Effect of AHSCT on inflammatory mediators in serum and CSF of RRMS patients in the HALT-MS study

Laura A. Cooney[1,5], Noha Lim[1], Kristina M. Harris[1], Pradeepthi Bathala[2], Jacob Wohlstadter[2], Martin Stengelin[2], Maria Teresa Cencioni[3], Jose I Fernandez Velasco[4], David A. Fox[5], Linda M. Griffith[6], Richard A. Nash[7], Luisa M. Villar[4], Paolo A. Muraro[3]

[1] Immune Tolerance Network, [2] Meso Scale Diagnostics, LLC., [3] Imperial College London, [4]Ramon y Cajal University Hospital, [5]University of Michigan, [6]NIAID / NIH, [7]Colorado Blood Cancer Institute

INTRODUCTION

In the HALT-MS study, twenty-four participants with relapsing-remitting multiple sclerosis (RRMS) underwent autologous hematopoietic stem cell transplantation (AHSCT), of which seventeen achieved durable remission (Nash et al. Neurology 2017). Our goal was to better understand mechanisms mediating increased immune regulation following AHSCT and biomarkers associated with or predictive of long-term disease remission. To achieve this goal, we analyzed soluble inflammatory markers in serum and cerebrospinal fluid (CSF) from HALT-MS participants before and after AHSCT.

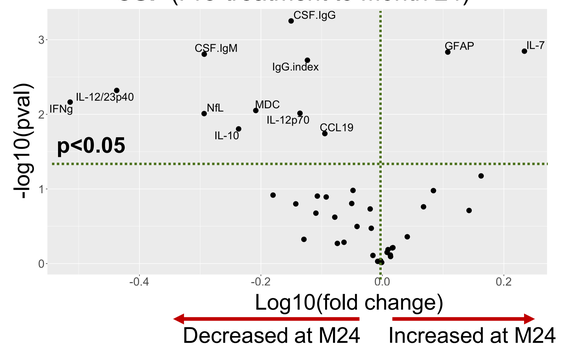
METHODS

Serum was collected at nine timepoints from baseline (prior to mobilization and conditioning) through 60 months post-transplant. Lumbar punctures were performed at three timepoints: screening, 24- and 48-months post-transplant. CSF was centrifuged, aliquoted, and transferred to -80C immediately after collection.

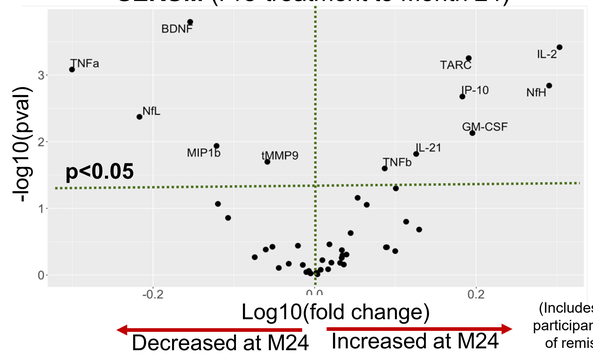
Approximately 40 Inflammatory mediators were measured in serum and/or CSF by Meso Scale Diagnostics, LLC. Four additional mediators (sCD27, CXCL13, CXCL10, and CCL19) were measured in CSF by ELISA in the Muraro lab. IgG and IgM concentration and oligoclonal bands in CSF were measured by the Villar lab.

Clinical data used in the analysis includes Expanded Disability Status Score (EDSS), total brain volume, T1 volume, and T2 volume by MRI (Nash et. al. 2017, available at ITNTrialShare.org)

Effect of AHSCT on inflammatory mediators in **CSF** (Pre-treatment to Month 24)

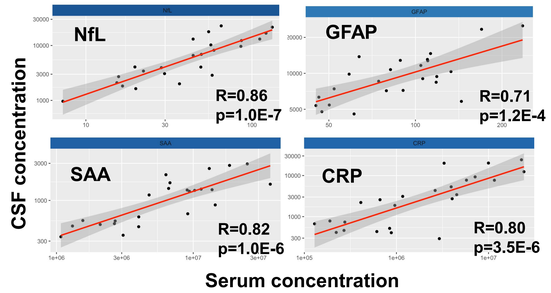


Effect of AHSCT on inflammatory mediators in **SERUM** (Pre-treatment to Month 24)

