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Short Report

Impact of disease-modifying therapies on evolving tissue damage in iron rim multiple sclerosis lesions

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Philipp Eisele, Matthias Wittayer, Claudia E Weber, Michael Platten, Lucas Schirmer and Achim Gass

Abstract: We investigated the impact of disease-modifying therapies (DMTs) on the evolving tissue damage in iron rim multiple sclerosis lesions using a novel post-processing magnetic resonance imaging (MRI) approach, the T1/T2 ratio. In this study, on baseline and 1-year follow-up, T1/T2 ratios of iron rim lesions (IRLs) in patients starting DMT (dimethyl fumarate, fingolimod, ocrelizumab) did not statistically differ compared to patients without DMT. At the second follow-up, T1/T2 ratios were significantly lower in IRLs in patients without DMT ($p = 0.002$), suggesting that DMTs have a beneficial delayed effect on lesion evolution and tissue matrix damage in IRLs.

Keywords: Multiple sclerosis, magnetic resonance imaging, iron rim lesions, chronic active lesions

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Correspondence to:
A Gass
Department of Neurology, Medical Faculty Mannheim and Mannheim Center of Translational Neurosciences (MCTN), Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.
achim.gass@medma.uni-heidelberg.de

Philipp Eisele
Matthias Wittayer
Claudia E Weber
Achim Gass
Department of Neurology, Medical Faculty Mannheim and Mannheim Center of Translational Neurosciences (MCTN), Heidelberg University, Mannheim, Germany

Michael Platten
Department of Neurology, Medical Faculty Mannheim and Mannheim Center of Translational Neurosciences (MCTN), Heidelberg University, Mannheim, Germany/German Consortium of Translational Cancer Research (DKTK), Clinical Cooperation Unit Neuroimmunology and Brain Tumor Immunology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Lucas Schirmer
Department of Neurology, Medical Faculty Mannheim and Mannheim Center of Translational Neurosciences (MCTN), Heidelberg University, Mannheim, Germany/Institute for Innate Immunoscience, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Introduction

Over the last years, there has been an increasing interest in "chronic active" or "smoldering" multiple sclerosis (MS) lesions indicating ongoing disease activity in the absence of contrast enhancement.[1] Histopathologically, chronic active lesions are characterized by a self-sustained low degree of chronic inflammation including demyelination and iron accumulation driven by proinflammatory macrophages/microglial cells at the lesion edge with ongoing axonal transection and neurodegeneration.[1–3] Recent combined magnetic resonance imaging (MRI)/histopathologic studies demonstrated that these lesions can be identified in vivo as iron rim lesions (IRLs) on susceptibility-weighted imaging (SWI).[1–3] IRLs are associated with higher disease severity, brain and spinal cord atrophy,[1,4] and could therefore represent a novel imaging marker of disease progression. Since studies analyzing effects of disease-modifying therapies (DMTs) on IRLs are scarce until now,[5] the aim of this study was to investigate the impact of DMTs on the evolving tissue damage in IRLs using a novel post-processing MRI approach, the T1/T2 ratio.[6,7]

Material and methods

In this retrospective study, MS patients (according to the 2010 revised criteria) ⩾18 years of age fulfilling the following criteria were included: the absence of neurological conditions other than MS, cardiovascular or respiratory disease, initiation of DMT with dimethyl fumarate, fingolimod, ocrelizumab, or without DMT (based on their own choice) for at least 6 months; baseline MRI within 6 months after initiation of DMT; two annual follow-up (FU) scans; and at least one IRL on MRI.

Three-dimensional (3D) magnetization-prepared rapid acquisition gradient-echo (MPRAGE, echo time (TE) = 2.49 ms, repetition time (TR) = 1900 ms, inversion time (TI) = 900 ms, spatial resolution = 0.9 mm × 0.9 mm × 0.9 mm), 3D fluid-attenuated inversion recovery (FLAIR, TE = 398 ms, TR = 5000 ms, TI = 1800 ms, spatial resolution = 0.5 mm × 0.5 mm × 0.9 mm), 2D turbo spin-echo (TSE) proton density/T2 (TE = 34/101 ms, TR = 3790 ms, slice thickness (ST) = 3 mm), and SWI (TE = 20 ms, TR = 27 ms, ST = 1.5 mm, voxel size = 0.9 mm × 0.9 mm × 1.5 mm) were acquired on a 3T scanner (Skyra, Siemens).

