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Systemic glucocorticoids confound SARS-CoV-2 acquisition or even clinical outcomes in autoimmune disease patients treated with biologics

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Letters to the Editor:

We read with great interest the brief report by Simon *et al*.[1] The authors assessed the immune responses to SARS-CoV-2 infection and vaccination in 14 autoimmune disease (AID) patients with B cell depletion, and found that both SARS-CoV-2 infection and vaccination developed lower anti-spike S1 IgG levels of 2.9±2.2 and 0.2±0.3 at 450nm respectively in rituximab-treated patients, as compared to 5.4±2.5 in healthy controls. Based on the above findings, B cell depletion may be associated with an increased risk of COVID-19 acquisition or even adverse outcomes in AID patients. In the last paragragh, Simon *et al*.[1] pointed out a large limitation is the small number of patients with B cell depletion who were exposed to SARS-CoV-2 infection or vaccination. However, any information on whether biologic medications with or without concomitant glucocorticoids was not given throughout this article, which is deemed as a confounding factor.

Glucocorticoids lead to broad immunosuppressive effects and are recommended by current guidelines as part of the standard care for AID.[2] In a national cohort from the Netherlands,[3] glucocorticoids were used alone or combined with biologics in 6% and 45% of AID patients respectively. During the COVID-19 pandemic, accumulative studies have

demonstrated that systemic glucocorticoids often increase the risk for SARS-CoV-2 acquisition or even adverse outcomes. In a retrospective cohort study of 213 AID patients from Detroit, glucocorticoids were associated with a 5.48-fold increased admission among those who tested positive for SARS-CoV-2 (OR:5.48, 95% CI:1.28-26.1).[4] In addition, Fagni *et al*.[5] performed a meta-analysis of COVID-19 susceptibility in AID patients, and showed that the usage of 2.5 mg or more of prednisone daily was associated with a significantly higher probability of SARS-CoV-2 acquisition (OR:2.89, 95% CI:1.26-6.62), and the intake of 10 mg or more of prednisone daily was associated with a doubled risk of hospitalization (OR:2.05, 95% CI:1.06-3.96). Generally, the relative risk associated with glucocorticoids is often linear to daily dosage and treatment duration;[6] nonetheless, evidence remains scarce about the effect of glucocorticoids plus biologics on SARS-CoV-2 acquisition in AID patients.

The available data have shown that glucocorticoids do not itself increase the risk for SARS-CoV-2 acquisition or even adverse outcomes. First, AID patients often receive courses of systemic glucocorticoids to reduce disease activity during the initial episode and subsequent flares, and thus a broad overlap is found between glucocorticoid usage and disease activity.[7] However, current studies do not allow identification of which of

the two variables is the major contributor to risk. Second, a higher proportion of connective tissue diseases (CTDs) confer a higher risk of SARS-CoV-2 acquisition. A meta-analysis encompassing 319025 patients from 62 studies showed that CTD patients had the highest prevalence of COVID-19 (3.4%) compared to other AIDs, which is likely due to a higher proportion of glucocorticoid usage (60.3%).[8] Third, an increased risk of SARS-CoV-2 acquisition associated with glucocorticoid usage comes as a consequence of the pandemic in low-resource settings,[9,10] which potentially exposes AID patients to adverse outcomes by comparison with their counterparts in high-income countries.

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