Gray Matter Volume and Myelination Assessed by Magnetization Transfer Ratio Predict Disease Progression in Secondary Progressive Multiple Sclerosis: Exploratory Analyses from the EXPAND Study

Robert J. Fox[1]; Ludwig Kappos[2]; Bruce A.C. Cree[3]; Gavin Giovannoni[4]; Amit Bar-Or[5]; Ralf Gold[6]; Patrick Vermersch[7]; Frank Dahlke[8]; Thomas Hach[8]; Goeril Karlsson[8]; Shannon Ritter[9]; Daniela Piani-Meier[8]; Douglas L. Arnold[10,11]

Introduction

- In the Phase 3 EXPAND study, siponimod compared with placebo significantly reduced the risk of disability progression, worsening in CPS, and MRI measures of disease in patients with SPMS[1,2]
  - Data from the extension part confirmed a sustained effect of siponimod on disability and CPS[3]
  - Siponimod (vs. placebo) significantly reduced both cGM and thalamic volume loss and exerted beneficial effects on MTR in the core part[4,5]
- Several studies suggest that GM volume loss reflects neurodegeneration[6,7] and is associated with long-term disability accumulation and cognitive decline[8-10]

Objective

- Data from the core + extension parts of the EXPAND study (median study duration: 54.1 months) were used to investigate the prognostic value of different baseline MRI variables for:
  - Disease progression according to EDSS
  - A composite[11] of EDSS and SDMT[a]
- MRI parameters included:
  - Conventional MRI parameters (e.g. acute inflammatory activity, lesion burden and NBV)
  - cGM and thalamic volume (measures of neurodegeneration)
  - MTR (a marker of myelin density and brain tissue integrity[12,13])

[a]For prognostic value of MRI parameters on disease progression on SDMT, please refer poster "*Benedict RHB, et al. Baseline MRI Predictors of Cognitive Processing Speed in Participants with Secondary Progressive Multiple Sclerosis from the Phase 3 EXPAND study*" (AAN 2021); cGM, cortical gray matter; CPS, cognitive processing speed; EDSS, Expanded Disability Status Scale; MRI, magneric resonance imaging; MTR, magnetization transfer ratio; NBV, normalized brain volume; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis; 1. Kappos L, et al. Lancet. 2018;391:1263–73; 2. Benedict RHB, et al. Neurology 2021;96(3): e377-e386; 3. Kappos L. et al. Presented at AAN 2020, S40.003; 4. Arnold DL, et al. Presented at AAN 2020, S40.006; 5. Fox RJ. et al. Presented at AAN 2020, S40.005; 6. Arnold DL. et al. Presented at ECTRIMS 2019, P1057; 7. Larochelle C. et al. Trends Neurosci. 2016;39:325–39; 8. Eshaghi A, et al. Ann Neurol. 2018;83:210–22; 9. Rocca MA, et al. Radiology. 2010;257:463–69; 10. Schoonheim MM, et al. Neurology. 2015;84:776–83; 11. Kappos L. et al. Presented at AAN 2019, S12.006; 12. Filippi M et al. Lancet Neurol. 2019;18(2):198–210; 13. Arnold D et al. J Neurol. 2014; 261(12): 2429–37.

Methods

- An exploratory analysis from the Phase 3 EXPAND study (core+extension[a] part; median study duration: 53.1 months) in SPMS patients that was restricted to patients randomized to receive siponimod during the core part (MRI cohort [n=1099]; MTR cohort [n=402]) to avoid confounding effects due to variable exposure to siponimod during the core part, and patients switching from placebo to siponimod in the extension part
- Patients were categorized into quartiles of baseline MRI parameters and the prognostic value of MRI parameters was assessed by comparing outcomes according to the 'worst versus best' quartile or 'presence versus absence' of Gd+ T1 lesions at baseline

cMRI			MTR
Brain volume (Q1 [worst] / Q4 [best])	**Lesion burden (Q4 [worst] / Q1 [best])**	**Acute inflammatory parameters (presence/absence)**	**Median normalized nMTR (Q1 [worst] / Q4 [best])**
NBV	T1 LV	Gd+ T1 lesions	nMTR-cGM
cGM	T2 LV		nMTR-NABT
Thalamic volume			nMTR-NAWM