Using FSL tools (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), bias-field corrected MPRAGE data sets were oriented to the MNI 152 space. The T2- and 3D-FLAIR images were then co-registered to the MPRAGE images. T1/T2 ratio maps were derived by dividing the T1 by the T2 signal value. IRLs were identified on SWI in consensus by two experienced raters. After lesion identification on SWI, the corresponding lesions were identified on co-registered 3D-FLAIR images. Lesion segmentation for each lesion on each timepoint was performed with ITK-SNAP (www.itksnap.org) by an experienced, blinded reader. The resulting lesions masks were applied to the T1/T2 ratio maps, mean values were extracted and used for statistical analysis. Statistics were performed with R, version 4.0.2. Metric variables were log-transformed to achieve normal distribution in all subgroups at all time-points. The main statistical analysis was performed with nested repeated measures analysis of variance (ANOVA) with the log-transformed T1/T2 ratio as dependent variable, group (DMT vs no DMT) as between subject factor, patient as case identifier and time point of the measurement as within subject factor. We also calculated a nested cross-sectional ANOVA for each time point with the T1/T2 ratio as a dependent variable and patient as a subject factor. For sphericity correction, we used the Huynh–Feldt correction. For those confirmatory tests, we corrected alpha for multiple comparison using Bonferroni's correction, resulting in a critical alpha level of $p < 0.0125$. Descriptive analyses of the clinical and imaging variables were additionally performed to ensure group homogeneity. As they were of explorative nature, we did not correct for multiple testing.

This study was approved by the local ethic committee; patient consent was waived due to the retrospective nature of the study and the lack of patient interaction.

Results

Clinical and MRI characteristics are summarized in the table. Fifty-five IRLs in 27 MS patients were included. We found a significant effect of the interaction term of treatment group × time point ($F = 10.56$, $p < 0.001$) in the nested repeated measures ANOVA. We did not find any effects of the factor "group" (DMT vs no DMT) in ANOVAs at baseline and FU1; however, there was a significant effect of the factor "group" at FU2 ($F = 10.89$, $p = 0.002$; see also Figure 1(a)). Figure 1(b) and (c) demonstrates the representative examples.

Discussion

In this study, we investigated the potential impact of DMT on the evolving tissue damage in IRLs using a relatively new post-processing MRI approach, the T1/T2 ratio. Initially proposed as marker of myelin content, MRI-pathology correlational studies suggested that T1/T2 ratio maps represent a broad marker of tissue integrity including demyelination, axonal damage, and neurite/dendrite loss with lower values indicating a more pronounced matrix destruction.[6] Therefore, T1/T2 ratio maps represent a sensitive (semi-)quantitative marker of microstructural tissue damage,[6,7] as it can observed in IRLs.[1,3]

In this study, T1/T2 ratios decreased in all IRLs, a finding that is in line with previous studies that used other quantitative MRI approaches to detect progressive tissue matrix damage in IRLs in vivo.[3,8] Of note, this decrease was significantly higher at the second FU in patients without DMT compared to MS patients starting DMT suggesting that DMTs have a beneficial, but delayed effect on evolving tissue damage in IRLs. Our results are supported by a study that demonstrated dimethyl fumarate–induced reduced susceptibility in IRLs, indicating a decreased activation state in microglial cells.[5] However, the exact corresponding mechanisms still need to be determined. Pathological hallmark of IRLs include ongoing active myelin breakdown and axonal transection driven by activated tissue-resident microglia at the lesion edge.[1,3] Dimethyl fumarate and fingolimod inhibit microglia activation by downregulation of proinflammatory cytokines,[9] whereas studies investigating the effect of B-cell depleting therapies are currently under investigation.

The main limitations of this study include its small sample size, the lack of randomization, the short-term FU, and the absence of an in vitro confirmation. Furthermore, due to the retrospective study design, it is likely that IRLs were of different ages or inflammatory stages at baseline. In addition, even though current studies demonstrated that T1/T2 ratio maps represent a sensitive marker of tissue damage,[6,7] the exact underlying pathological substrates are not completely known. Therefore, our results should be regarded as preliminary observations (Table 1).

