

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*.

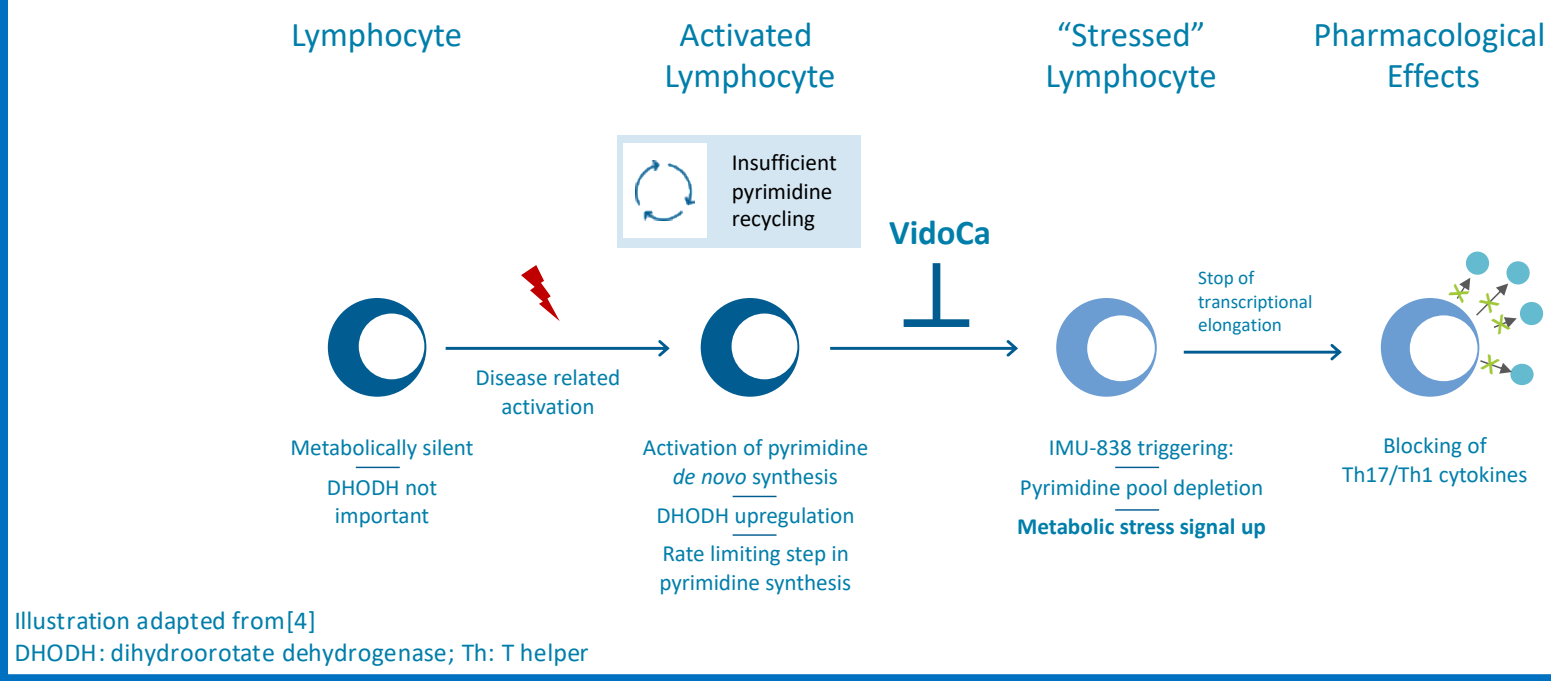
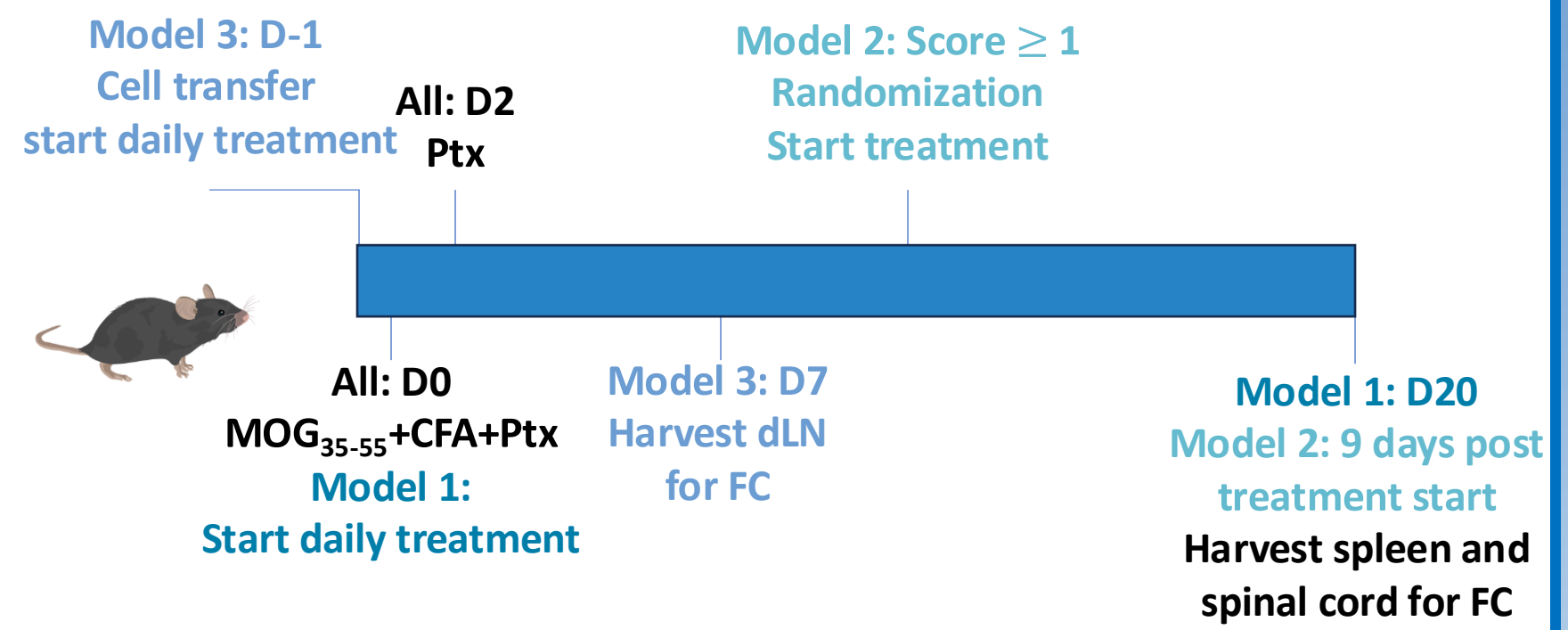