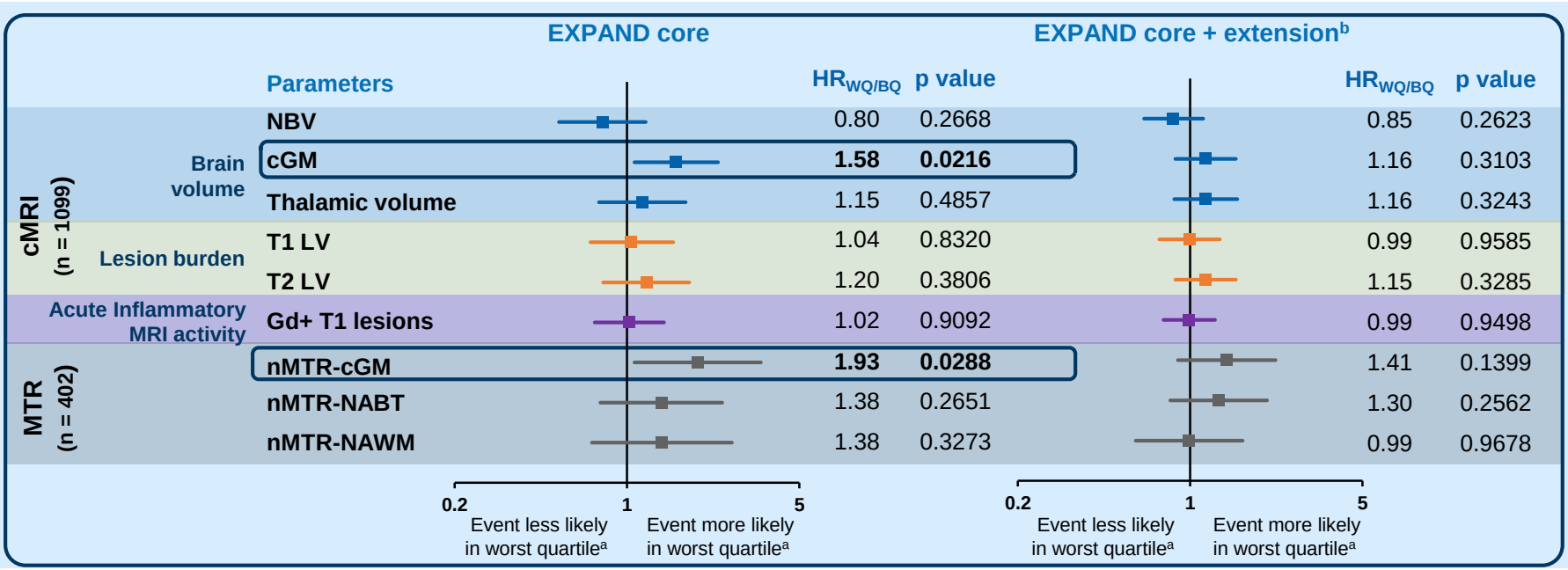
Statistical analysis

- Both short-term (core part) and longer-term (core+extension[a] part) outcomes were analyzed using a Cox regression analysis with the respective clinical outcome as a baseline covariate
- The Cox regression models were adjusted for EDSS score at baseline. For the composite endpoint, the models were adjusted for EDSS and SDMT scores at baseline
- P-values provided are nominal and no multiplicity adjustments were made, therefore, statistical interpretation should be made with caution

[a]Extension data cut-off: 06-Apr-2019 (Month 36 visit of extension]; total study duration (core+extension): ≤5 years; median duration of core part was 21 months; cGM, cortical gray matter; cMRI, conventional magnetic resonance imaging; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; NBV, total normalized brain volume; nMTR, normalized magnetization transfer ratio; NABT, normal appearing brain tissue; NAWM, normal appearing white matter; NBV, normalized brain volume; PY, patient year; SPMS, secondary progressive multiple sclerosis; T1 LV, T1 lesion volume; T2 LV, T2 lesion volume

Results – EDSS

Time to 6mCDP$_{EDSS}$ in Siponimod-treated Patients: Hazard Ratio (Worst versus Best Quartile)[a]