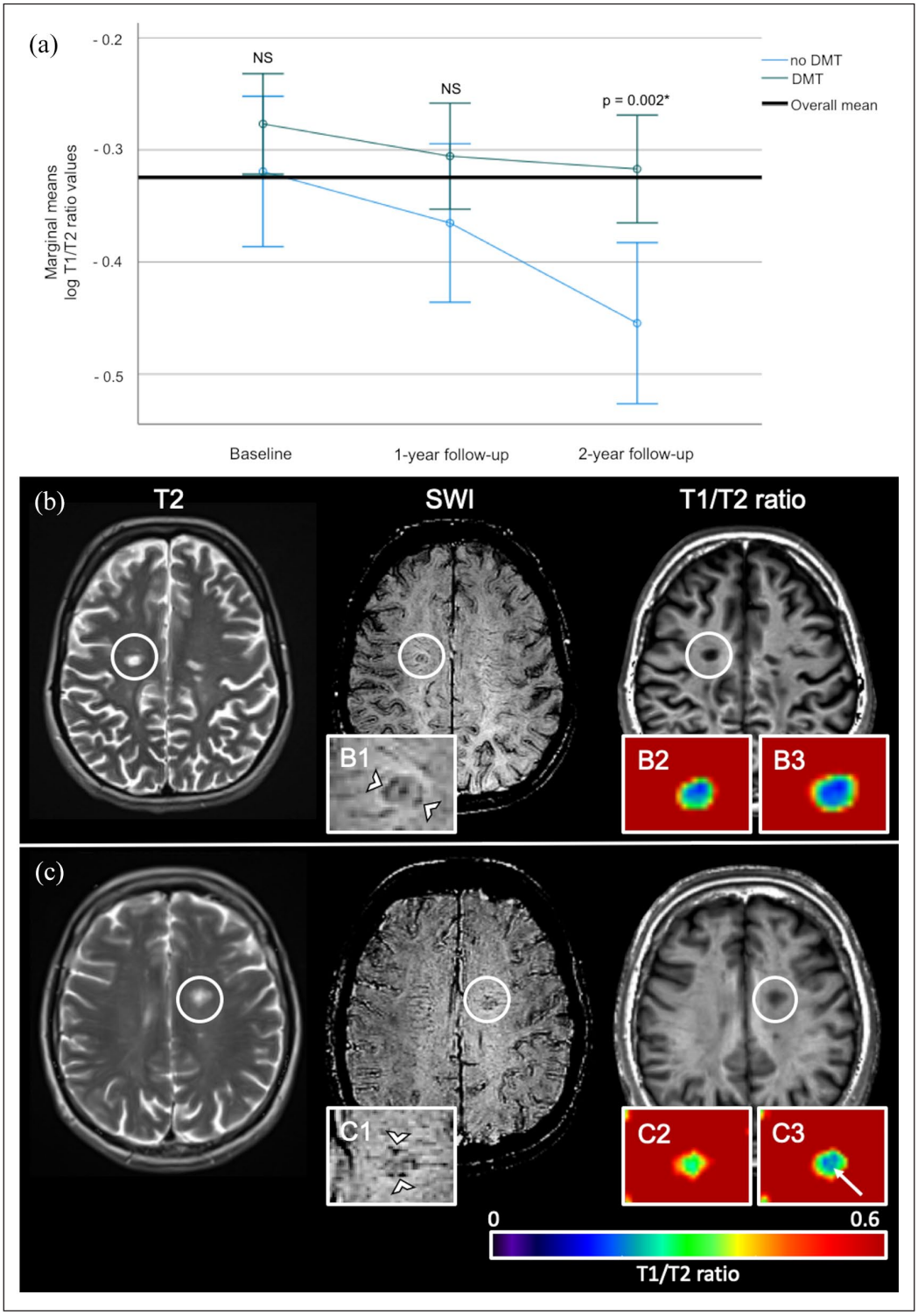

Figure 1. (a) Plot of log-transformed T1/T2 ratio values in iron rim lesions at baseline and follow-up. (b) and (c) From left to right: T2-weighted, susceptibility-weighted images (SWI) and magnification, and T1/T2 ratio maps in a patient starting DMT with fingolimod (b) and a patient without DMT (c). SWI and magnification (B1 and C1) demonstrate the representative examples of iron rim lesions (arrowheads). Color-coded T1/T2 ratio maps at baseline (B2 and C2) and at the 2-year follow-up (B3 and C3). Note the pronounced decrease of T1/T2 values during follow-up in the patient without DMT (arrow).
NS: not significant.
*Compared to no disease-modifying therapy.

