Development and Interrelation of Spatiotemporal Patterns of Brain Atrophy and Lesions During 5 Years' Treatment with Subcutaneous Interferon Beta-1a in Patients with a First Clinical Demyelinating Event in the REFLEX/ION Study

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CONCLUSIONS

Treatment modulates the concomitant spatial relation between inflammation and neurodegeneration.

Pseudoatrophy is more prominent in patients with signs of active inflammation processes.

NOTE:
Refer to Poster P430 for Further Analyses

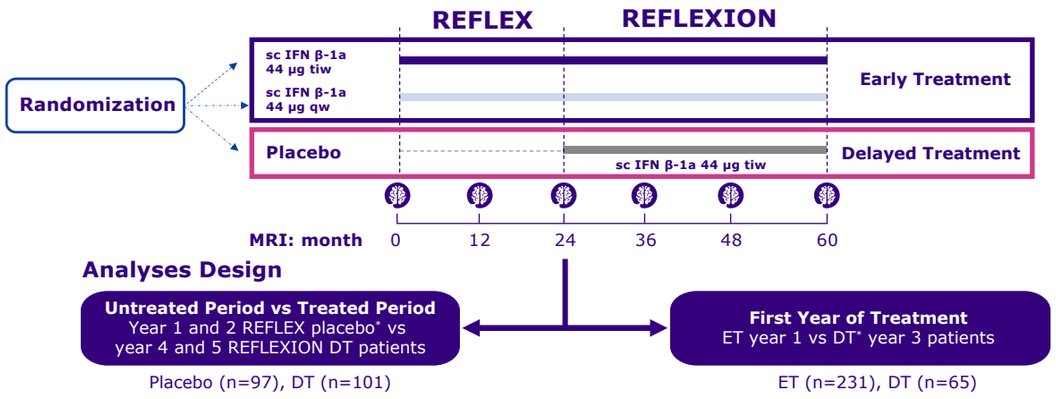
INTRODUCTION

- Inflammation (lesions) and neurodegeneration (atrophy) are present early in the disease course of multiple sclerosis (MS).
- Whether these two processes result from independent pathological mechanisms remains to be elucidated.
- In the 5-year REFLEX/ION study, treatment with subcutaneous interferon β-1a was associated with overall magnetic resonance imaging (MRI) reduced activity in early MS.[1,2] However, how therapy influenced the inter-relation between changes in white matter lesions and brain atrophy was not investigated.

OBJECTIVES

To evaluate treatment influence on the concomitant regional relationship between inflammation and neurodegeneration in the early phase of MS in the REFLEX/ION study.

METHODS



*Patients who converted to MS during the first 2 years of the study were excluded (as per the study protocol, they received treatment upon conversion, which in their cases was earlier than month 24).

DT, delayed treatment; **ET**, early treatment; **MRI**, magnetic resonance imaging; **sc IFN β-1a 44 µg tiw/qw**, treatment with subcutaneous interferon β-1a three times/once per week.

Longitudinal Brain Activity Quantification

- Yearly total lesion volume change (TLVC) was determined by an automated method based on subtraction imaging.
- Yearly percentage brain volume change (PBVC) and percentage ventricular volume change (PVVC) obtained by FMRIB Software Library-Structural Image Evaluation using Normalization of Atrophy (FSL-SIENA) were used as measures of whole-brain and central atrophy, respectively.

Statistical Analyses

- Linear mixed models and the FSL Randomize tool were used for performing whole-brain and voxel-wise analyses, respectively.
- Statistical models employed PBVC/PVVC and yearly cerebral edge displacement maps as dependent variables. TLVC was the independent variable. All the analyses were corrected for age, sex and site. Volumes of significant voxels (V, mm^3) are reported.

RESULTS

Untreated vs Treated Period Whole-brain Analyses

- *REFLEX placebo patients (months 0–24):* A significant positive relation between PBVC and TLVC (B=0.072, SE=0.029, *p*=0.013), and a significant negative relation between PVVC and TLVC (B=-0.917, SE=0.306, *p*=0.003) were found.
- *REFLEXION delayed treatment (DT) patients (months 36–60):* No significant results.

