May Vidofludimus Calcium Potentially be Used to Reduce Fatigue in Multiple Sclerosis by Blocking EBV Reactivation?

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Background

Fatigue represents the most common symptom in both multiple sclerosis (MS) and post COVID syndrome (PCS). However, the underlying pathogenesis of this clinical manifestation remains unclear. In case of PCS, reactivation of latent viruses including Epstein-Barr virus (EBV), autoantibodies, and lingering inflammation are discussed as a potential trigger.

Interestingly, EBV infection and reactivation is also known to induce strong fatigue and, thus, might be a potential driver for fatigue observed in both PCS and MS. We want to bring forward the hypothesis that the same mechanisms may trigger fatigue in both diseases. Vidofludimus calcium (VidoCa) is an orally available DHODH inhibitor and Nurr1 activator that exhibits a broad-spectrum antiviral activity and an anti-inflammatory effect.

Objective

Due to its antiviral and anti-inflammatory potential, we want to reflect on the possibility of VidoCa to reduce fatigue in MS as it was previously demonstrated for post COVID patients and to present available preclinical and clinical data of VidoCa regarding anti-EBV activity and fatigue.

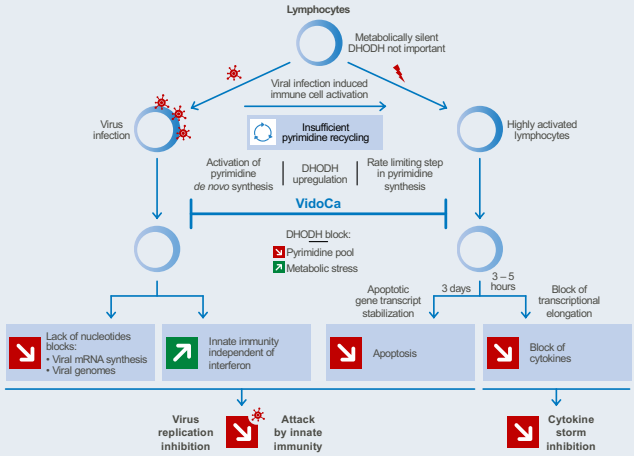
Methods

In the phase 2 CALVID-1 trial, patients aged 18 years or older who tested positive for COVID-19 were randomized to receive placebo or 45 mg VidoCa for 14 days with both groups receiving standard-of-care treatment. 27 patients responded to a post hoc questionnaire sent to the blinded investigators in three high enroller sites.

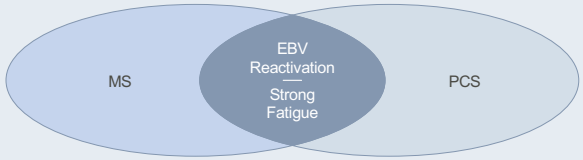
Results

Analysis of the antiviral activity of VidoCa revealed a dose-dependent reduction of lytic EBV reactivation in B cells as well as reduced lytic EBV production in Akata cells. Results from a post hoc analysis of PCS symptoms indicated a potential contribution of VidoCa to the prevention of long-term fatigue, one of the most common post COVID symptoms. In the CALVID-1 trail, 80% of patients who received placebo reported fatigue compared to 50% who received 45 mg VidoCa. Fatigue decreased in both treatment groups in the next 9–17 weeks to 33% for placebo and to 17% for VidoCa.

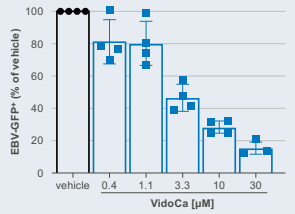
VidoCa, in development for multiple sclerosis (MS) treatment, is a safe and orally available dihydroorotate dehydrogenase (DHODH) inhibitory small molecule.



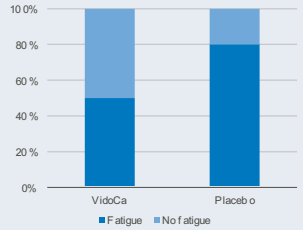
EBV reactivation is thought to drive fatigue in MS and PCS[1]



VidoCa showed concentration-dependent anti-EBV activity to spontaneous lytic EBV production and upon an anti-hIgG stimulation[2]



Proportion of patients with fatigue at study completion[3,4]



Conclusion

VidoCa has been shown to prevent PCS fatigue which is known to be related to EBV reactivation. By preventing the reactivation of EBV, VidoCa may contribute to the reduction of fatigue in MS patients as well. This hypothesis will be verified via Multidimensional Fatigue Symptom Inventory in the ongoing phase 3 ENSURE trials in relapsing MS.

1. https://www.nature.com/articles/s41586-023-06651-y
2. Data presented as poster presentation at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis 2021 with the title "IMU-838, a Small Molecule DHODH Inhibitor in Phase 2 Clinical Trial for Multiple Sclerosis, Shows Potent Anti-EBV Activity in Cell Culture-Based Systems: Potential Additional Benefits in Multiple Sclerosis Treatment".
3. This analysis was done by sending a post hoc questionnaire to investigators (who were still blinded to treatment assignments of their patients) in three high enroller sites. The participation was voluntary and a selection bias for participation cannot be fully excluded. The questionnaire requested the patient status regarding long-term COVID-19 symptoms at the individual study completion for each patient. Neuroinflammation may trigger impairment of neurotransmitters and, thus, be the mechanism for fatigue on post-COVID-19 patients (Ortelli et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. J Neurol Sci. 2021 Jan 15;420:117271).
4. NCT04379271, https://link.springer.com/article/10.1007/s40121-022-00690-0

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