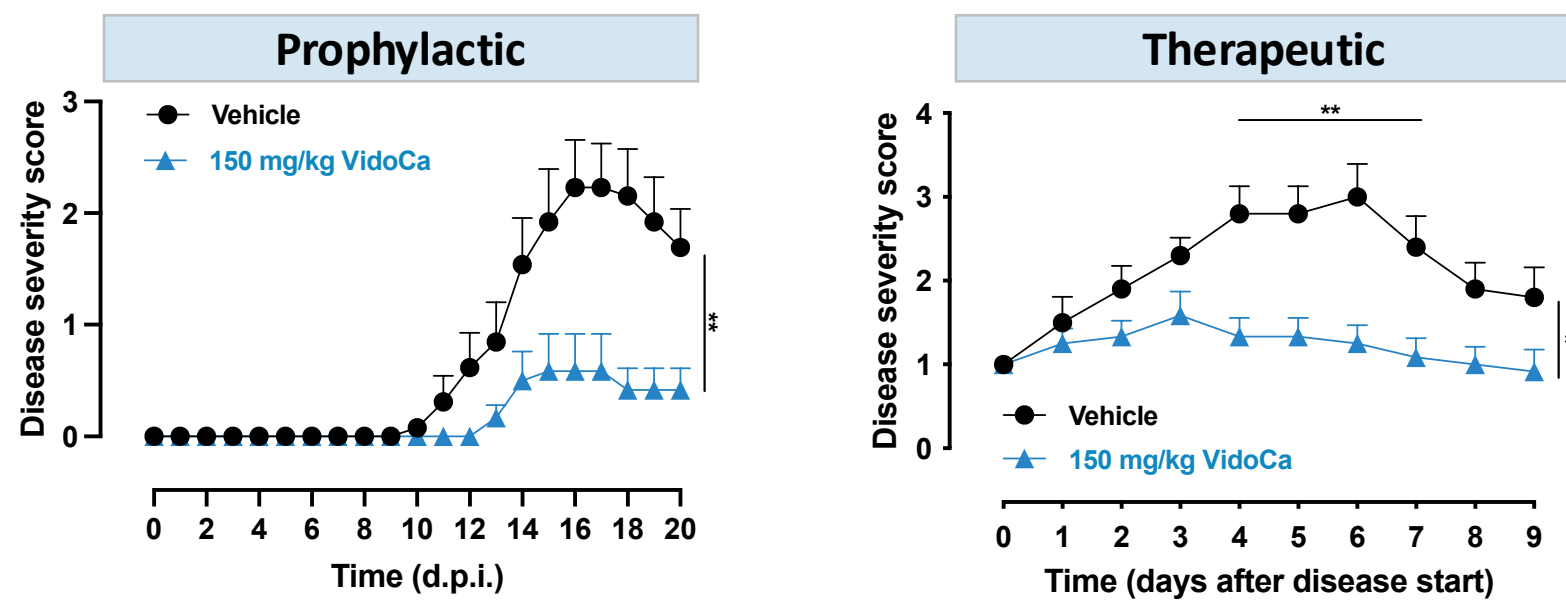
Illustration adapted from [4]
DHODH: dihydroorotate dehydrogenase; Th: T helper

