A PILOT TRIAL OF OCRELIZUMAB FOR MODULATION OF MENINGEAL ENHANCEMENT IN MULTIPLE SCLEROSIS

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Introduction

- Autopsy data suggests that meningeal inflammation in multiple sclerosis (MS) is driven by CD20+ B-cells. [1]
- Ocrelizumab is an anti-CD20 monoclonal antibody and thus might ameliorate meningeal inflammation in MS. [2]
- Leptomeningeal enhancement (LME) on MRI is suggested as a surrogate biomarker of meningeal inflammation in MS, and thus may be a way of monitoring for this treatment effect [3].
- For these reasons, we elected to perform a prospective treatment trial of ocrelizumab for modulation of meningeal enhancement in MS.

Methods

Participants: Twenty-two volunteers with MS recently prescribed ocrelizumab by their treating physician were enrolled in this prospective trial. The study was a clinical trial registered on clinicaltrials.gov as NCT03396822. Participants underwent 7T MRI of the brain prior to first infusion, with screening for the presence of LME. Fourteen patients had LME on the baseline scan and were invited to return for an additional 7T MRI after 1 year of treatment.

Comparison group: Fourteen MS patients on non-CD20 treatment from a separate observational cohort of annual 7T MRIs were used for comparison – matched for LME at baseline, age, and sex.

Image acquisition: Patients underwent 7T brain MRI imaging on a Philips Achieva scanner pre- and post-gadolinium contrast. Post-contrast FLAIR images were acquired approximately 23 minutes after contrast injection. 7T MRI images underwent pre-processing for creation of MP2RAGE T1-weighted and T1 maps, as described in our prior work [4]. 7T FLAIR images, pre-and post-contrast, were co-registered to the pre-contrast T1-weighted MP2RAGE image. All images were up- sampled to match the FLAIR resolution of 0.5 mm x 0.488 mm x 0.488 mm. A subtraction image was created by subtracting the pre-contrast FLAIR from post-contrast FLAIR. Methods for identification of foci of meningeal enhancement were as described in our prior publications on this topic. [5]

Image Analysis: Co-registered pre- and post-contrast FLAIR and subtraction images were reviewed for enhancements, which were characterized as LME if at the pial surface or subarachnoid space. Enhancements were characterized as paravascular or dural enhancement (PDE) if found immediately outside of vessel or sinus walls or within dural structures. These foci were counted and masked using semi-automated lesion filling tools in MIPAV.

Statistics: Wilcoxon sign ranked test was used evaluate the change in number and volume from baseline and Mann Whitney test was used to compare this change between ocrelizumab and non-ocrelizumab treated MS patients.

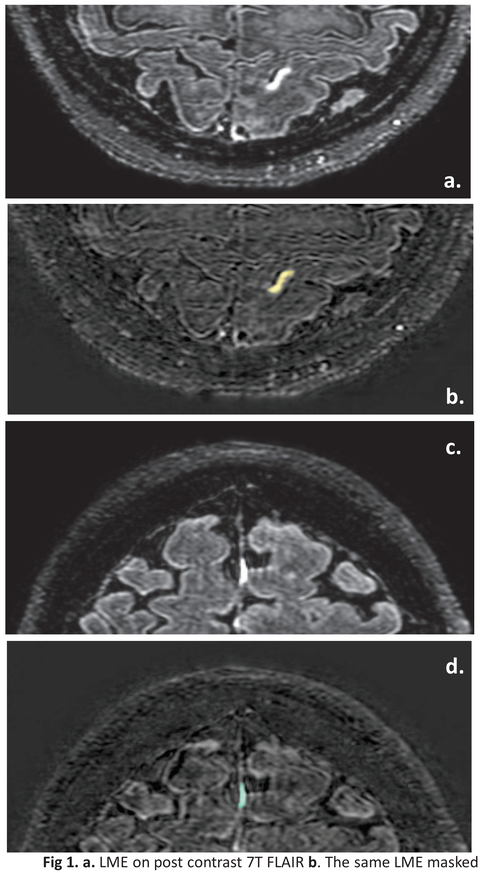

Fig 1. a. LME on post contrast 7T FLAIR **b**. The same LME masked in subtraction 7T FLAIR **c.** PDE on post contrast 7T FLAIR **d**. The same PDE masked in subtraction 7T FLAIR

Results

Table 1: Demographics and clinical history in Ocrelizumab and comparison groups

Parameters	Ocrelizumab group (N=14)	Comparison group (N=14)
Sex		
Men	3 (23)	3 (23)
Women	11(77)	11(77)
Age (Y)		
<40 yrs.	2 (14)	5 (36)
40-60 yrs.	8 (56)	7 (50)
>60 yrs.	4 (28)	2 (14)
Mean ± SD yrs.	47.8± 2.7	47.9± 10.5
Disease subtype at enrollment		
RRMS	9(62)	14(100)
SPMS	2(15)	0(0)
PPMS	3(23)	0(0)
Mean disease duration at enrollment (Months)	129±138	168±84

Note: Values in parentheses are %. RRMS- Relapsing remitting MS. PPMS- Primary progressive MS. SPMS- Secondary progressive MS.

