Immunological Markers and Conventional and Advanced MRI after Interferon Beta-1a for Relapsing–Remitting Multiple Sclerosis

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Disclosures

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*A subsidiary of Merck KGaA, Darmstadt, Germany.

Introduction

Pro-inflammatory cytokines appear to contribute to the inflammatory response and tissue injury in multiple sclerosis (MS)

- Anti-inflammatory cytokines are thought to play immunomodulatory roles

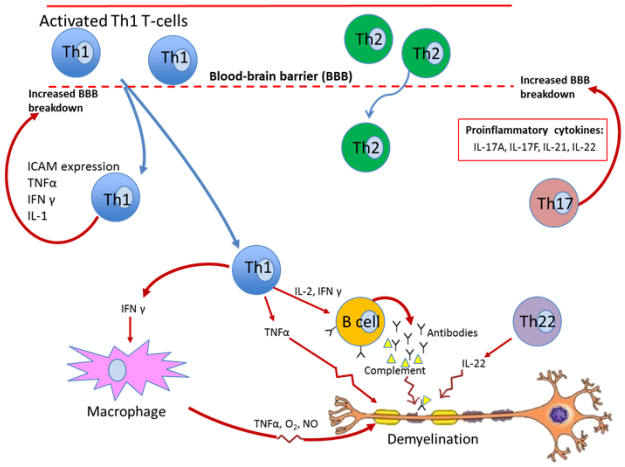
Interferon beta-1a 44 mcg subcutaneously three times weekly (IFN β-1a SC tiw) is well established as a safe and effective treatment option in patients with relapsing–remitting MS (RRMS)

- Mechanism of action of IFN β-1a SC tiw may be in part via modulation of inflammatory activity[1]

Conventional and advanced magnetic resonance imaging (MRI) techniques are increasingly recognized as a valuable tool in monitoring MS disease activity and response to treatment

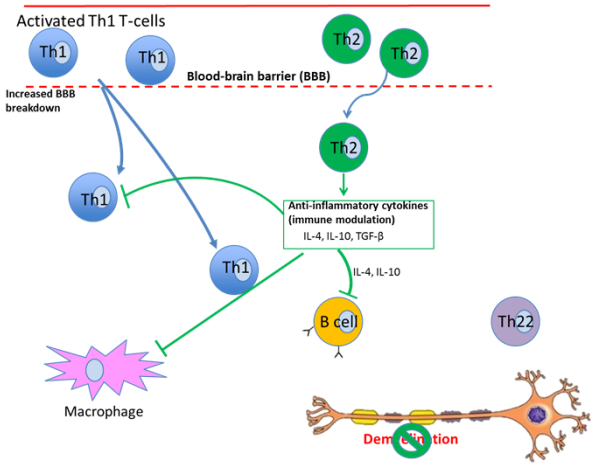
1. Keiseier, BC. *CNS Drugs* 2011:25;491–502.

Immunopathogenesis of MS



ICAM, intercellular adhesion molecule; IFN γ, interferon gamma; IL, interleukin; Th, T-helper; TNF, tumor necrosis factor

Immunopathogenesis of MS (continued)



Advanced MRI: Voxel-Wise Magnetization Transfer Ratio

Advanced MRI techniques allow greater sensitivity in detection of changes in brain lesions and normal-appearing brain tissue (NABT)

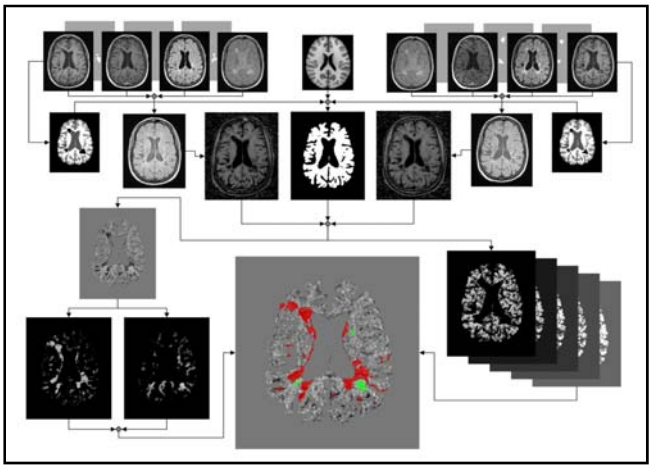
Voxel-wise magnetization transfer ratio (VW-MTR) imaging is an advanced MRI technique sensitive to myelin content changes in NABT and MS lesions of patients with RRMS[1-4]:

- Increasing VW-MTR signal is suggestive of remyelination
- Decreasing VW-MTR signal is suggestive of demyelination

Combining VW-MTR evaluation of disease progression with immunological biomarkers may provide better insight into the role of inflammatory cells in MS lesion formation, as well as into how these processes may be modulated by treatments such as IFN β-1a SC tiw

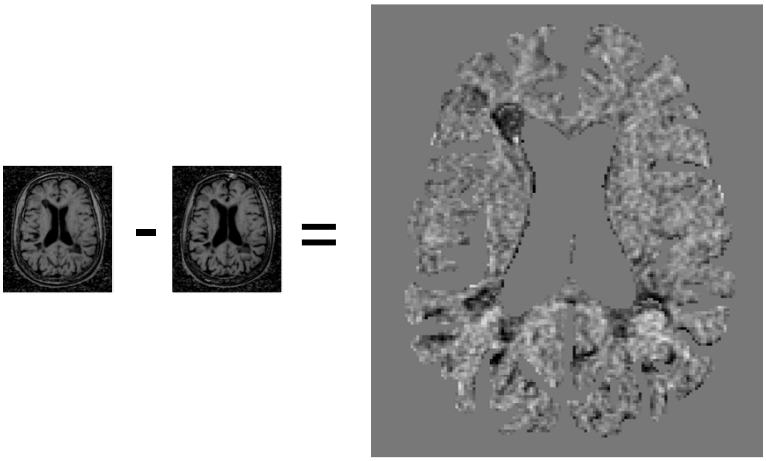
1. Deloire-Grassin MS, *et al. J Neurol Sci* 2000;178:10–6. **2.** Chen JT, *et al. Ann Neurol* 2008;63:254–6. **3.** Tjoa CW, *et al. J Neuroimaging* 2008;18:130–6. **4.** Dwyer M, *et al. J Neurol Sci* 2009;282:86–95.

VW-MTR



Dwyer M, *et al. J Neurol Sci.* 2009;282:86–95.

VW-MTR Methods: Subtraction Map

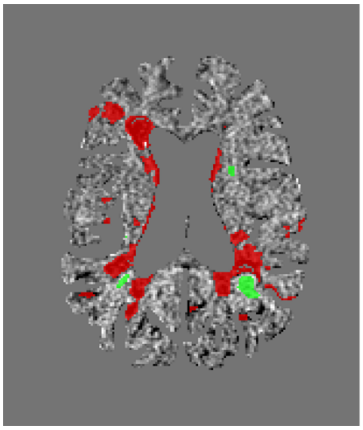


Dwyer M, *et al. J Neurol Sci.* 2009;282:86–95.

VW-MTR Methods: Monte Carlo Quantification

Full Monte Carlo simulation allows for flexibility in selecting thresholds:

- Voxel-wise uncorrected
- Family-wise error corrected
- False discovery rate corrected



Dwyer M, *et al. J Neurol Sci.* 2009;282:86–95.

Study Objective

To gain new insights into the role of inflammatory processes in RRMS pathology and their modulation by treatments such as IFN β-1a SC tiw by evaluating correlations between conventional and advanced MRI measures of disease progression and immunological biomarkers

Methods

Study details

- The Advanced MRI and Immunology Pilot Study was an open-label study conducted in 23 patients with RRMS treated with IFN β-1a 44 mcg SC tiw for 6 months (NCT01085318)[1]
  - Enrolled patients were aged 18–65 years with a diagnosis of RRMS according to the 2010 revised McDonald criteria
- Patients who had ≥1 relapse in the 12 months prior to participation in the pilot study (n=15) were selected for this *post hoc* subgroup analysis
- The percentages of cells expressing IFN gamma (IFN γ), IL-17A, IL-21, IL-22, IL-17F, and IL-4 and IL-10 in $CD4^+$ and $CD8^+$ T cells derived from study participants at baseline and at 6 months were determined using a BD FACSCalibur™ Flow Cytometer and CellQuest software

