Vidofludimus Calcium Shows T Helper Cell Modulatory Effects in Murine Experimental Autoimmune Encephalomyelitis: One of the Potential Mode of Action Pathways for MS Treatment

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Background

Vidofludimus calcium (VidoCa) has recently been shown to be a nuclear receptor related 1 (Nurr1) activator[1,2], in addition to being a potent inhibitor of dihydroorotate dehydrogenase (DHODH). At present, it is in phase 2 and phase 3 clinical development for progressive and relapsing multiple sclerosis (MS), respectively. As a Nurr1 activator, VidoCa could have neuroprotective effects, while as a DHODH inhibitor it plays a role in inhibiting the overshooting auto-immune reactivity from cells in or derived from the periphery[3]. Here, we investigate VidoCa's impact on T helper cell subtypes mainly driven by DHODH inhibition *in vivo*.

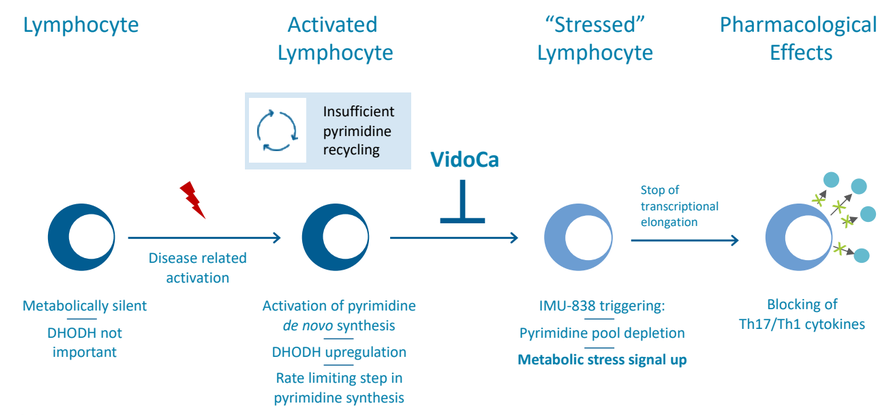
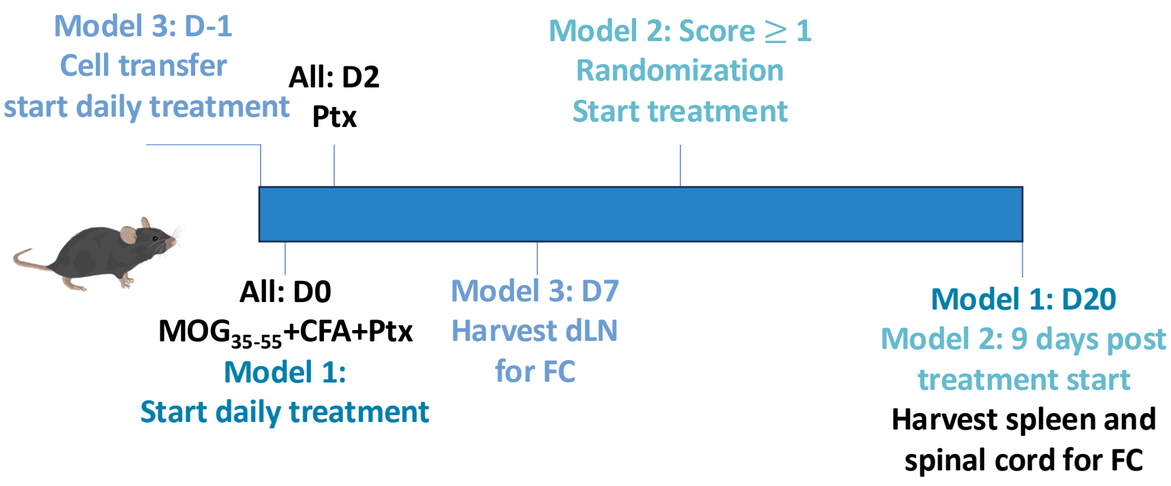