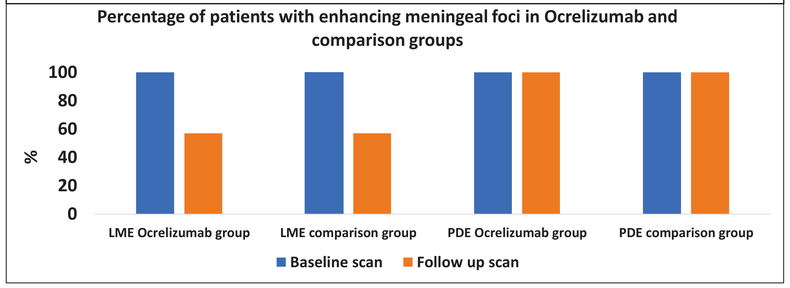

Fig 2. Meningeal enhancement in Ocrelizumab and comparison groups. The percentage of patients with LME and PDE at baseline and F/U scans in both groups were identical and changes from baseline were non-significant.

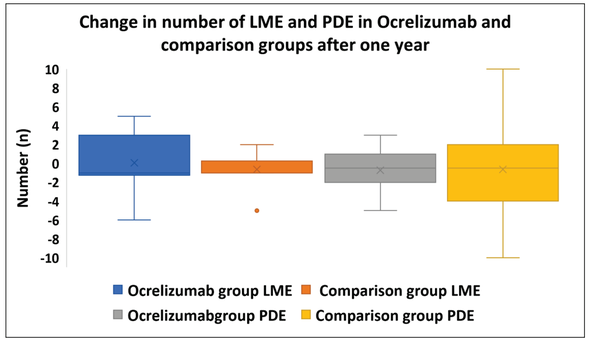

Fig 3. Change in number of LME and PDE in study and comparison groups. There were no statistically significant differences between groups. There were also no significant differences between baseline and follow up LME and PDE count within or between groups (not shown).

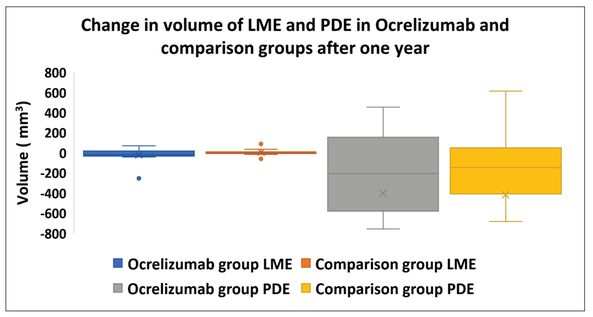

Fig 4. Change in volume of LME and PDE in Ocrelizumab and comparison groups. There were no statistically significant differences between groups. There were also no differences in the volume of LME and PDE within the subjects of both groups between their baseline and F/U scans or between groups (not shown).

Conclusion

- In this small pilot trial, ocrelizumab did not significantly reduce the number, volume, or percentage of foci of LME or PDE in MS patients and the change in foci was not different in the ocrelizumab-treated group and non-ocrelizumab treated comparison group.
- This study suggests that either that ocrelizumab may not have a treatment effect upon meningeal inflammation, or rather that LME and/or PDE may not be biologically specific or treatment responsive biomarkers of meningeal inflammation.

References

1. Serafini, B., et al. (2004). "Detection of ectopic B-cell follicles with germinal centres in the meninges of patients with secondary progressive multiple sclerosis." Brain pathology **14**(2): 164-174.
2. Montalban, X., et al. (2017). "Ocrelizumab versus placebo in primary progressive multiple sclerosis." New England Journal of Medicine **376**(3): 209-220.
3. Howell, O. W., et al. (2015). "Extensive grey matter pathology in the cerebellum in multiple sclerosis is linked to inflammation in the subarachnoid space." Neuropathology and applied neurobiology **41**(6): 798-813.
4. Iglesias, Mehmet, Samuel Jonas, Izlem Izbudak, Seongjin Choi, Alfonso Lema-Dopico, Jun Hua, Erin E O'Connor, and Daniel M Harrison. 2020. 'No association between cortical lesions and leptomeningeal enhancement on 7-Tesla MRI in multiple sclerosis', *Multiple Sclerosis Journal*, 26: 165-76.
5. Harrison, Daniel M, Kevin Y Wang, Julie Fiol, Kerry Naunton, Walter Royal III, Jun Hua, and Izlem Izbudak. 2017. 'Leptomeningeal enhancement at 7T in multiple sclerosis: frequency, morphology, and relationship to cortical volume', *Journal of Neuroimaging*, 27: 461-68.

Funding and Disclosures

Funding: Funding for the ocrelizumab study group was provided by Roche-Genentech. Funding for MRIs utilized as the comparison group is from NIH 1R01NS104403-01.
Disclosures: Dr. Harrison has received research funding from Roche-Genentech and EMD-Serono. Dr. Harrison has received consulting fees or royalties from Horizon Therapeutics, American College of Physicians, and Up To Date, Inc.