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

R.M. Mattiesing[1], G. Gentile[2,3], I. Brouwer[1], D. Jack[4], F. Barkhof[1,5], N. De Stefano[2], B.M.J. Uitdehaag[6], J.W.R Twisk[7], M. Battaglini[2,3], H. Vrenken[1]

[1]Department of Radiology and Nuclear Medicine, Amsterdam UMC, Location VUmc, The Netherlands; [2]Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy; [3]SIENA imaging SRL, Siena, Italy; [4]Merck Serono Ltd, Feltham, UK (an affiliate of Merck KGaA); [5]Institutes of Neurology and Healthcare Engineering, UCL London, London, UK; [6]Department of Neurology, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands; [7]Department of Epidemiology and Data Science, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands

CONCLUSIONS

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

NOTE:
Refer to Poster P458 for Further Analyses

INTRODUCTION

- White matter lesions (inflammation) and atrophy (neurodegeneration) are present early in the disease course of multiple sclerosis (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 magnetic resonance imaging (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 or delayed treatment.**
  - **Patients who converted to clinically definite MS during the study and those who did not.**

METHODS

- We analyzed yearly magnetic resonance images during 5 years in 392 patients presenting with FCDE from the REFLEX/ION study.
- Patients received early (from baseline; **ET**) or delayed (from year 3; **DT**) treatment with subcutaneous interferon β-1a.
- Clinically definite MS (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 non-converters 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 ventricles (PVVC), respectively.
- Yearly total lesion volume change (TLVC) in mL 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 at least one year oftreatment to prevent confounding by pseudoatrophy and resolving edema (first year was excluded for **ET** group, third year for **DT** group).

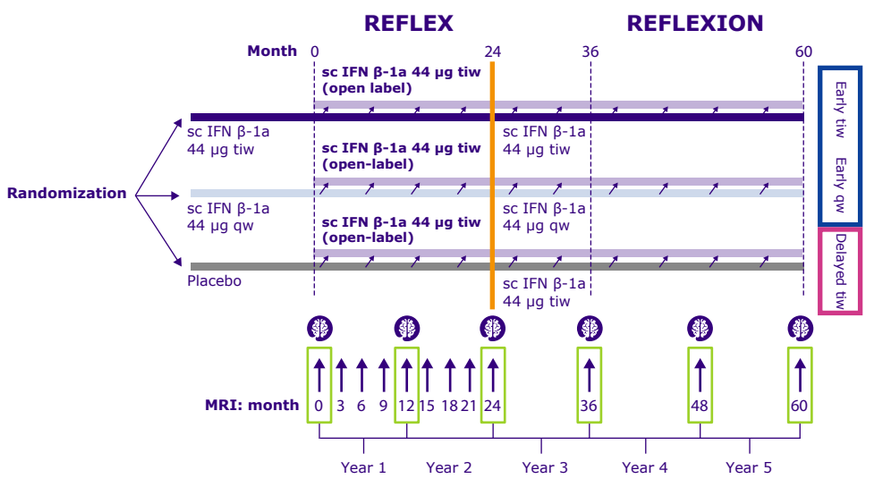
*__FSL-SIENA__, FMRIB's Software Library Structural Image Evaluation, using Normalization, of Atrophy; __VIENA__, modified version of the SIENA method to measure ventricular enlargement

Table 1. Demographics of Included Patients

	Converters to CDMS	Non-converters 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

CDMS, clinically definite multiple sclerosis; **N/n**, number; **SD**, standard deviation; **y**, years

