DMT33

Characterization of Peripheral Immune Cell Dynamics and Repopulation Patterns in the First 12 Months of Cladribine Tablets Treatment: MAGNIFY-MS Study

Heinz Wiendl,[1] Klaus Schmierer,[2,3] Suzanne Hodgkinson,[4] Tobias Derfuss,[5] Andrew Chan,[6] Finn Sellebjerg,[7] Anat Achiron,[8] Xavier Montalban,[9] Alexandre Prat,[10] Nicola De Stefano,[11] Frederik Barkhof,[12,13] Letizia Leocani,[14] Patrick Vermersch,[15] Anita Chudecka,[16] Sanjeev Roy,[17] Ursula Boschert[17]

[1]Department of Neurology, Institute of Translational Neurology, University of Münster, Münster, Germany; [2]Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, UK; [3]Clinical Board Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, UK; [4]Ingham Institute for Applied Medical Research, University of New South Wales Medicine, Sydney, Australia; [5]Department of Neurology, University Hospital Basel, Basel, Switzerland; [6]University Hospital of Berne, University of Berne, Berne, Switzerland; [7]Danish MS Center, Department of Neurology, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark; [8]Multiple Sclerosis Center, Sheba Academic Medical Center, Ramat Gan, Israel; [9]Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitari Vall d'Hebron, Barcelona, Spain; [10]Department of Neurosciences, Université de Montréal, Montréal, QC, Canada; [11]Department of Neurological and Behavioural Sciences, University of Siena, Siena, Italy; [12]Department of Radiology, VU University Medical Center, Amsterdam, The Netherlands; [13]UCL Institute of Neurology, London, UK; [14]Experimental Neurophysiology Unit, Vita-Salute San Raffaele University, Milan, Italy; [15]University of Lille, Inserm U1172 LilNCog, CHU Lille, FHU Precise, Lille, France; [16]Cytel Inc., Geneva, Switzerland; [17]Ares Trading S.A., Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

CONCLUSIONS

MAGNIFY-MS MRI results suggest an early onset of cladribine tablets action. This may be mediated through a specific pattern of sustained decrease and reconstitution of B and T cell subtypes.

The pronounced effect on B cells, especially memory B cells in the first 2 months of cladribine tablet treatment, suggests a contribution to early efficacy onset.

Sustained depletion of memory B cells and the moderate decrease across T cell subtypes may contribute to the long-term effect of cladribine tablets.

INTRODUCTION

- In the treatment of MS, immune reconstitution therapies are used for short, intermittent periods to allow for treatment-free periods[1,2]
- Long-term lymphocyte dynamics have been evaluated for CLARITY, CLARITY Extension, and PREMIERE studies,[3] indicating immune cell repopulation after treatment with cladribine tablets
- MAGNIFY-MS aims to determine the onset of action of cladribine tablets (3.5 mg/kg cumulative dose over 2 years) in patients with highly active relapsing MS*
- The action of cladribine tablets on immune cells may be key for both onset and durability of its effect in people with MS

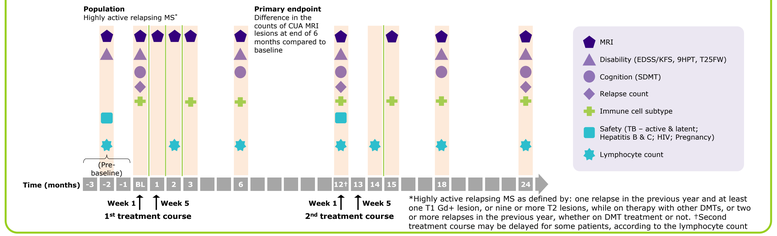
*Highly active relapsing MS as defined by: one relapse in the previous year and at least one T1 Gd+ lesion, or nine or more T2 lesions, while on therapy with other DMTs, or two or more relapses in the previous year, whether on DMT treatment or not.

OBJECTIVE

To report on peripheral immune cell subset dynamics and immunoglobulin levels in the first 12 months of cladribine tablets therapy

METHODS

- MAGNIFY-MS is an ongoing Phase IV, open-label, single-arm, multicenter, 2-year study
- Patients with highly active relapsing MS* received cladribine tablets, with 2 weeks active treatment per course (Week 1 and Week 5 of each year)

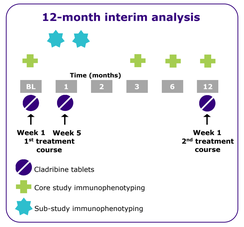


*Highly active relapsing MS as defined by: one relapse in the previous year and at least one T1 Gd+ lesion, or nine or more T2 lesions, while on therapy with other DMTs, or two or more relapses in the previous year, whether on DMT treatment or not. †Second treatment course may be delayed for some patients, according to the lymphocyte count

METHODS cont.