1. Zivadinov R, *et al. PLoS One* 2014;9:e91098.

Methods (continued)

MRI techniques

- Conventional MRI exams of the brain were performed on a 3T GE Signa LX Excite 12.0 scanner (T2 and T1 lesion volume measurements)
- For VW-MTR MRI:
  - Baseline and follow-up MTR, T1, T1+ gadolinium (Gd), and fluid-attenuated inversion recovery (FLAIR) images were co-registered into a common halfway space
  - Tissue segmentation in grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) was performed on the T1, and lesions were delineated on T1, T1+Gd, and FLAIR images
  - Next, VW-MTR difference maps were created by subtracting VW-MTR map pairs based on longitudinal time points
  - Threshold-free cluster enhancement (TFCE) was applied to the difference maps to increase classification sensitivity
  - A Monte Carlo process was used to derive statistically rigorous voxel-wise TFCE-enhanced p-values
  - Significant areas of increasing and decreasing MTR were extracted and overlaid on tissue and lesion maps to calculate per-region volumes

Statistics

Spearman's rank correlation was used to test the correlations between baseline immunological parameters and changes in conventional MRI/VW-MTR measures over 6 months in a *post hoc* subgroup of patients who had ≥1 relapse in the 12 months prior to study enrollment

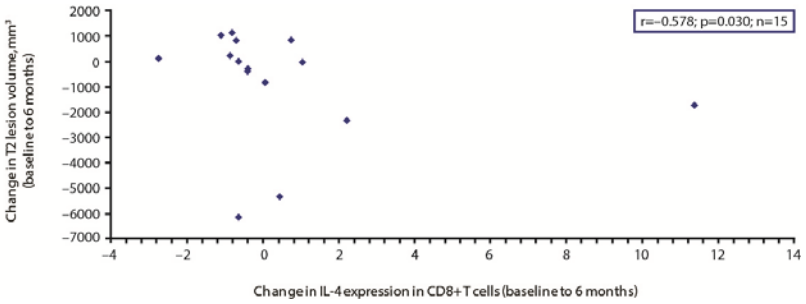
Baseline Characteristics

Baseline characteristics of all patients (n=23) and of patients with ≥ 1 relapse who had Month 6 data (n=15).

	All patients (n=23)	Patients with ≥ 1 relapse* (n=15)
Age, years, mean (SD)	39.9 (10.17)	38.1 (10.28)
Female, n (%)	14 (61)	9 (60)
Race, n (%)		
White	20 (87)	12 (80)
Black	3 (13)	3 (20)
Weight, kg, mean (SD)	79.9 (22.25)	82.2 (21.75)
Height, cm, mean (SD)	171.0 (8.48)	170.3 (8.73)
BMI, kg/m², mean (SD)	27.2 (6.90)	28.3 (6.96)
Multiple sclerosis history		
Years since multiple sclerosis diagnosis, mean (SD), range	6.6 (5.65), 0–20	7.2 (5.23), 1–20
Years since most recent relapse, mean (SD)	1.0 (1.14)	0.8 (0.58)
Number of relapses in past 12 months,† mean (SD)		
0, n (%)	7 (30)	-
1, n (%)	7 (30)	6 (40)
2, n (%)	7 (30)	7 (47)
4, n (%)	2 (9)	2 (13)
EDSS score, median (range)	2.5 (1.0–5.5)	2.3 (1.0–5.5)
Ambulation distance, meters, mean (SD)	475 (94.2)	463 (114.7)

BMI, body mass index; EDSS, Expanded Disability Status Scale; SD, standard deviation
*One patient had a relapse but did not have Month 6 data and so was not included in the analysis.
†Patients reported the same number of relapses for the past 24 months.