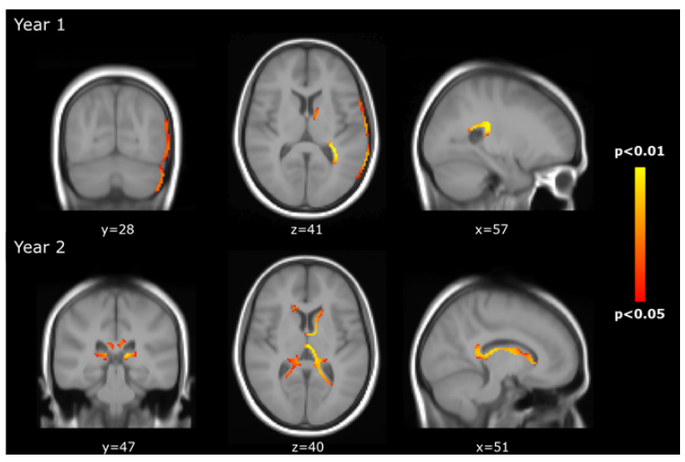
Overall, a similar relation between white matter (WM) lesion activity and brain atrophy was observed through the untreated and treated periods.

Untreated vs Treated Period Voxel-wise Analyses

- *REFLEX placebo patients (months 0–24):* In Year 1, lower TLVC was associated with concomitant faster periventricular, parietal, infratentorial, and temporal lobe atrophy (volume of significant voxels [V]=16,272). In Year 2, higher TLVC was associated with concomitant faster periventricular atrophy (V=11,712).
- *REFLEXION DT patients (months 36–60):* In Years 4 and 5, lower TLVC was associated with concomitant faster atrophy in the frontal, temporal, and periventricular areas (Year 4, V=1784; Year 5, V=8000).

WM lesion activity and brain atrophy showed a different relation across the untreated and treated periods.

Figure 1. Voxel-wise Analyses Within the First Two Years of the Untreated Placebo Period



Yellow-orange show voxels of significant regions where lower TLVC was related to faster atrophy (top row) and where higher TLVC was related to faster atrophy (bottom row).

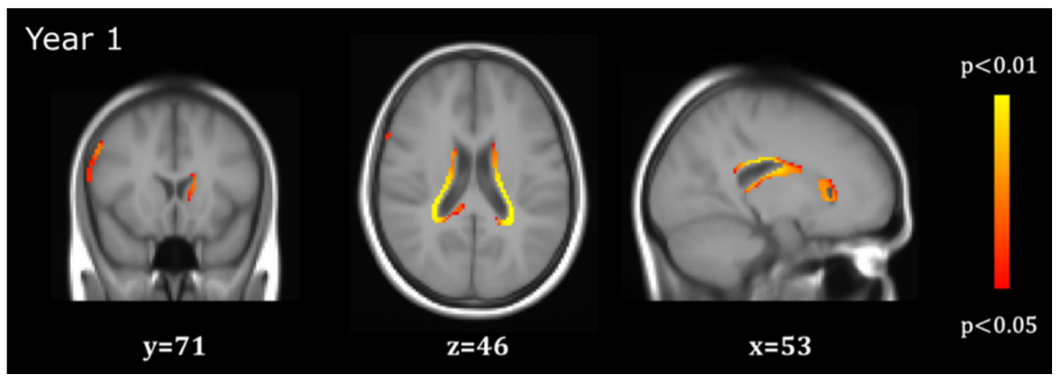
TLVC, total lesion volume change.

First Year of Treatment Early Treated (months 0–12) and Delay Treated (months 24–36)

- *Whole-brain analyses:* Faster whole (B=0.081, SE=0.027, *p*=0.003) and central (B=-1.08, SE=0.284, *p*<0.001) atrophy was associated with lower TLVC in patients who received early treatment. In DT patients, faster whole (B=-0.141, SE=0.065, *p*=0.032) and central atrophy (B=3.41, SE=0.677, *p*<0.001) was associated with higher TLVC.
- *Voxel-wise analyses:* In the first year of treatment, faster periventricular and frontal lobe atrophy was associated with lower TLVC (V=17,536) in ET patients. No significant relation was found for DT patients in Year 3.

Pseudoatrophy effect was present in the first year of therapy for ET patients only. No pseudoatrophy was detected in DT patients, probably related to a lack of WM lesion activity.

Figure 2. Voxel-wise Analyses Within the First Year of Treatment of ET Patients (Year 1)



Yellow-orange show voxels of significant regions where lower TLVC was related to faster atrophy.

ET, early treated; **TLVC**, total lesion volume change.

REFERENCES
1. Comi G, et al. *Lancet Neurol.* 2012; 11(1):33–41. 2. Comi G, et al. *J Neurol Neurosurg Psychiatry*. 2017;88:285–294.

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