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Impact of Cladribine Tablets on GFAP Levels and Intrathecal Biomarkers in RMS: Results From the MAGNIFY-MS Study

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RESEARCH IN CONTEXT

1. **These biomarker data align with previous investigations showing reductions and disappearance of OCBs and reductions in CNS NfL,[1] supporting potential links to clinical outcomes and informing treatment decisions.**
2. **Cladribine tablets, given as a short-course therapy, reduced CNS neurodegeneration and neuroinflammation, with sustained clinical improvements over 24 months without continuous immunosuppression.**

OBJECTIVE

To evaluate the effects of cladribine tablets on neuroinflammation and biomarkers in serum and cerebrospinal fluid (CSF) in people with relapsing multiple sclerosis (PwMS).

INTRODUCTION

Cladribine tablets, an immune reconstitution therapy, has demonstrated significant efficacy in reducing MS activity in the periphery and central nervous system (CNS).[1,2] Specific biomarkers and their ratios of CSF to serum concentrations (indices) can potentially provide rapid and reliable prediction of disease activity.

Cladribine tablets reduce CSF oligoclonal bands (OCBs), neurofilament light chain (NfL), kappa-free light chain (KFLC), and immunoglobulin G (IgG) indices, indicating decreased intrathecal Ig synthesis, neuroaxonal damage, and neuroinflammation.[1,2]

We evaluated the effects of cladribine tablets on peripheral biomarkers (glial fibrillary acidic protein [GFAP] and NfL) and CNS intrathecal activity markers (KFLC, IgG and C-X-C motif chemokine ligand 13 [CXCL-13] indices), aiming to determine if there is a correlation between changes in these markers and clinical outcomes.

METHODS

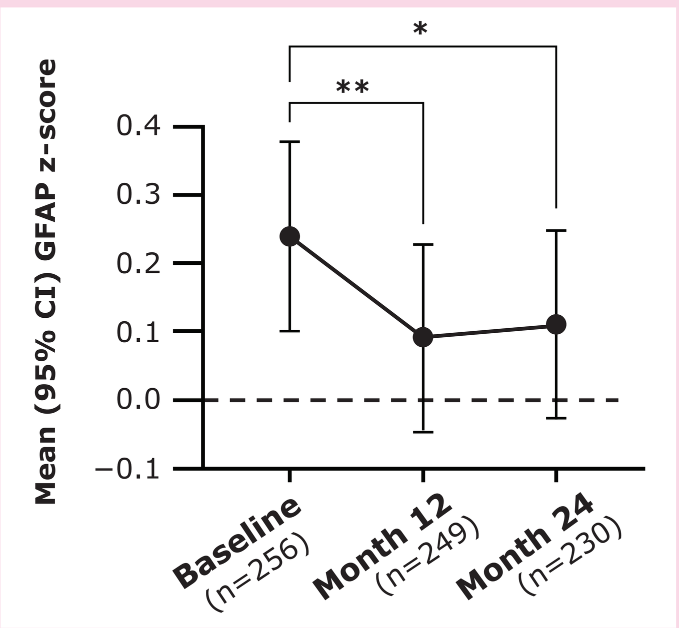
- In MAGNIFY-MS (NCT03364036), participants with highly active relapsing MS received cladribine tablets as two short treatment courses according to the label.[3]
- All biomarkers were measured at baseline, Month 12, and Month 24. Serum GFAP and NfL were measured for all participants (N=258); CSF biomarkers (KFLC, IgG and CXCL-13) were measured in serum and CSF for participants of the CSF sub study (N=28), and indices were calculated as previously described.[2,4]
- Serum GFAP and NfL levels were assessed using single molecule array, and z-scores were calculated (age- and body-mass index-adjusted) to show deviation from serum values in a reference healthy population.[5]
- CXCL-13 index calculations were corrected for passive transfer of serum CXCL-13 into the CSF using the following formula: CSF/serum ratios were expressed as Quotient $(Q)_{CXCL\text{-}13}$. Index $(I)_{CXCL\text{-}13}$. $I_{CXCL\text{-}13}$ was calculated as $(CSF_{CXCL\text{-}13}/serum_{CXCL\text{-}13})/(CSF_{albumin}/serum_{albumin})=Q_{CXCL\text{-}13}/Q_{albumin}$.[4]
- 6-month confirmed disability progression (6mCDP) was defined as follows: increased Expanded Disability Status Scale (EDSS) score from baseline of ≥1 point for baseline EDSS 0.5–5, ≥0.5 points for baseline EDSS >5, and ≥1.5 points for baseline EDSS=0; confirmed over a period of at least 6 months.
- Progression independent of relapse activity (PIRA) was assessed in accordance with the recommended harmonised method.[6]
- Associations between clinical outcomes (annualised percentage brain volume change [aPBVC], 6mCDP, PIRA, number of relapses) and biomarkers were evaluated using Pearson correlation (serum GFAP/NfL) or Spearman's rank correlation and Fisher's exact test (CXCL-13, KFLC, and IgG indices).

