

Anti-EBV T-cell Receptor Repertoire Reduction Is Linked to Enhanced Cognitive Performance in Progressive Multiple Sclerosis: Evidence from the Phase 2 CALLIPER Trial with Vidofludimus Calcium, a Direct Nurr1 Activator and Selective DHODH Inhibitor



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Conclusions

- In an exploratory analysis, vidofludimus calcium reduced the number of MHC-I-restricted EBV-specific TRB sequences in PMS patients over time.
- In a post hoc analysis, reduced EBV-specific TRB sequence matches corresponded to improved SDMT scores, suggesting an association between EBV-related immune activity and cognition in PMS.



Objectives

- Perform a predefined exploratory analysis to evaluate the effect of vidofludimus calcium, compared to placebo, on EBV by comparing anti-EBV and anti-Influenza A TCR sequence matches.
- Perform a post hoc analysis to evaluate changes over time in EBV-specific TCR signatures and cognitive function (SDMT) and assess any associations between them.

Background: Vidofludimus calcium is thought to be a direct activator of transcription factor nuclear receptor-related 1 (Nurr1), which is implicated in neuronal survival¹. It may also selectively inhibit dihydroorotate dehydrogenase (DHODH), suggesting a broad-spectrum, host-targeted antiviral and selective anti-inflammatory effects. Epstein-Barr virus (EBV) infection often precedes multiple sclerosis (MS), which is associated with a broader, putatively aberrant EBV-specific T-cell receptor (TCR) repertoire². Vidofludimus calcium has demonstrated anti-EBV effects in vitro and in clinical trials^{3,4}.



Methods

The phase 2 CALLIPER trial was a randomized, double-blind, placebo-controlled study in 467 patients aged 18-65 years with primary or secondary progressive MS (PMS), randomized 1:1 to 45 mg once daily vidofludimus calcium or placebo⁵. The primary outcome, change in whole brain volume loss vs. placebo, was not met⁶. In a subset of 87 randomly selected patients, MHC-I-restricted anti-EBV and as a control anti-Influenza A (non-chronic, not MS-associated) TCR sequence matches were analyzed in blood from baseline (Day 1) to week 48 by high-throughput ultradeep TCRβ chain (TRB) sequencing of genomic DNA; HLA information was imputed.

From this subset, 206 samples (87 patients; placebo 44; vidofludimus calcium 43) were analyzed. Mean sequencing depth was 126k unique TRB rearrangements per sample that was not reduced by vidofludimus calcium versus placebo. A linear mixed model was used with the covariates of age, sex, sequencing depth, HLA alleles and baseline matches, and patient as random intercept. Baseline samples and the placebo arm were grouped as “untreated”⁶ and compared to vidofludimus calcium treatment.

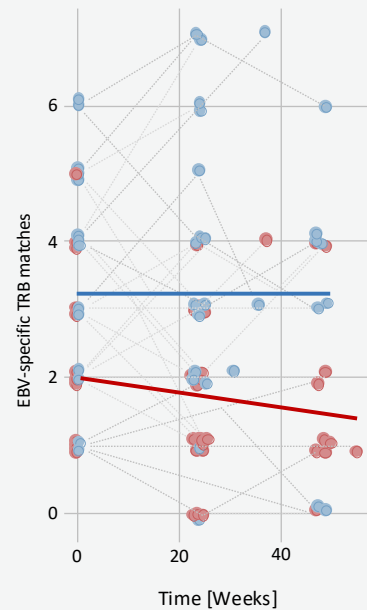
In a post hoc analysis, changes from baseline to Week 48 in EBV-specific TRB matches were correlated with the corresponding changes in the Symbol Digit Modalities Test (SDMT) score within each patient across both treatment arms, using the same linear mixed model approach.



Results

Vidofludimus calcium reduced MHC I restricted EBV-specific TRB matches versus untreated (-0.65 matches; $p=0.0004$), while Influenza A-specific TRB matches were unchanged (+0.08; $p=0.5983$; (data not shown)⁷. (B) Across all patients ($n=64$; 83 follow-up visits), changes in EBV-specific TRB matches were inversely associated with changes in SDMT: each increase of 0.1 EBV-specific matches per 10,000 productive rearrangements from baseline corresponded to a 1.20-point lower SDMT change (95% CI -2.33 to -0.06; $p=0.039$; linear mixed model with random intercept per patient) (left). In the PPMS subgroup ($n=31$; 40 visits), the estimate was of similar magnitude, but its confidence interval included zero (-1.38 points per 0.1 increase; 95% CI -2.87 to 0.10; $p=0.066$) (right). TEAEs in the phase 2 CALLIPER trial were seen in 69.4% of the vidofludimus calcium patients, and 68.5% of the placebo group⁸. This analysis does not assess the benefit-risk of vidofludimus calcium.

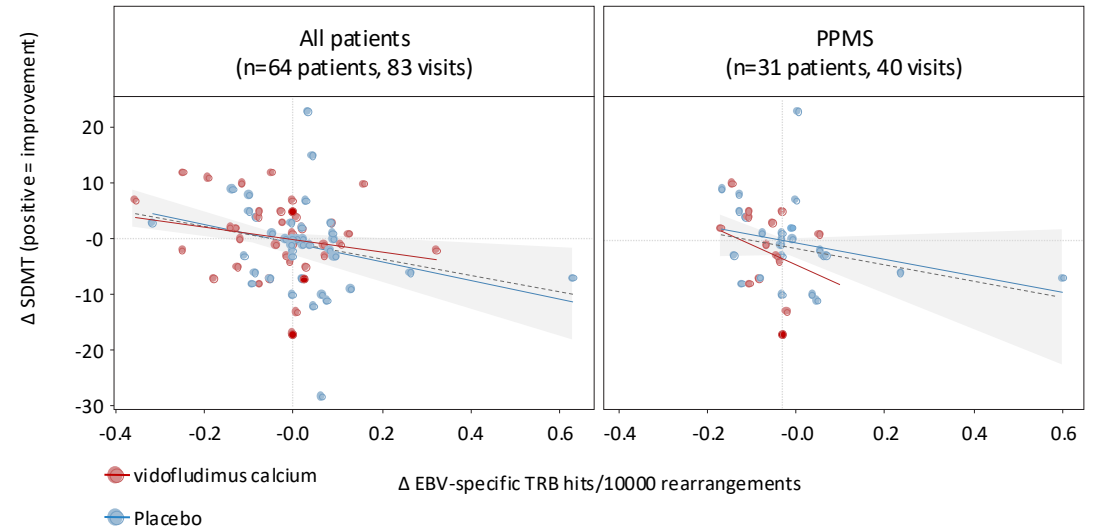
A – EBV-specific TRB Sequence Matches



B – Change in EBV-specific TRB Matches vs. change in SDMT Score

SDMT: Δ EBV vs Δ SDMT

Dashed grey = overall slope. Per-arm slope.



- Vidofludimus calcium reduced the number of MHC-I-restricted EBV-specific TRB sequences in PMS patients over time.
- Reduced EBV-specific TRB matches were linked to improved SDMT scores, supporting a connection between EBV-related immune activity and cognitive outcomes in PMS.

DHODH: dihydroorotate dehydrogenase, EBV: Epstein-Barr virus, HLA: Human Leukocyte Antigen, MHC-I: Major Histocompatibility Complex class I, MS: multiple sclerosis, PMS: progressive MS, PPMS: Primary Progressive Multiple Sclerosis, Nurr1: nuclear receptor-related 1, TCR: T-cell receptor, TEAE: Treatment Emergent Adverse Event, TRB: TCRβ chain,

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