Methods^[5,6]



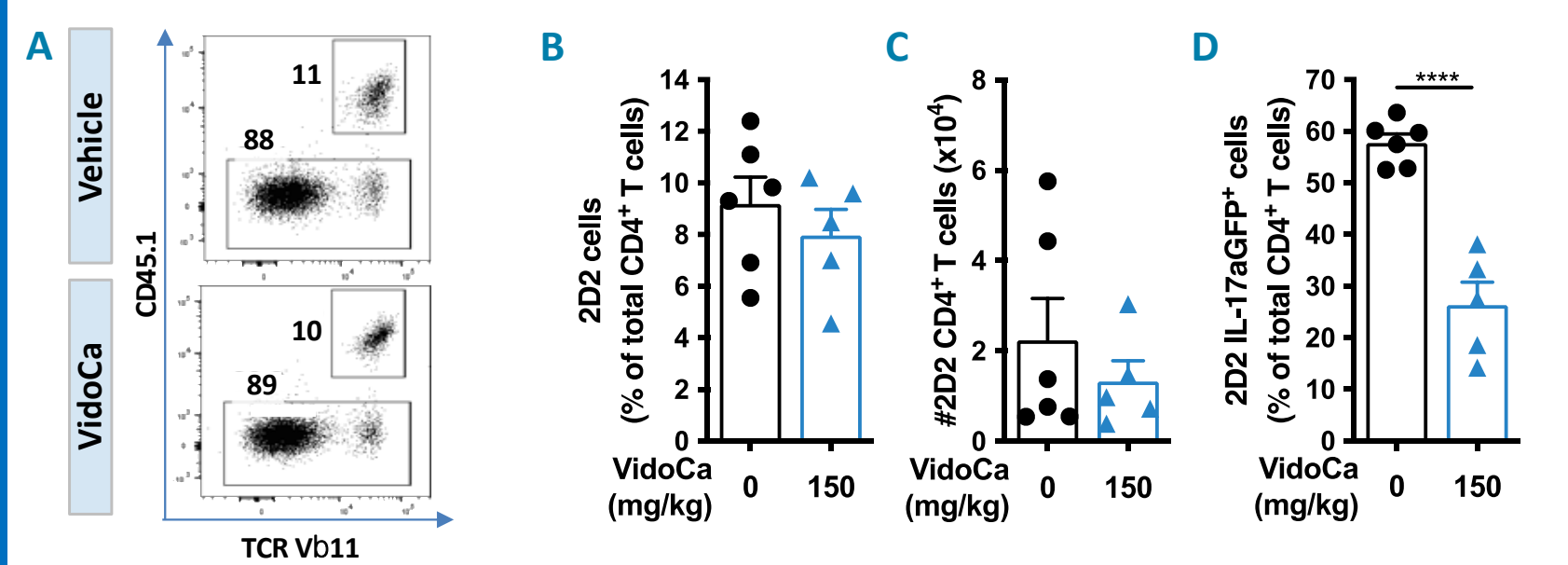
Model 1: prophylactic; Model 2: therapeutic; Model 3: prophylactic model with adoptive transfer of 1.5×10^5 CD45RB^{hi}CD25^{hi}IL17eGFP naive 2D2 T cells on a CD45.1 background into WT mice (CD45.2); CFA = complete Freund's adjuvant; D = days after immunization; dLN = draining lymph node; FC = flow cytometry; MOG = myelin oligodendrocyte glycoprotein; PtX = Pertussis toxin; MOG₃₅₋₅₅+CFA = immunization; treatment = vehicle (PEG400) or 150 mg/kg vidofludimus calcium (VidoCa). Graphs are shown with mean \pm SEM. * $p < 0.05$ is considered significant, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