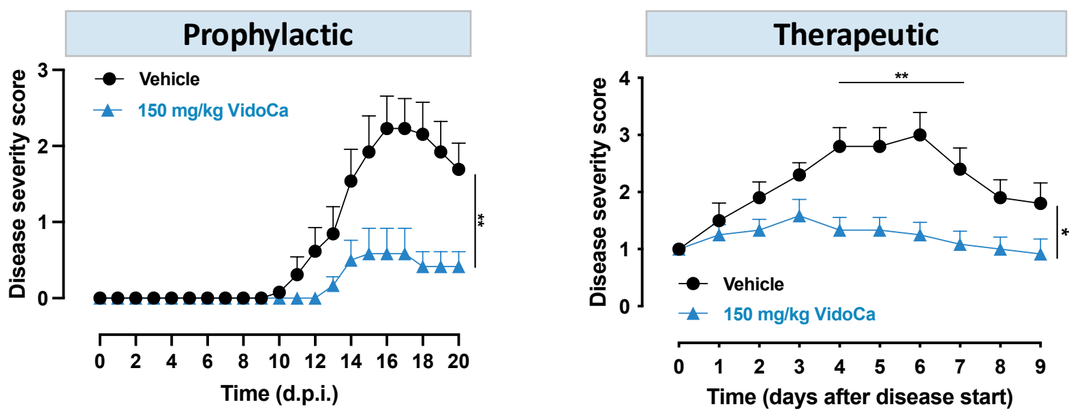
Illustration adapted from[4]
DHODH: dihydroorotate dehydrogenase; Th: T helper

Methods[5,6]



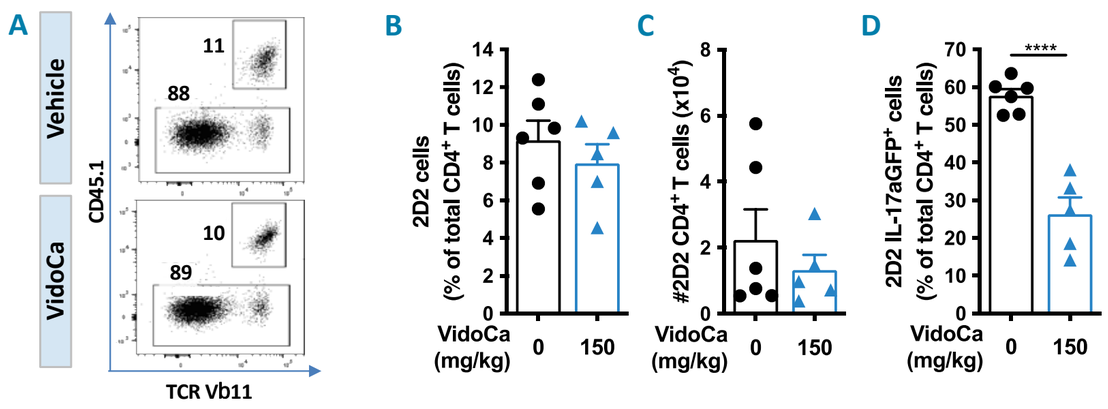
Model 1: prophylactic; Model 2: therapeutic; Model 3: prophylactic model with adoptive transfer of $1.5x10^5$ $CD45RB^{hi}CD25^{-}IL17eGFP$ naïve 2D2 T cells on a CD45.1 background into WT mice (CD45.2); CFA = complete Freund's adjuvant; D = days after immunization; dLN = draining lymph node; FC = flow cytometry; MOG = myelin oligodendrocyte glycoprotein; Ptx = Pertussis toxin; MOG_{35-55}+CFA = immunization; treatment = vehicle (PEG400) or 150 mg/kg vidofludimus calcium (VidoCa). Graphs are shown with mean ± SEM. *p<0.05 is considered significant, *p<0.05, **p<0.01, ***p<0.001, ****P<0.0001.

VidoCa showed activity in the MOG_{35-55} murine EAE model in a prophylactic and therapeutic setting