Table 1. Characteristics of the study population.

	Dimethyl fumarate group	Fingolimod group	Ocrelizumab group	No DMT group	Statistics
Number of patients	6	6	7	8	–
Age at BL, years, mean ± SD	36.3 ± 14	34.7 ± 11.4	42.7 ± 7.3	45.2 ± 12.3	ANOVA $p=0.29$, NS
Gender (female/male), *n*	4 / 2	5 / 1	4 / 3	6 / 2	Chi-square $p=0.76$, NS
RRMS/SPMS/PPMS, *n*	6/0/0	6/0/0	4/1/2	6/0/2	Chi-square $p=0.15$, NS
Disease duration at BL, years, mean ± SD	1.5 ± 1.8	4.8 ± 4.4	9.3 ± 7.2	6.8 ± 4.9	ANOVA $p=0.06$, NS
EDSS at BL, median (range)	1.5 (0–3)	2.25 (1.5–3.5)	3.5 (2–7)	3.25 (0–6)	ANOVA $p=0.056$, NS
EDSS at FU1, median (range)	1 (0–3)	2.5 (1.5–3.5)	3.5 (2–7)	3.25 (0–6)	ANOVA $p=0.044$; Tukey's post-hoc test $p=0.029$[a]
EDSS at FU2, median (range)	1 (0–3.5)	3.0 (1–6.5)	4.5 (2–7.5)	3.75 (0–7)	ANOVA $p=0.08$, NS
Number of patients with relapses at BL	1	3	0	0	Chi-square $p=0.037$
Number of patients with relapses between BL—FU1	0	2	0	0	Chi-square $p=0.056$, NS
Number of patients with relapses between FU1—FU2	0	2	0	1	Chi-square $p=0.2$, NS
Number of IRLs at BL, mean (range)	2.5 (1–6)	1.5 (1–3)	2 (1–6)	2 (1–6)	ANOVA $p=0.77$, NS
GM volume at BL (mL), mean ± SD	767.2 ± 65.08	783.8 ± 39.67	762.3 ± 47.41	742.73 ± 46.98	ANOVA $p=0.52$, NS
WM volume at BL (mL), mean ± SD	757.17 ± 62.43	715.04 ± 54.45	700.42 ± 30.36	723.18 ± 66.51	ANOVA $p=0.36$, NS
DGM volume at BL (mL), mean ± SD	34.50 ± 2.21	31.11 ± 4.31	31.57 ± 3.48	33.46 ± 5.96	ANOVA $p=0.49$, NS
Total T2 lesion volume at BL (mL), mean ± SD	3.65 ± 3.92	7.92 ± 8.26	6.06 ± 5.5	7.65 ± 12.16	ANOVA $p=0.95$, NS

BL: baseline; DGM = deep gray matter; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; FU: follow-up; GM: gray matter; IRLs: iron rim lesions; NS:
not significant; PPMS; primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; SD: standard deviation; WM: white matter.
[a]Ocrelizumab group compared to the dimethyl fumarate group.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: P.E. has received travel expenses from Bayer Health Care and is member of the Editorial Board of the Journal of Neuroimaging. M.W. reports personal fees from Novartis, Alnylam, Amicus, Biogen, Bristol Myers Squibb, Pfizer, Bial, and other from Boehringer Ingelheim Foundation. C.E.W. reports no disclosures. M.P. has a consultant relationship with Novartis, Merck, and Genentech/Roche, has received non-personal, institutional honoraria from Medac, Merck, Novartis, Teva, Genentech/Roche, and has research agreements with Bayer Health Care. L.S. reports no disclosures. A.G. has received honoraria for lecturing, travel expenses for attending meetings, and financial support for research from Bayer Schering, Biogen Idec, Merck Serono, Novartis, and Teva Neuroscience, and is member of the Editorial Board of the Journal of Neuroimaging.

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ORCID iDs

Philipp Eisele https://orcid.org/0000-0001-6831-4282
Lucas Schirmer https://orcid.org/0000-0001-7142-4116

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