Figure 1. Study Design of the REFLEX/ION Study

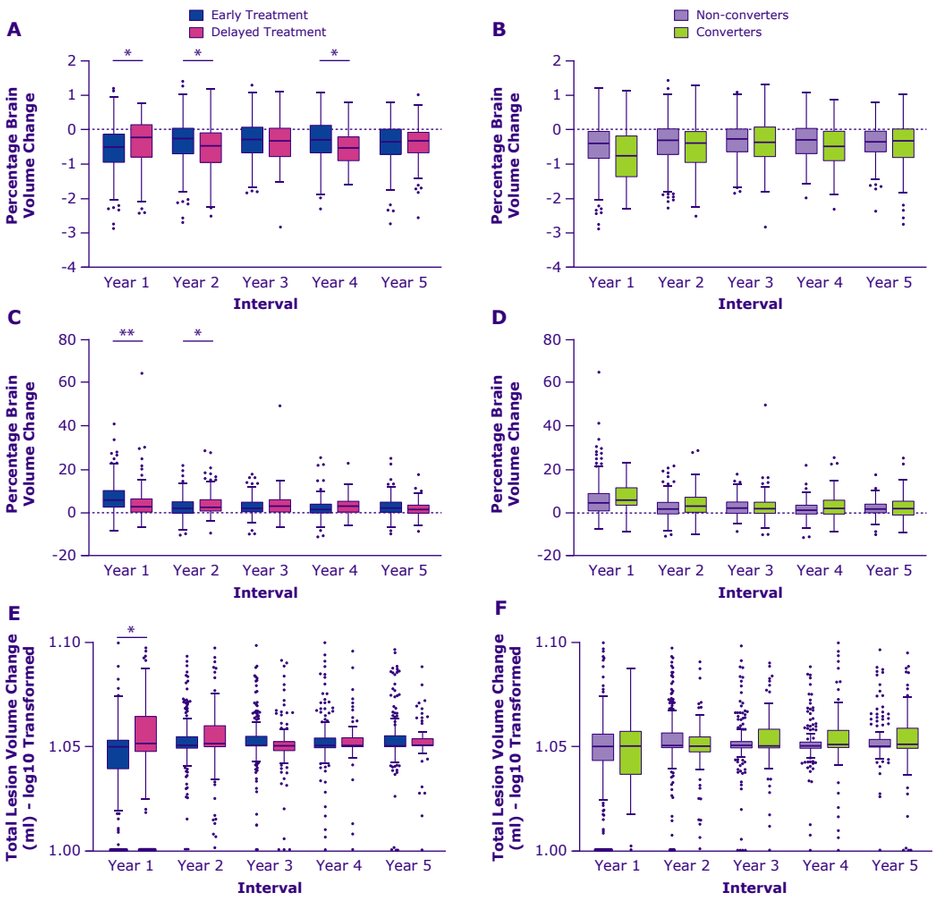


Highlighted in green are the five yearly MRI visits used in the current project. Short arrows indicate conversion to CDMS and the consequent switch to open-label treatment, which could happen at any time throughout the study.
CDMS, clinically definite multiple sclerosis; **IFN**, interferon; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **qw**, once weekly; **REFLEX**, Rebif FLEXible dosing in early MS; **REFLEXION**, REbif FLEXible dosing in early MS extension; **sc**, subcutaneous; **tiw**, three times weekly. Adapted from Comi et al. (2017).[1]

RESULTS

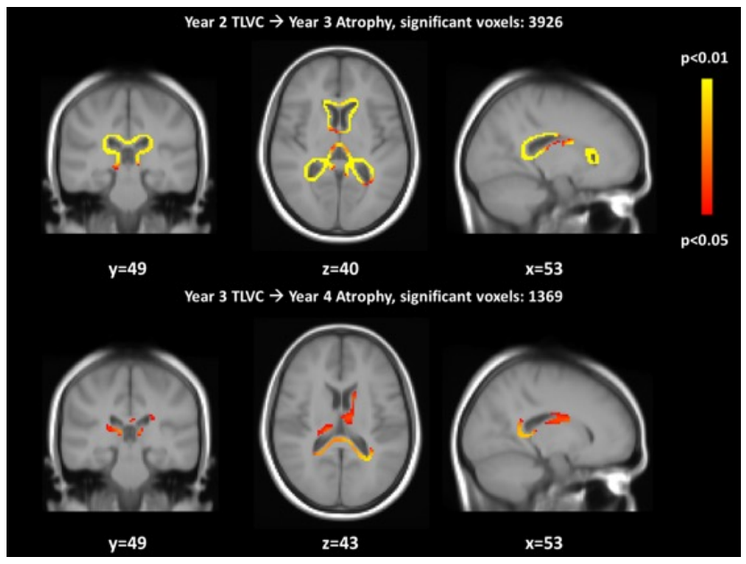
- Considering atrophy rates and changes in lesion volume separately, Figure 2 shows the behavior in the different groups over time. Linear mixed-model analyses showed that, across the whole study period, no measures differed between the treatment groups. However, in some intervals, **ET** and **DT** 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 non-converters. 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 2. Boxplots Depicting the Percentage Brain Volume Change, Percentage Ventricular Volume Change, and Total Lesion Volume Change Across All Years for the Early and Delayed Treatment Groups and Interval-specific Converters and Non-converters



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

Figure 3. Additional Voxel-wise Analyses in the Early Treatment 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. **TLVC**, total lesion volume change.

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

Disclosures: **RMM** has received research support from Merck. IB has received research support from Merck, Novartis, Teva, and the Dutch MS Research Foundation. **DJ** is an employee of Merck Serono Ltd, Feltham, UK (an affiliate of Merck KGaA). **FB** is supported by the NIHR Biomedical Research Centre at UCLH and is a consultant to Biogen, Combinostics, IXICO, Merck, and Roche. **NDS** is a consultant for Biogen, Merck, Novartis, Sanofi-Genzyme, Roche, and Teva; has grants or grants pending from FISM and Novartis, is on the speakers' bureaus of Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva; and has received travel funds from Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. **BMJU** has received consultancy fees from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. **HV** has received research support from Merck, Novartis, Pfizer, and Teva, consulting fees from Merck, and speaker honoraria from Novartis; all funds were paid to his institution. **GG**, **MB**, and **JWRT** have nothing to disclose.

Editorial support was provided by Clara Garcia-Gorro of inScience Communications, Springer Healthcare Ltd, UK, and was funded by Merck Healthcare KGaA, Darmstadt, Germany.

ClinicalTrials.gov identifier: NCT00813709.

Presented at ECTRIMS 2021 Virtual Congress | 13–15 October

This study was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945)