RESULTS

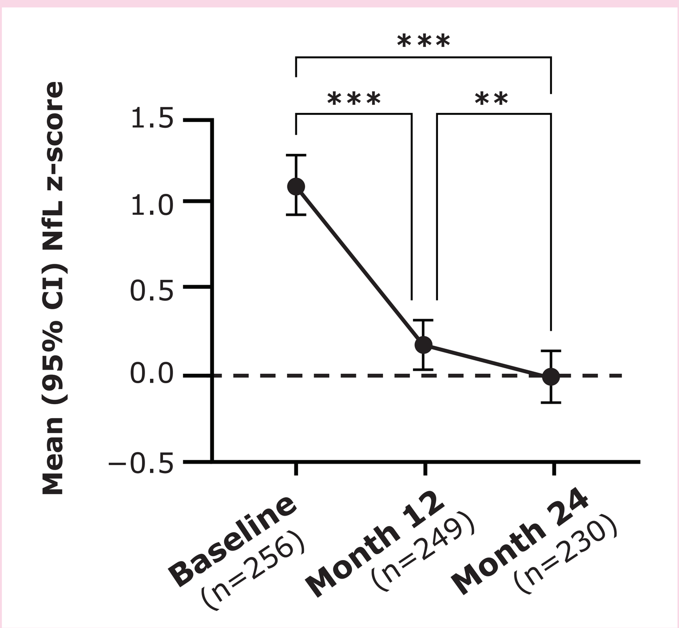
- Reductions in GFAP (**Figure 1A**) and NfL (**Figure 1B**) z-scores were seen following cladribine tablets treatment. Lower levels were significantly correlated with preservation of brain volume (**Figure 1C**).

Figure 1. Cladribine Tablets Treatment Significantly Reduced Serum GFAP (A) and NfL (B) z-scores, With Both Biomarkers Correlating With aPBVC (C)

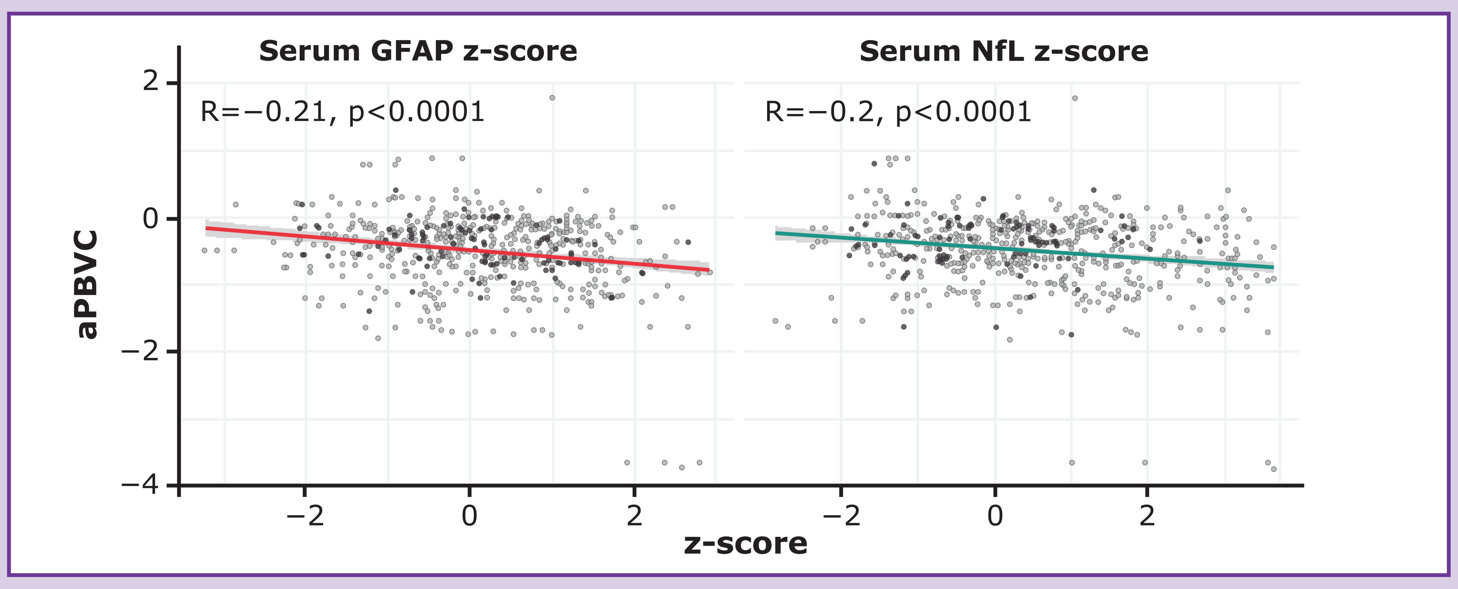
A. Serum GFAP z-score



B. Serum NfL z-score



C. Significant correlation of serum GFAP and NfL z-scores with brain volume loss after cladribine tablets treatment (n=256)