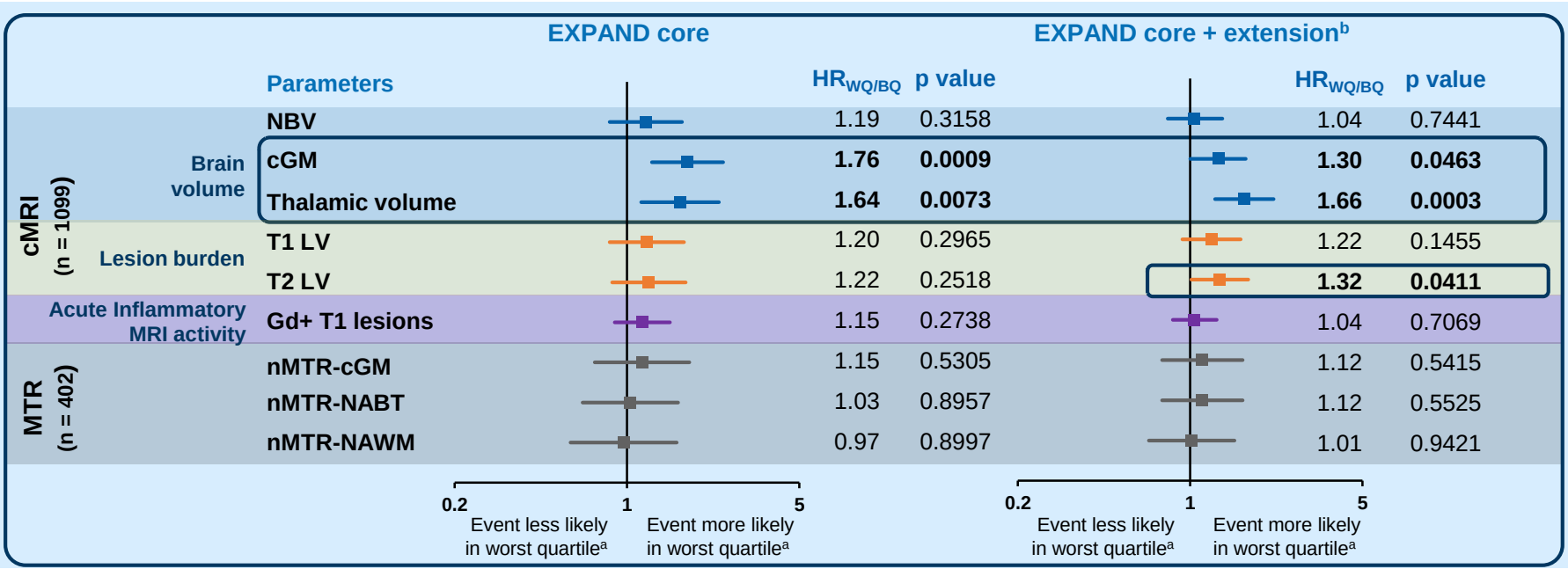


- Patients in worst quartile of nMTR cGM and cGM volume had a higher risk for 6mCDP$_{EDSS}$ versus patients in the best quartile during the core part; during the core + extension part, trends were observed for nMTR-cGM and nMTR-NABT
- A prognostic utility of baseline NBV, thalamic volume, lesion-based MRI measures (T1 LV and T2 LV) and acute inflammatory activity (Gd+ T1) for-disability progression in SPMS was not observed

[a]For acute inflammatory activity, the HR was based on presence versus absence of Gd+ lesions; [b]Extension data cut-off: 06-Apr-2019 (Month 36 visit of extension]; total study duration (core+extension): ≤5 years; median duration of core part was 21 months; 6mCDP$_{EDSS}$, 6-month confirmed disability progression in EDSS; cGM, cortical gray matter; cMRI, magnetic resonance imaging, EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; HR$_{WQ/BQ}$, hazard ratio (worst quartile versus best quartile); n. number of patients; nMTR, normalized magnetization transfer ratio; NABT, normal appearing brain tissue; NAWM, normal appearing white matter; NBV, normalized brain volume; PY, patient year; SPMS, secondary progressive multiple sclerosis; T1 LV, T1 lesion volume; T2 LV, T2 lesion volume

Results – EDSS + SDMT

Time to 6mCDP$_{EDSS/SDMT}$ in Siponimod-treated Patients: Hazard Ratio (Worst versus Best Quartile)[a]



- Patients in the worst quartile of cGM and thalamic volume at baseline were more likely to progress on the composite EDSS-SDMT measure during short (core part) and longer terms (core + extension part); T2 LV became significantly prognostic only during the longer term (core + extension part)
- Associations between other baseline MRI measures and disease progression on the composite EDSS-SDMT measure were not observed

[a]For acute inflammatory activity, the HR was based on presence versus absence of Gd+ lesions; [b]Extension data cut-off: 06-Apr-2019 (Month 36 visit of extension]; total study duration (core+extension): ≤5 years; median duration of core part was 21 months; 6mCDP$_{EDSS/SDMT}$, 6-month confirmed disability progression in composite EDSS and SDMT; cGM, cortical gray matter; cMRI, conventional magnetic resonance imaging; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; HR$_{WQ/BQ}$, hazard ratio (worst quartile versus best quartile); n. number of patients; nMTR, normalized magnetization transfer ratio; NABT, normal appearing brain tissue; NAWM, normal appearing white matter; NBV, normalized brain volume; PY, patient year; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis; T1 LV, T1 lesion volume; T2 LV, T2 lesion

