Effect of Vidofludimus Calcium, a Novel Nurr1 Activator and DHODH Inhibitor, on the Anti-EBV T-cell Receptor Repertoire in Progressive Multiple Sclerosis: Data from the Phase 2 CALLIPER Trial

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1. Background

Vidofludimus calcium (VidoCa) is an orally available activator of the transcription factor nuclear receptor-related 1 (Nurr1)[1], a neuroprotective target in neurodegenerative diseases, and is currently being studied in Phase 3 trials in relapsing multiple sclerosis (MS).

It also selectively inhibits dihydroorotate dehydrogenase (DHODH), resulting in broad-spectrum, host-targeted antiviral effects and selective anti-inflammatory effects on B- and T-cells.

Epstein-Barr virus (EBV) infection precedes MS pathology and MS is also associated with a broader EBV-specific T-cell receptor (TCR) repertoire, consistent with an aberrant anti-EBV immune response in MS[2]. VidoCa has been shown to have an anti-EBV effect in *in vitro* experiments[3,4].

2. Objective

Evaluate the effect of VidoCa on EBV reactivation before and alongside treatment with VidoCa compared to placebo by comparing anti-EBV and anti-Influenza A TCR sequence matches.

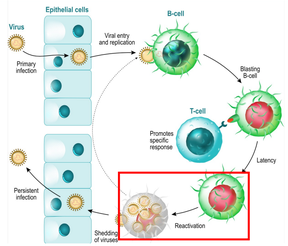


Figure 1: The EBV replication cycle including EBV reactivation – the return of active viral replication from latency in a previously infected host.

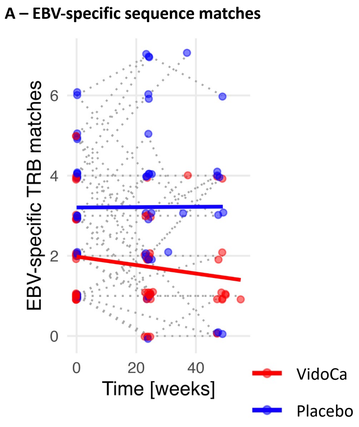
3. Methods

The phase 2 CALLIPER trial was a randomized, double-blind, placebo-controlled study including 467 participants aged 18-65 with primary or secondary progressive MS (PMS). Participants were randomized 1:1 to receive 45 mg once daily VidoCa or placebo[5]. 87 randomly selected patients were analyzed for anti-EBV and as a control anti-Influenza A (non-chronic, not MS-associated viral infection) major histocompatibility complex class I (MHC-I)-restricted TCR sequence matches from blood samples from baseline (Day 1) to Week 48. High-throughput ultradeep resolution TCRβ chain (TRB) sequencing of genomic DNA was performed. Human Leukocyte Antigen (HLA) information was imputed.

Numbers of anti-EBV T-cell matches (EBV-specific TRB matches) were compared between treatment and placebo indicating how many T cells in a patient's blood could target EBV.

What is the EBV T-cell receptor repertoire?
The total number and overall diversity of antigen-specific T-cell receptors in a person.

4. Results



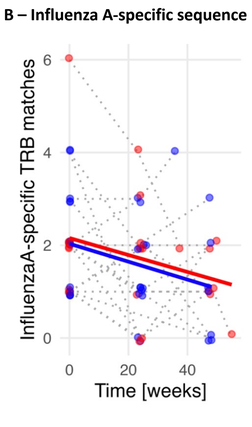


Figure 2: VidoCa reduced EBV-specific TRB matches compared to untreated

(A) While during placebo treatment (blue) the number of EBV-specific matches remained stable over time, indicating persistent exposure of T-cells to EBV, patients treated with VidoCa (red) showed a ***progressive decline of EBV-specific matches***, consistent with a lowered rate of EBV reactivations. The comparison of untreated and treated samples was statistically significant (p=0.0004).

(B) Influenza A-specific TRB matches (control) did not differ between placebo and VidoCa-treated patients over time (treated vs untreated samples: non-significant, p=0.0938).

Data from 206 blood samples (87 patients; placebo 44; VidoCa 43), were analyzed. The mean obtained sequencing depth was 126k unique TRB rearrangements per sample and was not reduced by VidoCa compared to placebo. Data was analyzed using a linear mixed model with the covariates age, sex, sequencing depth, HLA alleles, and baseline matches with the patient added as random intercept. The baseline samples and placebo arm were grouped together as "untreated"[6] and compared to VidoCa treatment.

5. Conclusions

- **VidoCa reduced the number of MHC-I-restricted EBV-specific TRB sequences in PMS patients over time.**
- **Results are consistent with the hypothesis that the broad-spectrum antiviral effects of VidoCa cause a lowering of EBV reactivations, potentially improving the MS disease activity.**
- **The relationship between clinical outcomes of the PMS trial and the anti-EBV T-cell response are to be investigated.**

References

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Abbreviations

VidoCa: Vidofludimus calcium, MS: multiple sclerosis, PMS: progressive MS, Nurr1: nuclear receptor-related 1, DHODH: dihydroorotate dehydrogenase, EBV: Epstein-Barr virus, HLA: Human Leukocyte Antigen, MHC-I: Major Histocompatibility Complex class I, TCR: T-cell receptor, TRB: TCRβ chain

Disclosures

A.S., M.O., J.M., F.G., V.S. and A.M. are employees of the study sponsor, holding shares and/or stock options of the parent company, Immunic, Inc.. A.M. is an inventor of patients covering the investigational medication. T.S.-H. received research support from Novartis and travel support from Roche. N.S. received funding from Biogen, Roche, and the DFG (grant numbers 445569437and 445569437) outside the scope of this study. RJF reports personal consulting fees from Astoria Biologica, Biogen, Bristol Myers Squibb, Cognito, EMD Serono,Galvani, Immunic, INmune Bio, Kiniksa, Novartis, Sanofi, Siemens, and TG Therapeutics and has served on advisory committees for AB Science, Biogen, Immunic, Novartis, and Sanofi, and received clinical trial contract and research grant funding from Biogen, Novartis, and Sanofi.

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