Inverse Correlation between IL-4 Expression in CD8+ T Cells and T2 Lesion Volume (Conventional MRI)



Increased percentage of IL-4–expressing CD8+ T cells was associated with decreased T2 lesion volume from baseline to 6 months in patients with ≥1 relapse prior to enrollment

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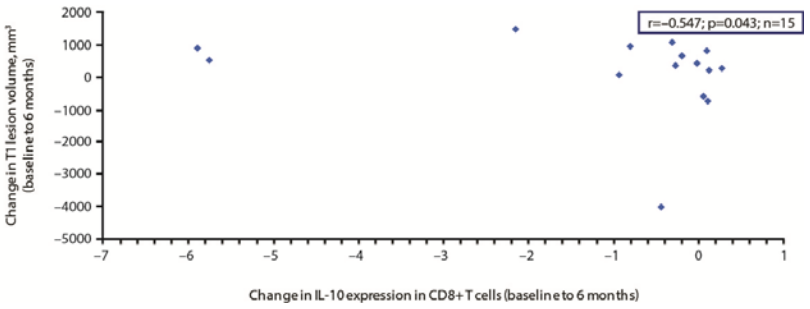
Inverse Correlation between IL-10 Expression in CD8+ T Cells and T1 Lesion Volume (Conventional MRI)



Increased percentage of IL-10–expressing CD8+ T cells was associated with decreased T1 lesion volume from baseline to 6 months in patients with ≥1 relapse prior to enrollment

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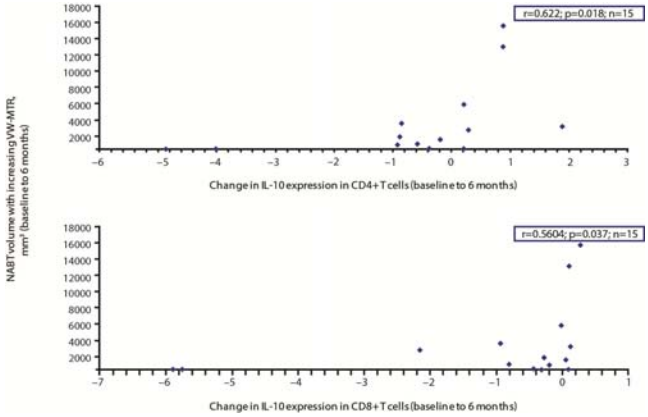
IL-10 Expression in CD4+ and CD8+ T Cells and NABT Volume with Increasing VW-MTR



Increased percentage of IL-10–expressing CD4+ and CD8+ T cells was associated with greater NABT volume with increasing VW-MTR from baseline to 6 months, suggestive of increased remyelination

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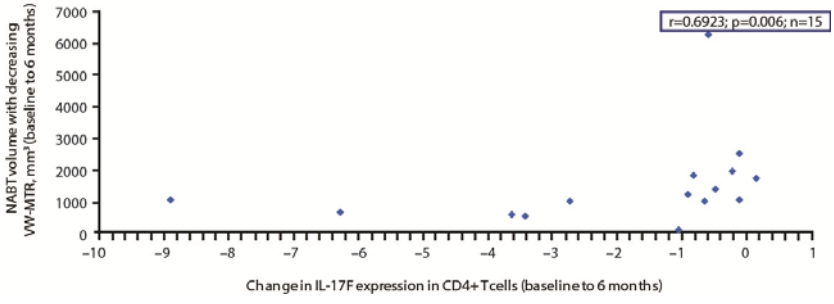
IL-17F Expression in CD4+ T Cells and NABT Volume with Decreasing VW-MTR



Greater percentage of IL-17F–expressing CD4+ T cells was associated with higher volume of NABT with decreasing VW-MTR, suggestive of increased demyelination

Treatment with IFN β-1a SC may reduce inflammation and lead to less demyelination in patients with RRMS

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Conclusions

This *post hoc* analysis supports the potential clinical applicability of VW-MTR imaging in MS

These results highlight correlations between peripheral cells producing pro-inflammatory and immunomodulatory cytokines and myelination changes during treatment with IFN β-1a SC tiw

These correlations could underlie the demonstrated therapeutic efficacy of IFN β-1a SC tiw in RRMS