Conclusions

- In SPMS patients treated with siponimod, nMTR cGM followed by cGM volume were prognostic for disease progression assessed by EDSS (6mCDP$_{EDSS}$) in the core part of the study
- Thalamic volume and cGM volume were prognostic for disease progression assessed by the composite EDSS/SDMT (6mCDP$_{EDSS/SDMT}$) outcome during both the short and longer-term; T2 LV was prognostic during the longer term only
- Other baseline MRI measures including NBV, T1 LV and acute inflammatory activity (Gd+ T1) were not associated with disability progression in siponimod-treated SPMS patients
- These data underscore the clinical relevance of cGM pathology for disease progression in SPMS

Disclosures

Robert J. Fox has received personal consulting fees from Actelion, Biogen, Celgene, EMD Serono, Genentech, Immunic, Novartis and Teva. He has served on advisory committees for Actelion, Biogen, Immunic and Novartis, and received clinical trial contract and research grant funding from Biogen and Novartis.; **Ludwig Kappos**' institution (University Hospital Basel) has received the following exclusively for research support: Steering committee, advisory board, and consultancy fees (Actelion, Addex, Bayer HealthCare, Biogen Idec, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB, and Xenoport); speaker fees (Bayer HealthCare, Biogen Idec, Merck, Novartis, Sanofi, and Teva); support of educational activities (Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi, and Teva);license fees for Neurostatus products;and grants (Bayer HealthCare, Biogen Idec, European Union, InnoSwiss, Merck, Novartis, Roche Research Foundation, Swiss MS Society, and Swiss National Research Foundation); **Bruce A.C. Cree** reports personal fees for consulting from Alexion, Atara, Autobahn, EMD Serono, Novartis, Sanofi, Therini and TG Therapeutics and received research support from Genentech**; Gavin Giovannoni** is a steering committee member on the daclizumab trials for AbbVie, the BG12 and daclizumab trials for Biogen, the fingolimod and siponimod trials for Novartis, the laquinimod trials for Teva and the ocrelizumab trials for Roche. He has also received consultancy fees for advisory board meetings for oral cladribine trials for Merck KGaA, Sanofi Genzyme, and in relation to DSMB activities for Synthon BV, as well as honoraria for speaking at the Physicians' summit and several medical education meetings. He is also the Co-Chief Editor of Multiple Sclerosis and Related Disorders (Elsevier); **Amit Bar-Or** has participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from: Janssen/Actelion; Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Roche/Genentech, Medimmune, Merck/EMD Serono, Novartis, Sanofi-Genzyme; **Ralf Gold** has received compensation for serving as a consultant or speaker from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience. He, or the institution he works for, has received research support from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience. He has also received honoraria as a Journal Editor from SAGE and Thieme Verlag; **Patrick Vermersch** has received compensation for consulting and/or research and registration, travel, and accommodation for meetings from Biogen, Roche, Novartis, Sanofi, Teva, Merck, Celgene, Imcyse and AB Science; **Douglas L. Arnold** has received honoraria from Acorda, Biogen Idec, Genentech, Genzyme, Novartis, F. Hoffmann-La Roche and Sanofi-Aventis; research support from Novartis and Biogen; and has an equity interest in NeuroRx Research, which performed the MRI analysis for the trial.

Frank Dahlke, **Thomas Hach**, **Goeril Karlsson**, **Shannon Ritter** and **Daniela Piani-Meier** are employees of Novartis.

Funding source: This study is supported by Novartis Pharma AG, Basel, Switzerland.

Acknowledgments: Writing support was provided by Jitendriya Mishra and Paul Coyle (Employees of Novartis). The final responsibility for the content lies with the authors.

Affiliations

[1]Center for Treatment and Research in Multiple Sclerosis, Neurological Institute, Cleveland, OH, USA; [2]Neurologic Clinic and Policlinic and Research Center for Clinical Neuroimmunology and Neuroscience, Departments of Medicine,Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland; [3]UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco,San Francisco, CA, USA; [4]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [5]Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [6]Department of Neurology, St Josef-Hospital/Ruhr University Bochum, Bochum, Germany; [7]Univ. Lille, Inserm U1172, Lille Neuroscience and cognition, CHU Lille, FHU Precise, Lille, France; [8]Novartis Pharma AG, Basel, Switzerland; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]Brain Imaging Centre, Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada; [11]NeuroRx Research, Montreal, QC, Canada

Poster Presented at the American Academy of Neurology (AAN) 2021, April 17-22, 2021