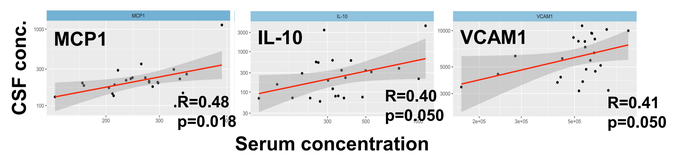


(Includes all available participants, regardless of remission status)

Strong correlation between serum and CSF:



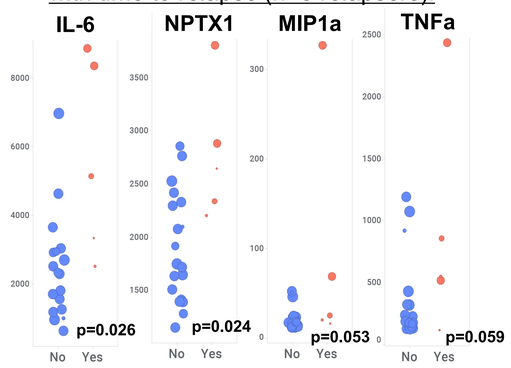
Weak correlation between serum and CSF:



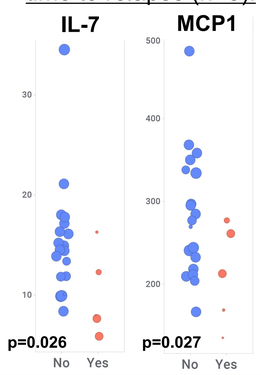
No significant correlation between serum and CSF (p>0.05):

NfH	IL-2	IL-16	MIP1b	IL-12p70
tTau	IL-6	IL-22	TARC	IL-12/23p40
ICAM1	IL-7	IP-10	VEGF	
GM-CSF	IL-15	MDC	TSLP	

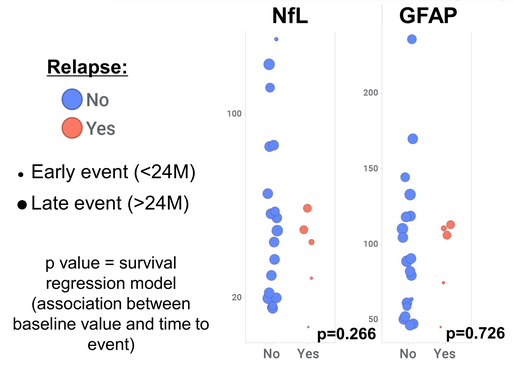
Baseline serum cytokines **positively** associated with time to relapse (n=5 relapsers):



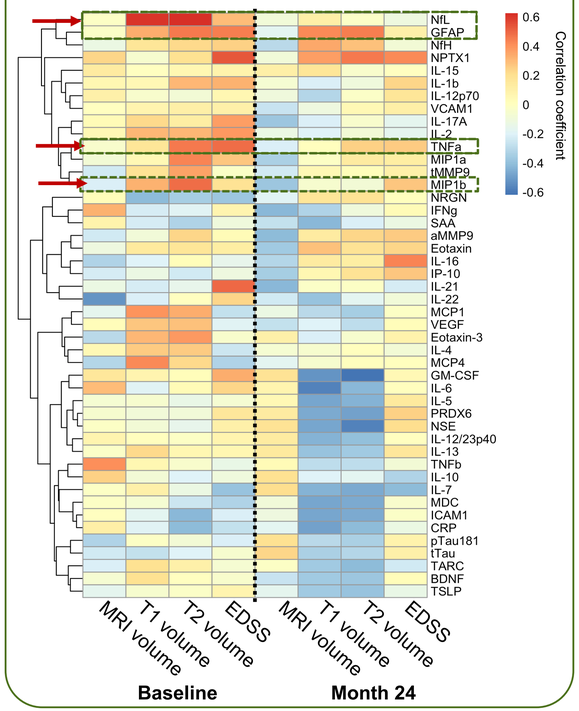
Negatively associated with time to relapse (n=5):



Biomarkers of MS activity **NOT** associated with time to relapse (n=5):



Correlation between serum mediators and clinical disease measures at baseline and month 24



RESULTS & CONCLUSIONS

- AHSCT resulted in significant changes in many soluble inflammatory mediators in serum and CSF.
- Serum cannot be used as a surrogate measure of inflammatory mediators in CSF, except for NfL & GFAP.
- As expected, serum NfL and GFAP strongly correlated with measures of MS disease activity. The serum cytokines most strongly associated with clinical activity over all time points were TNFα and MIP1β.
- Baseline levels of several serum cytokines were associated with time to relapse and may be useful in future studies of predictive modeling.

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