VidoCa showed activity in the MOG₃₅₋₅₅ murine EAE model in a prophylactic and therapeutic setting



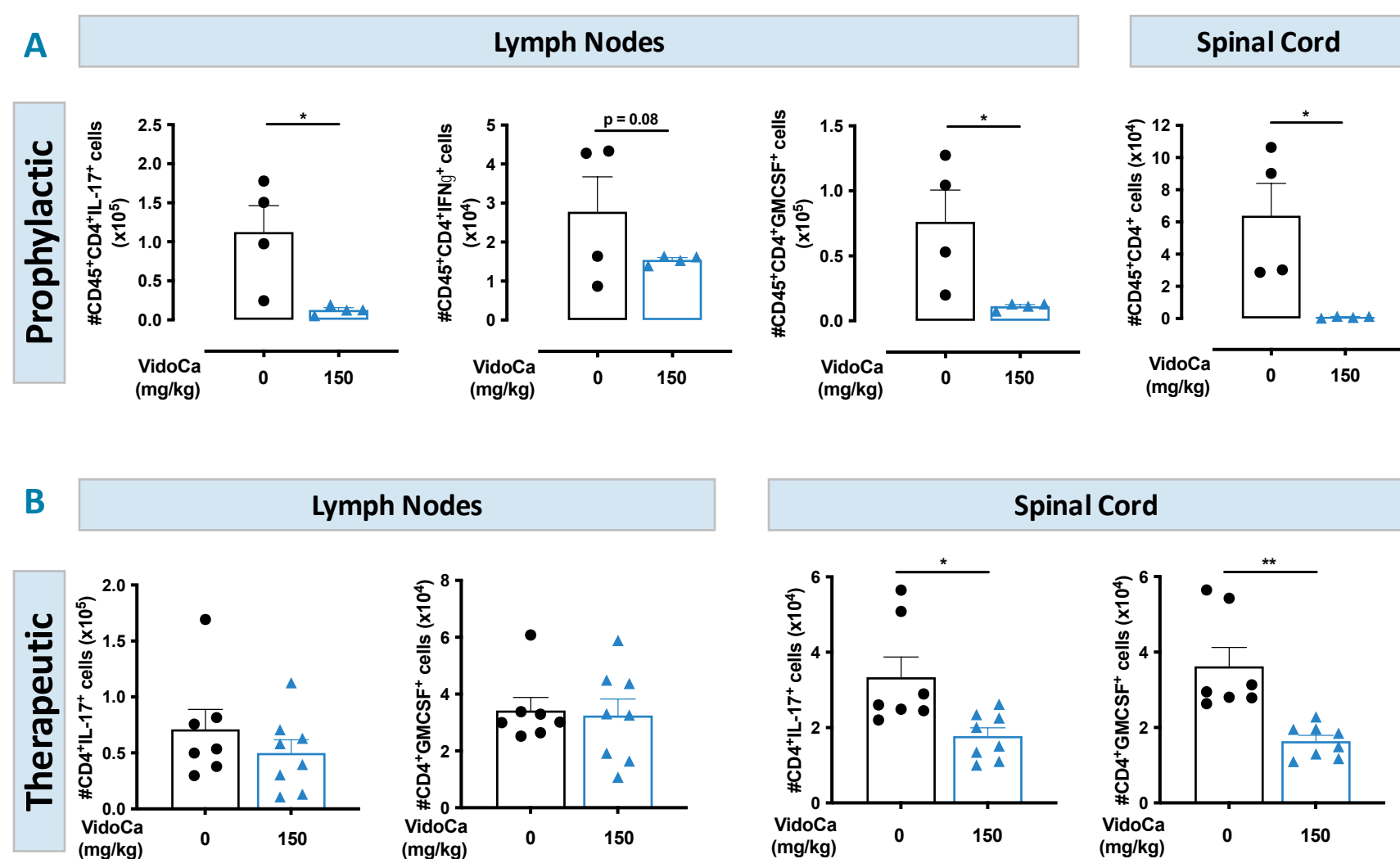
VidoCa reduced disease incidence and severity in a prophylactic EAE model with 63% of mice treated with VidoCa versus 15% of the mice in the vehicle group remaining disease free. Disease severity was also significantly reduced in a therapeutic EAE model.

