DMT22

Development and Interrelation of Whole-Brain Atrophy and Lesion Volume 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

In patients with a first clinical demyelinating event and early multiple sclerosis, a higher white matter lesion volume change in a study year was related to a faster atrophy rate in the following year.

NOTE:
Refer to Poster DMT21
for Further Analyses

INTRODUCTION

- White matter lesions (inflammation) and atrophy (neurodegeneration) are present early in the disease course of MS
- It is unclear whether inflammation and neurodegeneration are temporally related pathological processes
- In the 5-year REFLEX/ION study, early treatment with subcutaneous interferon β-1a was associated with an overall reduction in MRI activity and conversion to clinically definite MS compared to delayed treatment[1]

OBJECTIVES

- **To elucidate whether there is a temporal relation between the development of white matter lesions and atrophy in patients with a first clinical demyelinating event (FCDE) and early MS**
- **To study if these possible associations differ between:**
  - **Patients receiving either early treatment (ET) or delayed treatment (DT)**
  - **Patients who converted to clinically definite MS (CDMS) during the study and those who did not**

METHODS

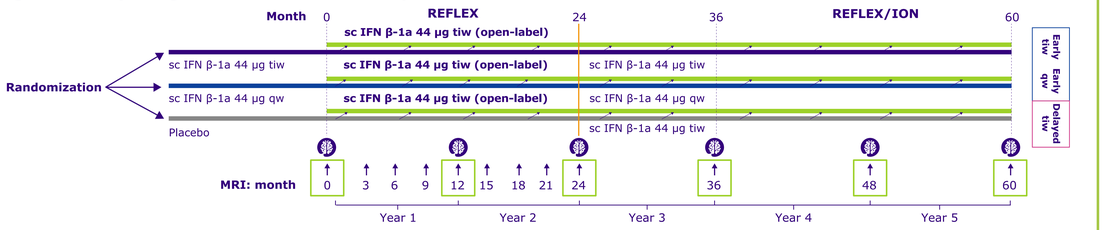
- We analyzed yearly MR images during 5 years in 392 patients presenting with FCDE from the REFLEX/ION study
- Patients received ET (from baseline) or DT (from year 3) with subcutaneous interferon β-1a
- CDMS was defined by a relapse accompanied by an abnormal MRI scan or a sustained increase in EDSS score of ≥1.5 points. Depending on the analysis, converters and nonconverters were either categorized considering the whole study period or using each patient's time-dependent yearly interval CDMS status
- Global and central atrophy were assessed using FSL-SIENA/VIENA to provide yearly percentage volume change of brain (PBVC) and percentage volume change of ventricles (PVVC), respectively
- Yearly total lesion volume change (TLVC) in milliliters was determined by an automated method based on subtraction imaging
- Linear mixed models correcting for age and sex were used for statistical analysis. By applying a time-lag in our models, we investigated whether TLVC was associated with PBVC/PVVC in the following year
- Additional voxel-wise analyses were performed using regional SIENA-R analyses
- Analyses were performed on the stable treatment period where patients had received ≥1 year of treatment to prevent confounding by pseudoatrophy and resolving edema (first year was excluded for ET group, third year for DT group)

Table 1. Demographics of included patients

	Converters to CDMS	Nonconverters to CDMS	Early Treatment	Delayed Treatment	Overall
Patients (N)	162	230	262	130	392
Female, n (%)	95 (58.6)	147 (63.9)	162 (61.8)	80 (61.5)	242 (61.7)
Age, y (mean±SD)	30.32±7.99	32.23±8.52	31.68±8.43	30.97±8.19	31.44±8.35

METHODS (CONT.)

