hand improved significantly at 9 months (both $p<0.05$). No new safety signals were observed during the study.
Conclusions: Ofatumumab treatment was associated with decreased CoGM microglial activation, decreased brain iron, and reduced NfL and chemokine levels at 9 months and was preceded by peripheral CD19+ cell depletion. The relationship between changes in cortical microglial activation, brain iron, serum NfL and chemokine levels, in response to ofatumumab, warrants further investigation.

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