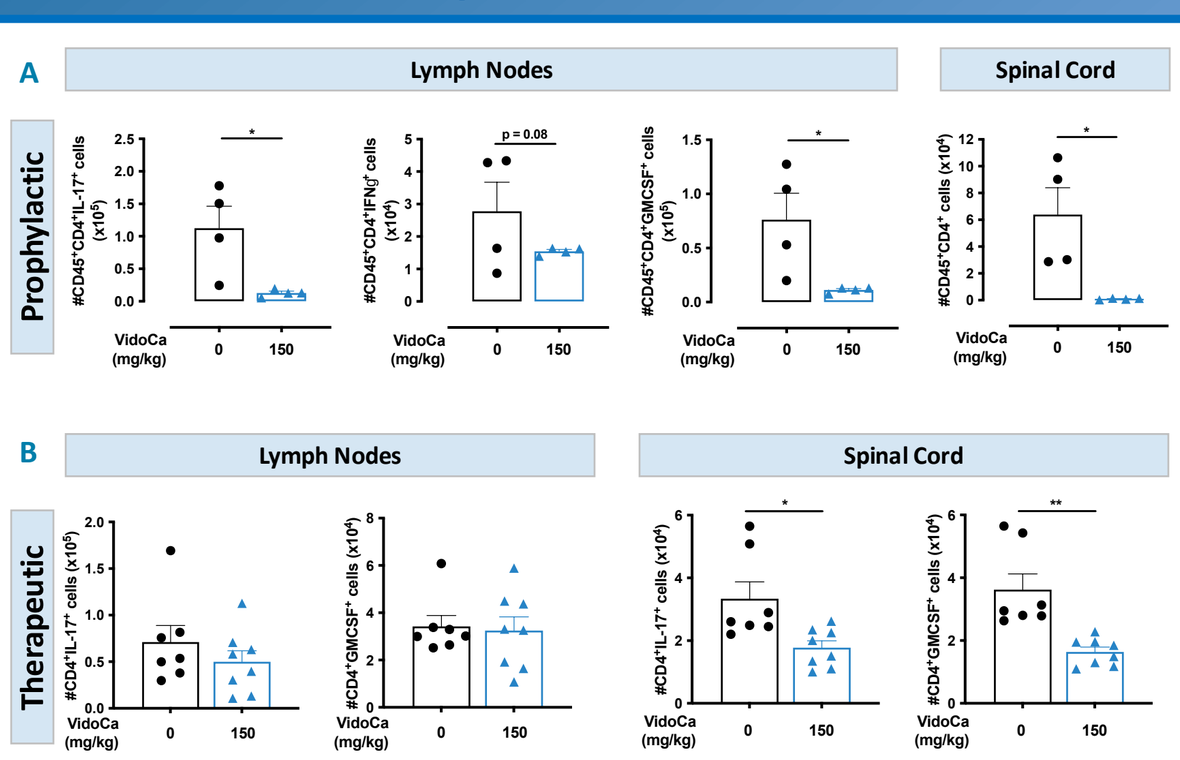
VidoCa reduced disease incidence and severity in a prophylactic EAE model with 63% of mice treated with VidoCa versus 15% of the mice in the vehicle group remaining disease free. Disease severity was also significantly reduced in a therapeutic EAE model.

VidoCa did not affect the donor 2D2 T cell population, but inhibited the frequency of pathogenic $IL17^{+}CD4^{+}2D2$ T cells



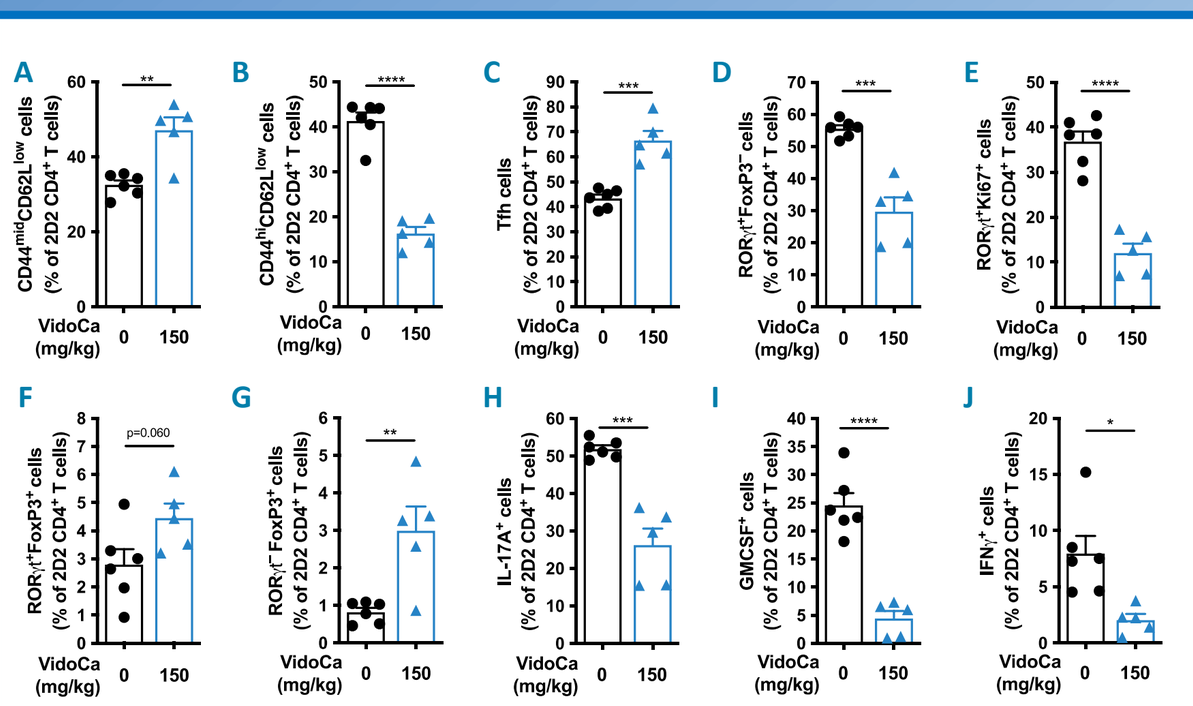
A) Gating strategy for MOG specific (2D2, donor cells, $CD45.1^{+}TCR\ V\beta11^{+}$) and recipient (WT, $CD45.2^{+}$) T cells. B,C) VidoCa did not influence the frequency or total number of 2D2 T cells. D) However, $IL\text{-}17^{+}$ 2D2 T cells (positive for GFP) are strongly reduced upon treatment with VidoCa in the prophylactic model.