Figure 1. Study Design of the REFLEX/ION Study

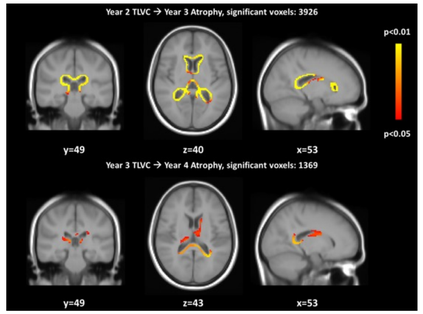


Highlighted in green are the five yearly MRI visits used in the current project. Short arrows indicate conversion to CDMS and the consequent switch to open-label treatment, which could happen at any time throughout the study. Adapted from Comi et al. (2017).[1]

RESULTS

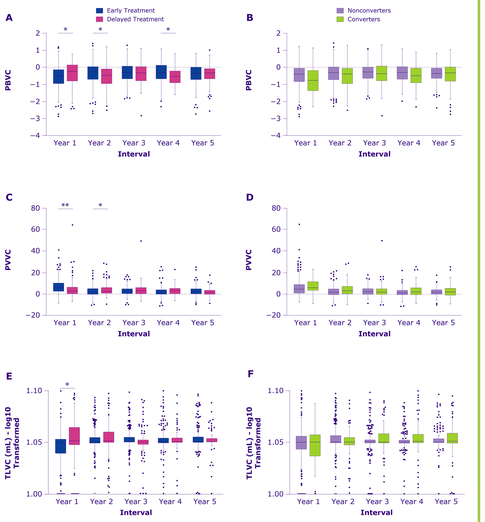
- Considering atrophy rates and changes in lesion volume separately, Figure 2 shows the behavior in the different groups over time. Linear mixed model analyses showed that, across the whole study period, no measures differed between the treatment groups. However, in some intervals, ET and DT patients differed (**Figure 2**). TLVC (B=0.217, SE=0.062, p<0.001) and PBVC (B=−0.112, SE=0.035, p=0.001) increased faster in interval-specific converters to CDMS compared with nonconverters. This was also the case for PVVC for CDMS status across the study period (B=1.206, SE=0.357, p<0.001). At a regional level, voxel-wise analyses confirmed these differences in Years 1, 2, and 4
- During stable treatment, we found that higher lesion volume changes were related to faster global atrophy (PBVC: B=−0.113, SE=0.022, p<0.001) and central atrophy (PVVC: B=1.156, SE=0.164, p<0.001) in the following year. These relations did not differ between patients who did and did not convert across the whole study period. TLVC*treatment was only significant for central atrophy (B=0.972, SE=0.421, p=0.021). In ET patients only, increasing TLVC was associated with faster central atrophy in the following year (B=1.348, SE=0.181, p<0.001)
- Additional voxel-wise analyses showed that, during stable treatment, higher TLVC in Years 2 and 3 in ET patients was related to faster periventricular atrophy in the following year (**Figure 3**). In Year 4 this was the case for both treatment groups

Figure 3. Additional Voxel-wise analyses in the ET group



Significant regions where higher TLVC in Year 2 (top row) and Year 3 (bottom row) was related to faster periventricular atrophy in the following year.

Figure 2. Boxplots depicting the PBVC, PVVC, and TLVC across all years for the ET and DT groups and interval-specific converters and nonconverters



Outliers beyond the y-axis range are shown on the x-axis (panels E and F). The difference within separate years was only tested between the treatment groups. *p<0.05. **p<0.001

Abbreviations: CDMS, clinically definite MS; **DT**, delayed treatment; **EDSS**, Expanded Disability Status Scale; **ET**, early treatment; **FCDE**, first clinical demyelinating event; **FSL-SIENA**, FMRIB's Software Library Structural Image Evaluation, using Normalization, of Atrophy; **MRI**, magnetic resonance images; **MS**, multiple sclerosis; **N/n**, number; **PBVC**, percentage volume change of brain; **PVVC**, percentage volume change of ventricles; **SD**, standard deviation; **TLVC**, total lesion volume change; **VIENA**, modified version of the SIENA method to measure ventricular enlargement; **y**, years

References: **1.** Comi G, et al. *J Neurol Neurosurg Psychiatry*. 2017;88:285–294.

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