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Correspondence

To the editors: Impact of mass vaccination on SARS-CoV-2 infections among multiple sclerosis patients taking immunomodulatory disease-modifying therapies in England

To the editor:

We read with great interest the findings of Garjani and colleagues on the impact of disease-modifying therapies (DMT for multiple sclerosis (MS) on the incidence of COVID-19 (Garjani et al., 2021). Also, we find it noteworthy that natalizumab had no apparent effect on the risk of SARS-CoV-2 infection. Natalizumab is a humanized recombinant monoclonal antibody that binds to α4-integrin, and blocks its binding to its ligands vascular cell adhesion molecule (VCAM)−1 via α4β1-integrin, and mucosal vascular addressin cell adhesion molecule (MAdCAM)−1 via α4β7-integrin (Shirani and Stuve, 2018). Consequently, α4-integrin expressing leukocytes are sequestered out of the central nervous system (CNS) and gastrointestinal tract. Not surprisingly, a therapeutic α4-integrin receptor-saturation with natalizumab roughly doubles the number of lymphocytes in the peripheral circulation (Plavina et al., 2017). Also, at least some of the lymphocyte subsets sequestered into peripheral organs appear to differentiate to a more inflammatory phenotype. Krumbholz and colleagues demonstrated that natalizumab therapy increased $CD19^+$ mature B cells in peripheral blood 2–3-fold more than that of other lymphocytes and monocytes compared to pre-treatment levels (Krumbholz et al., 2008). The increase of immature $CD19^+CD10^+$ pre-B cells in peripheral blood was 7.4-fold. Kivisakk et al. showed that the frequency of $CD4^+$ T cells producing interferon gamma (IFNγ), tumor necrosis factor, and interleukin (IL)−17 upon anti-CD3 stimulation increased 6 months after initiation of natalizumab treatment and remained elevated throughout the follow-up (Kivisakk et al., 2009). The frequency of $CD4^+$ T cells expressing CD25, HLA-DR., and CCR6 ex vivo was increased at one or more time points during treatment.

Based on these observations, it would be conceivable that this increase in lymphocyte numbers would be associated with enhanced adaptive immune responses and host defense outside of the CNS and gastrointestinal tract, and that it may lower the risk of viral infections, including COVID-19. Evidently, that is not so.

Search of the literature failed to show data to support a beneficial effect of therapeutically induced lymphocytosis in infectious diseases. Furthermore, α4-integrin is a costimulatory molecule that is capable of providing a potent signal to CD3-mediated T-cell activation. Specifically, the very late antigen (VLA)−4 (α4β1-integrin)-mediated interaction of resting human $CD4^+$ T lymphocytes with fibronectin has been shown to promote CD3-mediated T cell proliferation (Shimizu et al., 1990). Davis et al. showed that immobilized fibronectin enhances anti-CD3 induced proliferation of both $CD45RA^{dim}$ and $CD45RA^{bright}$ $CD4^+$ and $CD8^+$ T cell subsets (Davis et al., 1990).

In summary, the natalizumab experience suggests that it is a specific qualitative immune response to SARS-CoV-2, the infectious agent that causes COVID-19, and not the number of available immune cells within a normal range that determines host defense. This is relevant for the identification of biomarkers associated with outcomes from COVID-19.

Declaration of Competing Interest

O.S. serves on the editorial boards of Therapeutic Advances in Neurological Disorders. has served on data monitoring committees for Genentech-Roche, Pfizer, Novartis, and TG Therapeutics without monetary compensation, has advised EMD Serono, Celgene, Genentech, Genzyme, TG Therapeutics, and VYNE, currently receives grant support from EMD Serono and Exalys, is a 2021 recipient of a Grant for Multiple Sclerosis Innovation (GMSI), Merck KGaA, and is funded by a Merit Review grant (federal award document number (FAIN) BX005664-01 from the United States (U.S.) Department of Veterans Affairs, Biomedical Laboratory Research and Development.

N.M. and S.T. have nothing to disclose.

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