- This sub-study of MAGNIFY-MS involved longitudinal evaluation of peripheral blood immune cells in patients receiving cladribine tablets
- 57 patients were treated
- Absolute cell counts and % change from baseline were assessed for adaptive immune cell subtypes and immunoglobulins
- Immunophenotyping was completed at baseline and at months 1*, 2*, 3, 6, and 12

*Months 1 and 2 are available for TBNK and B cell panels.

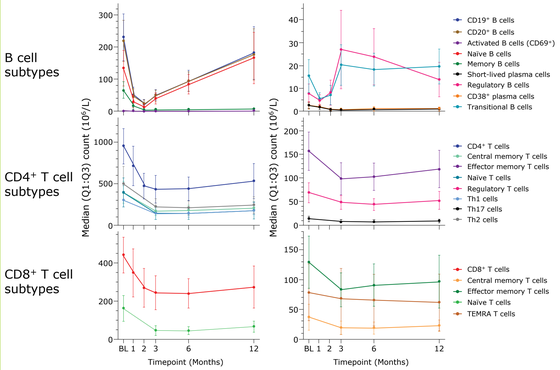


Immune cell panels in MAGNIFY-MS

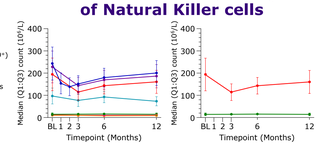
T cell panel	**CD4 naïve** (CD3⁺, CD8⁻, CD4⁺, CD45RA⁺, CCR7⁺) **CD4 central memory** (CD3⁺, CD8⁻, CD4⁺, CD45RA⁻, CCR7⁺) **CD4 effector memory** (CD3⁺, CD8⁻, CD4⁺, CD45RA⁻, CCR7⁻) **CD8 naïve** (CD3⁺, CD4⁻, CD8⁺, CD45RA⁺, CCR7⁺) **CD8 central memory** (CD3⁺, CD4⁻, CD8⁺, CD45RA⁻, CCR7⁺) **CD8 effector memory** (CD3⁺, CD4⁻, CD8⁺, CD45RA⁻, CCR7⁻) **CD8 TEMRA** (CD3⁺, CD4⁻, CD8⁺, CD45RA⁺, CCR7⁻) **Th1** (CD3⁺, CD8⁻, CD4⁺, CCR7⁻/⁺, CXCR3⁺) **Treg** (CD3⁺, CD8⁻, CD4⁺, CD25^{bright}, CD127$^{dim/-}$) **Th17** (CD3⁺, CD8⁻, CD4⁺, CD45RA⁻, CCR7⁻/^{dim}, CCR6⁺, CD146⁺) **Th2** (CD3⁺, CD8⁻, CD4⁺, CXCR3⁻, CCR6⁻)
B cell panel	**CD19 B cells** (CD45^{bright}, SSC^{low}, CD3⁻, CD14⁻, CD56⁻, CD19⁺) **CD20 B cells** (CD45^{bright}, SSC^{low}, CD3⁻, CD14⁻, CD56⁻, CD20⁺) **Activated B cells** (CD45^{bright}, SSC^{low}, CD3⁻, CD14⁻, CD56⁻, CD19⁺, CD20⁺, CD69⁺) **Naïve B cells** (CD45^{bright}, SSC^{low}, CD3⁻, CD14⁻, CD56⁻, CD19⁺, CD20⁺, IgD⁺, CD27⁻) **Memory B cells** (CD45^{bright}, SSC^{low}, CD3⁻, CD14⁻, CD56⁻, CD19⁺, CD20⁺, CD27⁺) **Short-lived plasma cells** (CD45^{bright}, SSC^{low}, CD3⁻, CD14⁻, CD56⁻, CD19^{dim}, CD20⁻/^{dim}, CD27^{bright}) **Breg** (CD45^{bright}, SSC^{low}, CD3⁻, CD14⁻, CD56⁻, CD19⁺, CD24^{bright}, CD38^{bright}) **CD38^{bright} plasma cells** (CD45^{bright}, SSC^{low}, CD3⁻, CD14⁻, CD56⁻, CD19^{dim}, CD20⁻, CD38^{bright}) **Transitional B cells** (CD45^{bright}, SSC^{low}, CD3⁻, CD14⁻, CD56⁻, CD19⁺, CD20⁺, IgD⁺, CD10⁺, CD27⁻)
NK cell panel	**NKp46 NK cells** (SSC^{low}, CD45⁺, CD19⁻, CD3⁻, CD16⁺ CD56⁺, CD335⁺) **CD16 NK cells** (SSC^{low}, CD45⁺, CD19⁻, CD3⁻, CD16⁺ CD56⁺) **CD16^{bright} CD56^{dim} NK cells** (SSC^{low}, CD45⁺, CD19⁻, CD3⁻, CD56^{dim}, CD16^{bright}) **CD16^{low} CD56^{bright} NK cells** (SSC^{low}, CD45⁺, CD19⁻, CD3⁻, CD56^{bright}, CD16⁻/⁺) **CD16⁻ CD56^{dim} NK cells** (SSC^{low}, CD45⁺, CD19⁻, CD3⁻, CD56^{dim}, CD16⁻) **CD16⁺ CD56⁻ NK cells** (SSC^{low}, CD45⁺, CD19⁻, CD3⁻, CD56⁻, CD16⁺) **CD16⁺ CD56⁺ NK cells**
Immunoglobulins	**IgG** **IgM**

