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Effect of teriflunomide on gray and white matter brain pathology in multiple sclerosis using volumetric and diffusion-tensor imaging MRI measures

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ABSTRACT

Objectives: To investigate the effect of teriflunomide on microstructural pathology in the gray matter (GM) and white matter (WM), as measured by changes in brain volume and diffusion-tensor imaging (DTI) in patients with multiple sclerosis (MS).

Methods: 30 relapsing MS patients and 20 healthy controls (HCs) were enrolled in the study and followed prospectively for 12 months with clinical and 3T MRI examinations. Of those, 26 MS patients and 18 HCs completed the 6-month and 22 MS and 16 HCs patients the 12-month follow-up. Whole brain, GM, WM and thalamus volumes, and global and tract-based spatial statistics (TBSS) DTI measures of fractional anisotropy, mean, axial and radial diffusivity were obtained in the thalamus and normal appearing WM (NAWM). MRI differences between the groups were compared using non-parametric statistical methods due to sample size limitations, followed by post-hoc covariate-adjusted models.

Results: At baseline, MS patients showed more severe brain volume and DTI measures compared to HCs ($p < .05$). At follow-up, no significant differences for brain volume and global and TBSS DTI measures between MS patients and HCs were found. No clinical progression or serious adverse events occurred in MS patients over the follow-up.

Conclusions: MS patients did not significantly deteriorate over the follow-up in brain volume or thalamus/NAWM global or TBSS DTI measures, compared to HCs. This suggests that treatment with teriflunomide could potentially slow down accumulation of microstructural tissue damage in the GM and NAWM.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the human central nervous system that affects both the white matter (WM) and gray matter (GM). Both the etiology and cure for MS remain elusive and for many years, scientific research into the pathogenesis of MS has been heavily focused on a disease considered as principally affecting the central nervous system WM.

However, a number of recent neuropathological and neuroimaging studies have clearly demonstrated extensive involvement of the neocortex, thalamus and basal ganglia in patients with MS. [1–8] Neuropathological data implicate significant demyelination and neuro-axonal and synaptic loss in both the early and late phases of the disease process [3,5-7], affecting both cortical and subcortical GM [4,8-11]. The clinical validity of GM and thalamic atrophy measurements has been proven in a number of recent short-, mid- and long-term studies [1,2,8,9,12,13].

Non-conventional MR imaging acquisition and post-processing techniques allow for a more advanced study of neurodegenerative processes at the microstructural level and in specific anatomical structures, such as thalamus and normal appearing WM (NAWM) [14]. One such technique is diffusion tensor imaging (DTI), which is widely used to detect the tissue microstructural integrity changes [15–18]. DTI abnormalities are associated with cognitive impairment, as well as with neurologic disability. DTI has been used to determine the severity of GM and WM pathology in MS patients [16–19].

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There has been an increasing interest in understanding the effects of disease-modifying treatment (DMT) on slowing down GM and WM atrophy and preservation of tissue microstructure integrity, as indicators of effectiveness of treatment [20–22]. Teriflunomide is a novel oral compound approved for the treatment of relapsing MS that inhibits a key enzyme (mitochondrial dihydroorotate-dehydrogenase) in the de-novo pyrimidine synthesis pathway, likely preventing proliferation of T and B cells [23]. The clinical efficacy of teriflunomide was established in phase II and III clinical trials [24–28]. Teriflunomide showed an effect in suppressing inflammatory MRI activity and slowing down brain atrophy progression, however the effects of this treatment on the development of GM atrophy and microstructural changes in GM and WM are unknown.

Against this background, we aimed to elucidate the effect of teriflunomide on GM and thalamic pathology, as well as on the accumulation of microstructural damage in the NAWM in relapsing MS patients over 12 months. The thalamus was particularly chosen as a subcortical target structure for the current study, due to its high susceptibility to atrophy, microstructural changes and its relevance to cognitive function and disability progression [4]. The effect of teriflunomide on these MRI metrics in MS patients were compared to changes in age- and sex-matched healthy controls (HCs) imaged prospectively.

2. Methods

This was a prospective, observational, longitudinal study of the effect teriflunomide on GM and WM pathology over 12 months that recruited 30 MS patients and 20 age- and sex-matched HCs (ClinicalTrials.gov: NCT01881191). The main inclusion criteria were: a) age 18–65, b) MS according to the McDonald criteria, [30] c) relapsing MS, d) Expanded Disability Status Scale (EDSS) scores ≤ 5.5, e) disease duration < 30 years, f) signed informed consent, and g) none of the exclusion criteria. The main exclusion criteria were: a) MS patients with hepatic impairment, b) nursing mothers or pregnant women, c) women of childbearing potential not using reliable contraception, d) patients previously treated with leflunomide, e) clinically significant infectious or neurological illness (for HC only), f) other pathology related to brain MRI abnormalities, and g) normal kidney function (creatinine clearance > 59 mL/min) (patients only).