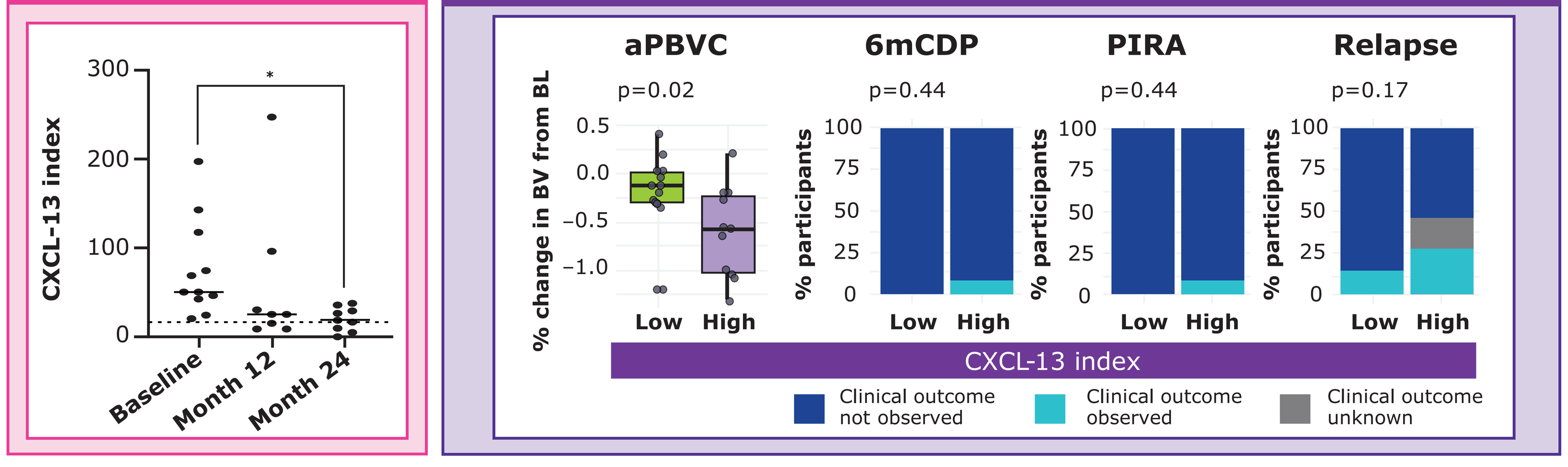
*p≤0.05. **p≤0.01. ***p≤0.0001. R is the correlation coefficient. R=1 indicates a perfect positive linear relationship; R=0 indicates no linear relationship; and R=−1 indicates a perfect negative linear relationship. **aPBVC**, annualised percentage brain volume change; **CI**, confidence interval; **GFAP**, glial fibrillary acidic protein; **NfL**, neurofilament light chain.

- A significant decrease in CXCL-13 index was seen 24 months after treatment with cladribine tablets, indicating reduced intrathecal B-cell recruitment (**Figure 2A**).
- A lower CXCL-13 index was associated with a significantly higher preservation of BV than a high CXCL-13 index. A high CXCL-13 index was seen in PwMS who experienced 6mCDP, PIRA, and relapses (**Figure 2B**).

Figure 2. CXCL-13 Index Reduction After Cladribine Tablets Treatment (A) and Its Association With Clinical Outcomes (B)