Reduced numbers of infiltrating pro-inflammatory T helper cells by VidoCa treatment



VidoCa prevented immune cell infiltration into the spinal cord in a prophylactic EAE model and reduced the proinflammatory phenotype within the lymph nodes (A). Although VidoCa did not affect the number of proinflammatory T cells within the lymph nodes in the therapeutic EAE model, it reduced the number of infiltrating pro-inflammatory T helper cells in the spinal cord (B).

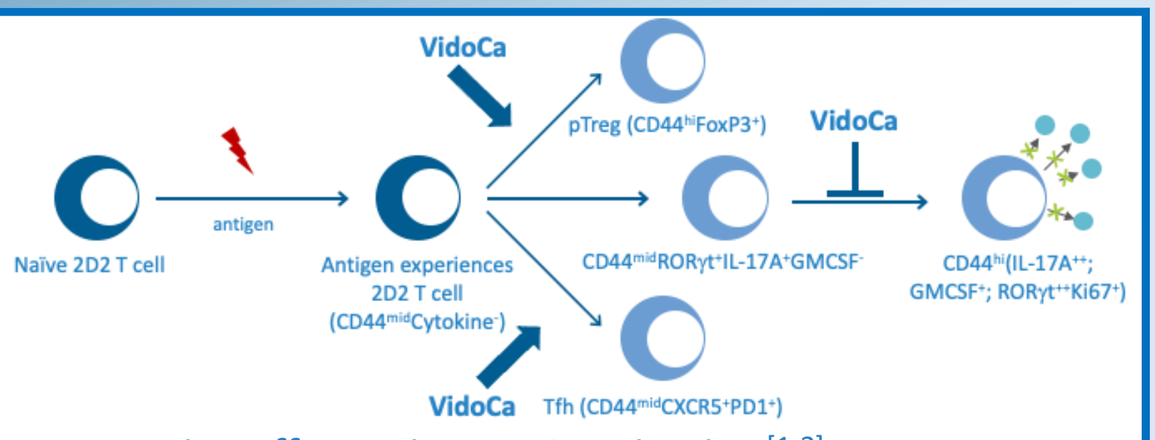
VidoCa reduced pro-inflammatory pathogenic T cell and increased regulatory T cell frequencies in the periphery



MOG (2D2) specific T cell differentiation into pathogenic proinflammatory $CD44^{high}CD62L^{low}$ cells is inhibited by VidoCa (B) resulting in increased 2D2 follicular T helper (C; Tfh, $PD1^{+}CXCR5^{+}$) cell frequencies which are primarily found within the $CD44^{mid}CD62L^{low}$ T cell population (A). Reduced 2D2 $ROR\gamma t^{+}FoxP3^{-}$ cell frequencies and proliferation (D, E), an increase in regulatory T cells ($FoxP3^{+}$, F,G) and reduced proinflammatory cytokine expressing cells ($IL\text{-}17A^{+}$, $GMCSF^{+}$, $IFN\gamma^{+}$, H-J) further support that VidoCa prevents pathogenic proinflammatory T cell differentiation. The recipient $CD4^{+}$ T cells (non-2D2 cells) were less affected.

Conclusions

- VidoCa reduces disease severity in murine EAE models.
- Proinflammatory T cell infiltration into the spinal cord is reduced upon VidoCa treatment in a prophylactic and therapeutic setting.
- VidoCa inhibits antigen specific T cell differentiation into proinflammatory cells and enhances the development of Tregs.
- Phase 2 clinical trial data showed activity for VidoCa in RRMS[7,8].



This mode of action combined with its potential neuroprotective effects via Nurr1 activation[1,2] could make VidoCa a potential effective treatment for MS.

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References

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