Toward the Use of Paramagnetic Rim Lesions in Proof-of-Concept Clinical Trials for Treating Chronic Inflammation in Multiple Sclerosis

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Background

- Effective treatment for disability progression in MS remains an urgent unmet need.
- Development of robust biomarkers could facilitate efficient screening of drug candidates.
- 10–20% of white matter lesions in MS demonstrate persistent chronic inflammation, and these are found in 50–60% of MS patients.
- These “chronic active” or “smoldering” lesions can expand slowly over time and appear to play a role in disease progression. Such lesions can be identified on 7T phase MRI as paramagnetic rim lesions (PRL), which persist for years.
- PRL are visible on MRI due to iron within microglia/macrophages phagocytes at the lesion edge.
- Evidence of colocalized ongoing demyelination is also present.
- Modulation of the paramagnetic rim (reduction or resolution) would imply alteration of the local immune cell populations.
- Concurrent or subsequent changes in lesion morphology (return toward normal) could suggest repair.

Frischer et al. 2015, *Ann Neurol* 78:710
Absinta et al. 2016, *JCI* 126:2597
Dal-Bianco et al. 2016, *Acta Neuropath* 133:25
Absinta et al. 2019, *JAMA Neurol* 76:1474

Objectives

We describe a novel trial design applied to 2 phase IIa interventional studies targeting microglia with primary outcome of modulation of PRL

Trial 1: ATaC-MS

Study drug: anakinra

- *commercially available, recombinant human IL-1R antagonist*
- *IL-1β is important in innate inflammation and produced mainly by microglia → anakinra could inhibit destructive microglial activation*

Trial 2: BRaKe-MS

Study drug: tolebrutinib

- *investigational, brain-penetrant, oral Bruton's tyrosine kinase (BTK) inhibitor*
- *BTK is involved in cell signaling of B cells and microglia → BTK inhibition may curtail microglia activation*

Statistical Considerations

- Prior NINDS natural history data: 1/29 individuals (3.4%) experienced subtle changes in at least one PRL over a period of ~5 years.
- Very few to no participants, in the absence of effective treatment, would experience PRL changes over a short period (3 -12 months).
- As such, even a single participant experiencing short-term (<1-year) changes in PRL would potentially be clinically meaningful.

Study Design

Eligibility Criteria:

- Patients with progressive or stable MS
- ≥ 1 PRL
- No new lesions or relapse within the prior 6 months

Both trials are actively enrolling

Trial 1: ATaC-MS *(NCT 04025554)*
anakinra added to DMT
24-week, single arm, open label
Sample size: 5 patients

Trial 2: BRaKe-MS *(NCT04742400)*
tolebrutinib vs ocrelizumab
96-week, non-randomized, two arm, open label
Sample size: 20 patients

Outcome Measures

Primary outcome:

Modulation of PRL at Week 12 (ATaC-MS) and Week 48 (BRaKe-MS)

Secondary and exploratory outcomes:

Clinical outcomes

- Standardized disability measures including EDSS, SDMT, 9HPT, 25FTW

Laboratory outcomes

- Analysis of immune cell populations in blood and CSF by flow cytometry and single-cell RNA sequencing
- Biomarkers of inflammation and tissue destruction including serum/CSF cytokine analysis and NfL

Imaging outcomes

- Changes in size of, and T1 relaxation time within, PRL
- Slowly evolving lesions

Can a smoldering lesion be cured?

ATaC-MS and BRaKe-MS are the first steps toward application of a novel trial design using an emerging outcome measure to address a critical but unmet clinical need in MS

Secondary and exploratory clinical, imaging and biological outcomes will assess whether PRL modulation, if achieved, facilitates lesion repair or impacts relevant biomarkers of inflammation or tissue injury