A. CXCL-13 index[a]

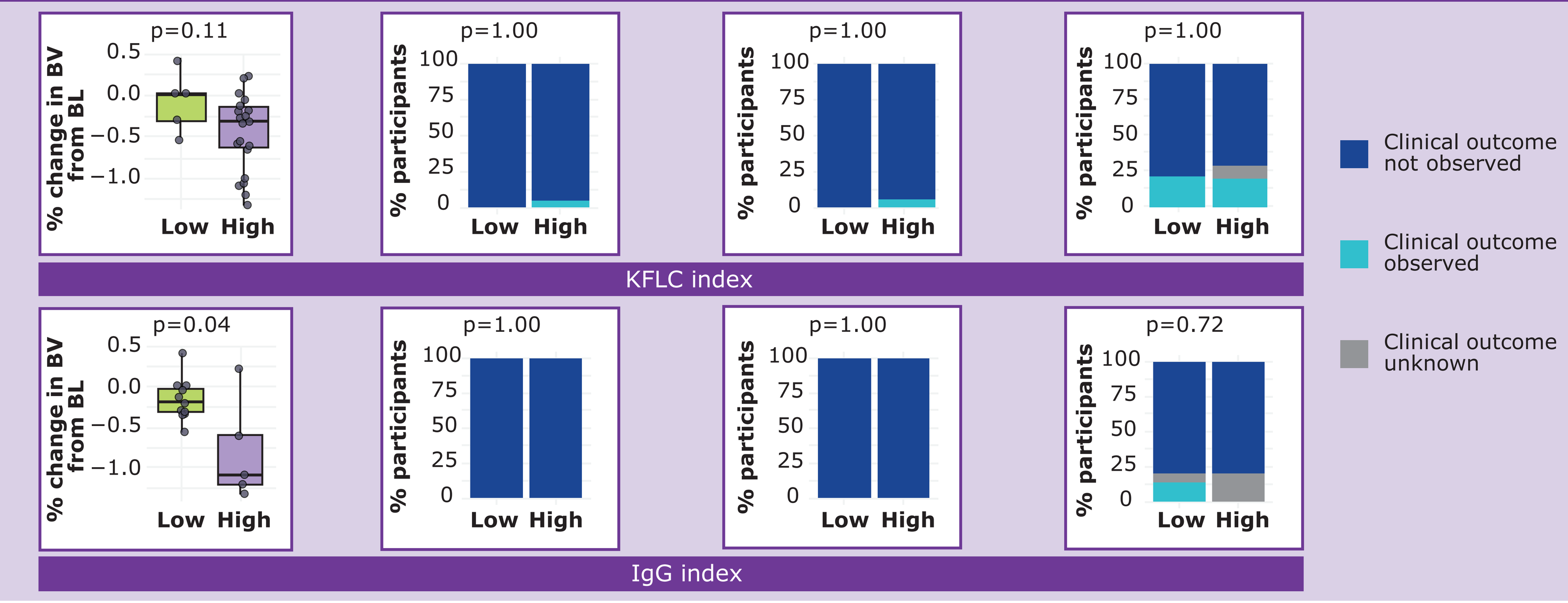
B. Association of clinical outcomes with CXCL-13 index



[a]Data for 11 individuals with CXCL-13 index >18.06 at BL. *p≤0.05 **Low** denotes baseline CXCL-13 index ≤18.06 at BL (n=14); **High** denotes CXCL-13 index >18.06 at BL (n=11). P values are nominal.
6mCDP, 6-month confirmed disability progression; **aPBVC**, annualised percentage brain volume change; **BL**, baseline; **BV**, brain volume; **CXCL-13**, C-X-C motif chemokine ligand 13; **PIRA**, progression independent of relapse activity.

- In participants with high baseline indices, reductions were seen in KFLC and IgG indices over 24 months, indicating reduced intrathecal production of autoimmune antibodies.[2] High KFLC and IgG indices were associated with increased brain volume loss (**Figure 3**).

Figure 3. Association of KFLC and IgG Indices With Clinical Outcomes



For KFLC index, **Low** denotes <6.1 at BL (n=5) and **High** denotes ≥6.1 at BL (n=22); for IgG index, **Low** denotes ≤0.7 at BL (n=15) and **High** denotes >0.7 at BL (n=5). P values are nominal.
6mCDP, 6-month confirmed disability progression; **aPBVC**, annualised percentage brain volume change; **BL**, baseline; **BV**, brain volume; **IgG**, immunoglobulin G; **KFLC,** kappa-free light chain; **PIRA**, progression independent of relapse activity.

Limitations

- MAGNIFY-MS was an open-label, single-arm study without a control group, limiting comparative analysis. CSF biomarkers were available for only a small subset of participants, and very few experienced 6mCDP, PIRA, or relapses, reducing statistical power to detect significant associations.

CONCLUSIONS

- **Cladribine tablets effectively reduced biomarkers of chronic neuroinflammation (GFAP), neuroaxonal damage (NfL), and disease progression.**
- **Strong correlations of biomarkers with aPBVC were detected in serum and CSF. A trend towards association with 6mCDP, PIRA, and relapses was observed for CXCL-13 and KFLC indices. These results could aid in future individualised treatment decision making.**
- **Taken together with previously reported impact on OCBs and NfL,[2] these results highlight potential benefits of cladribine tablets on reducing neurodegeneration and neuroinflammation beyond its previously established clinical efficacy in relapsing MS.**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

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Supplementary Materials:

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