Baseline assessments included physical and neurologic exams and MRI scans. Study subjects were re-evaluated with neurologic and MRI examinations at 6 and 12 months. Neurologic examinations were not blinded. The MRI analysis was rater-blinded. The protocol was approved by the University at Buffalo Health Sciences Institutional Review Board and all subjects provided their informed consent.

2.1. MRI acquisition

All scans were carried out on a 3T GE Signa Excite HD 12.0 (General Electric, Milwaukee, WI, USA), using a multi-channel head and neck (HDNV) coil. The following scans covering the entire brain were acquired:

- 2D multi-planar dual fast spin-echo (SE) proton density (PD) and T2-weighted images (WI): (TE)1/TE2/repetition time (TR) = 9/98/5300 ms, flip angle (FLIP) = 90°, echo train length (ETL) = 14, voxel size 1x1x3 mm^3 with no gap.
- 2D SE T1-WI: TE/TR = 16/600 ms, FLIP = 90°, voxel size 1x1x3 mm^3 with no gap.
- Fluid-Attenuated Inversion-Recovery (FLAIR): TE/TI/TR = 120/2100/8500 ms (TI-inversion time), FLIP = 90°, ETL = 24, voxel size 1x1x3 mm^3 with no gap.
- 3D high resolution (HIRES) T1-WI using a fast, spoiled, gradient echo with magnetization-prepared inversion recovery pulse (IR-FSPGR), TE/TI/TR = 2.8/900/5.9 ms, FLIP = 10°, voxel size 1x1x1 mm^3.
- 2D echo-planar imaging (EPI) DTI: TE/TR = 90.9/8600 ms, 96 × 96 matrix, FOV 32 cm × 24 cm (in-plane resolution of 3.33 mm × 3.33 mm), FLIP = 90°, ETL = 1, voxel size 3.33× of 3.33 × 3 mm^3 with no gap. DTI-specific parameters included a b-value of 800 s/mm^2 and 30 volumes with non-collinear diffusion gradients.

2.2. MRI analyses

2.2.1. Lesion and brain volume measures

The number of new brain T2 and T1 lesions was based on semi-automated tracing on the digital images. [8] T2 and T1 lesion volumes (LVs) were measured using a semi-automated edge detection contouring-thresholding technique, as previously described [31].

Brain volume measures were determined on 3D T1-WI that were modified by using an inpainting technique to avoid tissue misclassification [32]. At baseline, whole brain, GM and WM tissue volumes, normalized for head size, were calculated using the SIENAX method, [33] whereas for longitudinal changes, the SIENA method was used to calculate the percentage brain volume change (PBVC), [33] and the SIENAX multi-time point method [34] was used to obtain GM volume and WM volume changes. The thalamus volumes were estimated using FMRIB's Integrated Registration and Segmentation Tool (FIRST) [35].

2.2.2. DTI global analysis

DTI image analyses were performed with FSL 5.0 Toolbox [www.fmrib.ox.ac.uk/fsl] and quantitative maps of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were obtained. In order to reduce the gradient distortion inherent in echo-planar imaging (EPI) sequences, a two-step process was executed. First, the b = 0 images were linearly co-registered into the same space as the corresponding 3D TI using FSL Linear Registration Tool (FLIRT) with the boundary-based registration cost-function. The images were then non-linearly co-registered using the Advanced Normalization Tools (ANTs, http://www.picsl.upenn.edu/ANTS) package [36]. The transformations were then applied to bring the DTI-derived maps into the 3D T1 space, using trilinear interpolation. Summary measures were then calculated for the NAWM and thalamus as a whole by using the thalamic segmentations from FIRST [35].

2.2.3. DTI TBSS analysis

Tract-based spatial statistics (TBSS) was used to perform voxel-wise statistical analysis of FA, MD, RD, and AD, as previously described [37]. Additional details regarding the statistical analysis are provided below. A standard space thalamic region of interest, obtained from the Harvard-Oxford atlas, was used to investigate diffusivity measures within the WM tracts passing through the thalamus.

2.3. Statistical analyses

Analyses were conducted using SPSS for Windows version 23.0 (IBM Corp., Armonk, NY). The demographic and clinical characteristics at baseline were compared using chi-square and Student's *t*-test. MRI characteristics were compared using non-parametric statistical methods due to sample size limitations, followed by post-hoc covariate-adjusted models. Differences between MS patients and HCs for brain volume measures were compared using non-parametric Mann-Whitney *U* test and analysis of covariance (ANCOVA), adjusted for age and sex. To reduce the number of comparisons, the left and right thalamic values for a given measure were averaged and used in subsequent statistical analyses. Between group and interaction effects of study group (MS/HCs) and time (baseline to 6 and 12 months), indicating whether MS patients and HCs had differing slopes of change over time, were performed using non-parametric Kruskal-Wallis test and two-way repeated measures analysis of covariance (RM-ANCOVA) adjusted for age, sex