RESULTS

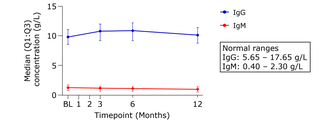
Absolute values (10^6/L) of B and T cells



Absolute values (10^6/L) of Natural Killer cells



Absolute values (g/L) of immunoglobulins



Percentage change from baseline of B cell subtypes

Key: Nadir value | Values above baseline level

Subtype	Month 1	Month 2	Month 3	Month 6	Month 12
CD19⁺ B cells	-77% n=46	**-90%** n=44	-80% n=46	-60% n=35	-35% n=42
Memory B cells	-74% n=45	**-93%** n=44	-93% n=46	-90% n=34	-87% n=42
Activated B cells (CD69⁺)	-64% n=45	**-81%** n=44	-73% n=46	-53% n=34	-45% n=42
CD38⁺ plasma cells	-11% n=45	-66% n=44	**-71%** n=46	-51% n=34	-51% n=42
Short-lived plasma cells	-28% n=45	-65% n=44	**-78%** n=46	-58% n=34	-51% n=42
Naïve B cells	-80% n=45	**-90%** n=44	-75% n=46	-43% n=34	-5% n=42
Transitional B cells	**-61%** n=45	-63% n=44	**+28%** n=46	**+34%** n=34	**+36%** n=42
Regulatory B cells	**-45%** n=45	-16% n=44	**+176%** n=46	**+171%** n=34	**+50%** n=42

- There is an early onset of action, with most B cell subtypes reaching nadir levels by Month 2
- Reduction in memory B cells was sustained to Month 12; regulatory B cells recovered by Month 3, and then increased over baseline levels

Percentage change from baseline of T cell subtypes

Key: Nadir value | Values above baseline level

Subtype	Month 1	Month 2	Month 3	Month 6	Month 12
CD4⁺	-22% n=46	-51% n=44	**-54%** n=46	-51% n=35	-40% n=42
CD8⁺	-18% n=46	-39% n=44	**-50%** n=46	-43% n=35	-36% n=42
CD4⁺ Th1	-	-	**-51%** n=46	-45% n=34	-35% n=42
CD4⁺ Th17	-	-	**-35%** n=45	-34% n=34	-24% n=41
CD4⁺ CM/EffM	-	-	**-56%/-35%** n=46	-52%/-35% n=34	-40%/-15% n=42
CD8⁺ CM/EffM	-	-	-39%/-29% n=46	**-46%/-22%** n=34	-29%/-16% n=42
CD4⁺naïve/ CD8⁺ naïve	-	-	-63%/-73% n=46	**-64%/-70%** n=35/n=34	-53%/-58% n=42
CD4⁺ Treg	-	-	-30% n=46	**-38%** n=34	-21% n=42
CD8⁺ TEMRA	-	-	**-26%** n=46	-15% n=34	-19% n=42

- T cell subtypes show reductions at later time points

Percentage change from baseline of NK cell subtypes

Key: Nadir value | Values above baseline level

Subtype	Month 1	Month 2	Month 3	Month 6	Month 12
CD16^{low} CD56^{bright}	-	-	-7% n=46	-2% n=34	**-9%** n=42
CD16⁺ CD56⁺	-34% n=46	**-40%** n=44	-34% n=46	-17% n=35	-14% n=42
CD16^{bright} CD56^{dim}	-	-	**-40%** n=46	-19% n=34	-12% n=42

- No changes were seen for other NK cell subtypes

Abbreviations: **9HPT**, 9-hole peg test; **BL**, baseline; **Breg**, B regulatory; **CUA**, combined unique active; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium enhancing; **HIV**, human immunodeficiency virus; **Ig**, immunoglobulin; **KFS**, Kurtzke Functional System; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **NK**, natural killer; **Q1:Q3**, interquartile range; **SDMT**, symbol digit modalities test; **T25FW**, timed 25-foot walk; **TB**, tuberculosis; **TEMRA**, terminally differentiated effector memory RA⁺; **Th**, T helper; **Treg**, T regulatory | **References**: 1. Wiendl H. Nat Rev Neurol. 2017;13:573–574. 2. Giovannoni G. Neurotherapeutics. 2017;14:874–887. 3. Comi G, et al. Mult Scler Relat Disord. 2019;29:168–174. | **Acknowledgments**: The poster was previously presented at the AAN 2021 Virtual Congress (17–22nd April). Medical writing assistance was provided by Joe Ward of inScience Communications, Springer Healthcare Ltd, UK, and was funded by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945). The MAGNIFY-MS study: NCT03364036.

Presented at the Consortium of Multiple Sclerosis Centers (CMSC) 2021 Congress | 25 — 28th October

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