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Statins, Regulatory T Cells and Amyotrophic Lateral Sclerosis

The interesting paper by Edwards et al.[1] reports a disproportionate increase in the incidence of amyotrophic lateral sclerosis (ALS) or an ALS-like syndrome with HMG-CoA reductase inhibitor ('statin') therapy. Recent data shed light on the mechanisms by which this may occur. This needs our attention, given the widespread and expanding use of statins at high doses.[2]

Statins increase the number of CD4+CD25+ regulatory T cells (T_{regs}) *in vivo* by inducing the transcription factor forkhead box P3 (FOXP3).[3] This pleiotropic effect may stabilize atherosclerotic plaque by reducing T-cell responses in the atheroma;[4] however, it may also perpetuate neurodegenerative disorders by impairing neuroprotective autoimmunity.[5]

Elevated CNS extracellular glutamate concentrations promote excitotoxicity, which has been implicated in acute CNS trauma and chronic neurodegenerative disorders, including ALS.[6] Self reactive T helper 1 (T_h1) cells minimize the glutamate induced neuronal damage.[6,7] T_{regs} down-regulate T_h1 cell-mediated protection and, as a result, potentially impair the neuroprotective immune response.[8] That is the paradox of a statin-induced increase in T_{regs}: atheromatous plaques are stabilized at the expense of destabilizing neurodegenerative disorders.

Therefore, we strongly agree with Edwards et al.[1] that statins should not be used in patients with ALS or ALS-like syndromes. Furthermore, physicians must be particularly vigilant in reporting any adverse neurological outcomes in patients taking statins.

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