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



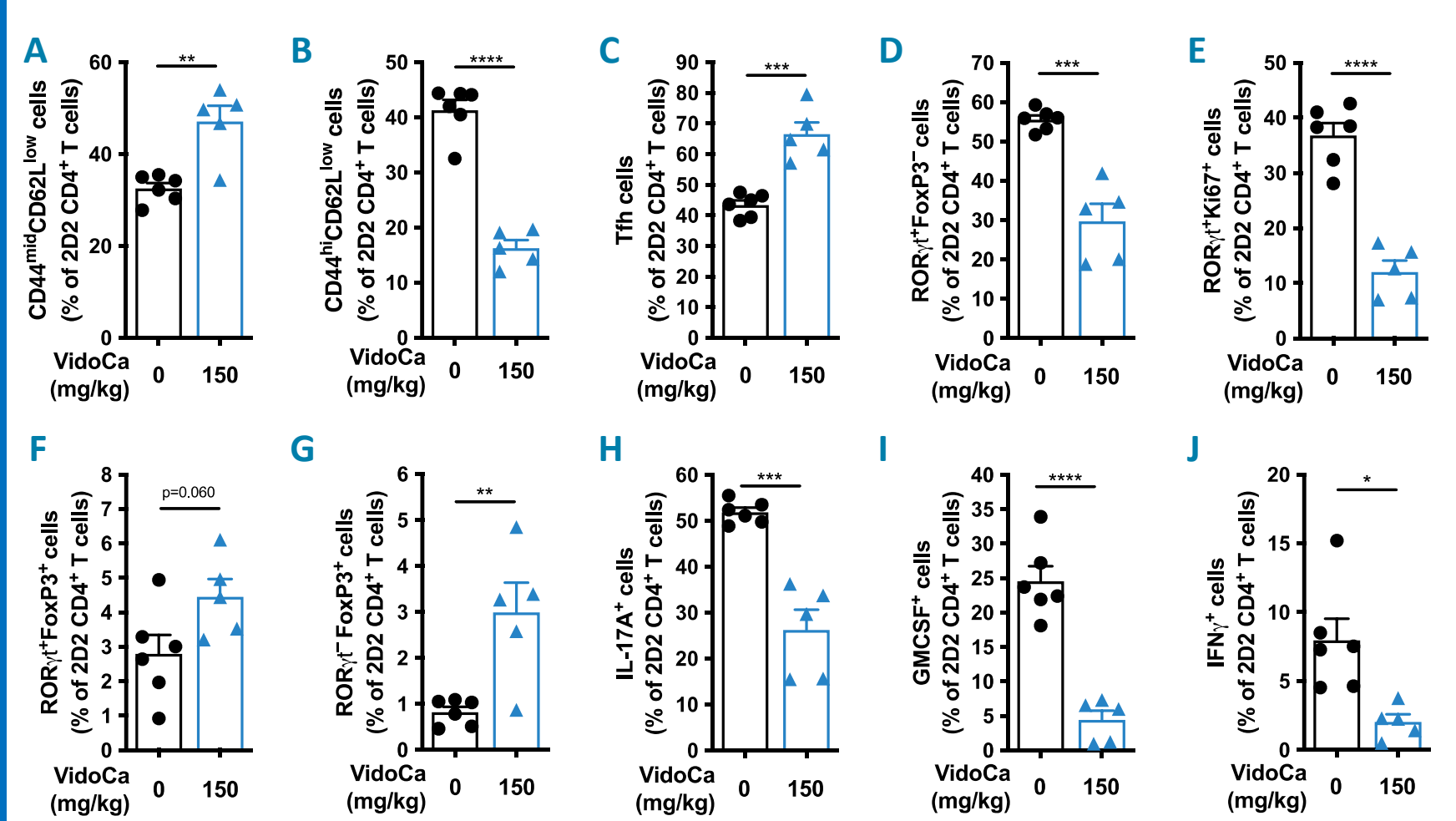
A) Gating strategy for MOG specific (2D2, donor cells, CD45.1⁺TCR Vβ11⁺) and recipient (WT, CD45.2⁺) T cells. B,C) VidoCa did not influence the frequency or total number of 2D2 T cells. D) However, IL-17⁺ 2D2 T cells (positive for GFP) are strongly reduced upon treatment with VidoCa in the prophylactic 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 RORγt⁺FoxP3⁺ cell frequencies and proliferation (D, E), an increase in regulatory T cells (FoxP3⁺, F,G) and reduced proinflammatory cytokine expressing cells (IL-17A⁺, GMCSF⁺, IFNγ⁺, 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.

