#1892: Evidence for Improved Myelination in Patients Treated with Siponimod: Results from the Phase 3 EXPAND MRI Substudy

Authors

D. L. Arnold[1], P. Vermersch[2], B. A. C. Cree[3], A. Bar-or[4], G. Giovannoni[5], R. Gold[6], D. Piani-Meier[7], S. Arnould[7], S. Ritter[8], G. Karlsson[7], L. Kappos[9], R. J. Fox[10]; [1]NeuroRx Research, Montreal, Quebec/Canada, [2]University Lille, Lille/France, [3]UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, California/USA, [4]Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania/USA, [5]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London/United Kingdom, [6]Department of Neurology, St Josef-Hospital/Ruhr-University Bochum, Bochum/Germany, [7]Novartis Pharma AG, Basel/Switzerland, [8]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey/USA, [9]Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel/Switzerland, [10]Mellen Center for Treatment and Research in Multiple Sclerosis, Neurological Institute, Cleveland, Ohio/USA

Type

Abstract

Topic

MS and related disorders

Category

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Background and aims

Changes in magnetisation transfer ratio (MTR) are widely used as a marker of changes in myelin density in brain. In preclinical studies, siponimod showed evidence of remyelinating effects. This exploratory analysis assessed the effect of siponimod on MTR versus placebo in different brain regions, and MTR recovery within lesions.

Methods

This prospective, MTR EXPAND substudy included 633 secondary progressive multiple sclerosis (SPMS; siponimod [n=409]; placebo [n=224]) patients. MTR was analysed in normal-appearing brain tissue, cortical grey matter and normal-appearing white matter at baseline, Month (M)12 and M24. MTR was normalised to reduce MTR variability across scanners. Median absolute normalised MTR (nMTR) change from baseline expressed in percent units was derived from mixed models for repeated measures. MTR recovery metrics were assessed in new MTR lesions comparing nMTR decrease from pre- to post-lesion timepoints for siponimod versus placebo.

Results

Siponimod reduced median nMTR decrease from baseline to M12 and M24 versus placebo across brain tissues. Decrease was lower with siponimod at M24 across tissues by −55% to −98% (p<0.05; **Table).** In normal-appearing white matter, siponimod appeared to have fully prevented a decrease in nMTR. Lesion MTR recovery favoured siponimod (−1.321) versus placebo (−1.506; difference, 0.185 [0.056; 0.314]; p=0.005).

Table. Absolute change from baseline in median normalised MTR (percent unit) by brain tissue

Brain tissue	Adjusted means		% Reduction; p-value
	Siponimod (N=409) (N'=327)	Placebo (N=224) (N'=180)	
Normal-appearing brain tissue			
M12	−0.016	−0.024	−38%; p=0.3178
M24	−0.022	−0.056	−61%; p=0.0187
Cortical grey matter			
M12	−0.019	−0.026	−27%; p=0.4236
M24	−0.025	−0.056	−55%; p=0.0468
Normal-appearing white matter			
M12	0.002	−0.019	−105%; p=0.0209
M24	−0.001	−0.045	−98%; *P*=0.0018

N, number of patients included in the MTR sub-study (with any MTR data)
N', number of patients included in the analysis (i.e with at least one result post-baseline)
Absolute median normalised MTR change from baseline was derived from mixed models for repeated measures adjusted for treatment, region, age, visit, baseline median normalised MTR of the respective brain tissue, baseline number of gadolinium-enhancing T1 lesions, baseline T2 lesion volume and treatment by visit and baseline median normalized MTR by visit interactions as covariates
M, month; MTR, magnetisation transfer ratio

Table. Absolute change from baseline in median normalised MTR (percent unit) by brain tissue

Conclusion

Siponimod demonstrated a consistent and significant effect on the MTR decrease over time in normal-appearing white matter and cortical grey matter versus placebo, and improved MTR recovery in newly formed lesions. These data are consistent with observations in preclinical models and support potential beneficial effects of siponimod on remyelination in SPMS patients.

Disclosure

This study was funded by Novartis Pharma AG, Basel, Switzerland. A detailed disclosure from each author will be included in the oral/poster presentation. Abstract also submitted to AAN 2020; acceptance pending.

Affirmations

Authors agreement: I confirm, that all authors mentioned in the author block of this abstract have been informed about, and agreed to this submission. (I confirm)

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