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Letter to the Editor

Corticosteroids and mRNA Vaccines: A Word of Caution

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We recently published a paper in *Molecular Therapy* that studies the impact of corticosteroids and cellulose-based purification on the innate immunity, translation, and efficacy of self-amplifying mRNA (sa-mRNA) vaccines.[1] With this Letter to the Editor, we want to highlight the relevance of a particular subset of data for the ongoing mRNA vaccination campaign against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In our work, we demonstrated in mice that a short course of dexamethasone, hydrocortisone, or clobetasol significantly reduced the type I interferon (IFN) responses and improved the *in vivo* translation of sa-mRNA vaccines.[1] This is an important observation because it might bring sa-mRNAs for protein (replacement) therapies closer to the clinic. Corticosteroids are also used to suppress immune reactions against Luxturna, an approved adeno-associated virus-based gene therapy for retinal dystrophy. However, for mRNA vaccines, the elicited type I IFN response is considered beneficial because it results in the release of cytokines that shape and promote the adaptive immune responses.[2–4] Nevertheless, a too-strong type I IFN response is known to impede mRNA translation and inhibit the adaptive immune response.[5–7]

To maximize the efficacy of mRNA vaccines, it seems that a well-balanced type I IFN response is required. Therefore, we wondered whether this balance could be disturbed when mRNA vaccines were combined with corticosteroids. Surprisingly, a short course of topical clobetasol at the vaccination site completely blunted the humoral (antibody) response elicited by a sa-mRNA vaccine against Zika virus (ZIKVac-sa-mRNA vaccine). In addition, topical hydrocortisone and oral dexamethasone demonstrated a comparable decrease in type I IFN response at the injection site.[1] Therefore, a similar inhibitory effect on the efficacy of mRNA vaccines is expected with oral dexamethasone and topical hydrocortisone. More evidence for the devastating effects of corticosteroids on mRNA vaccines comes from the work of Vormehr et al.[8] These authors found that the number of antigen-specific T cells elicited by an mRNA cancer vaccine was significantly lower if the mice received intraperitoneal dexamethasone 3 h before vaccination. Even more alarming is the observation that their mRNA vaccine started to induce regulatory T cells (Tregs) when combined with dexamethasone. The latter may indicate that immune tolerance is lurking around the corner when mRNA vaccines are given together with certain corticosteroids. In our study, we administered the sa-mRNA vaccine intradermally using electroporation, while Vormehr et al.[8] gave their lipid formulated mRNA vaccine intravenously. Both studies were performed in mice. The current coronavirus disease 2019 (COVID-19) mRNA vaccines are formulated in lipid nanoparticles and given intramuscularly.[9,10] Despite these differences, it is still very plausible that the vaccination efficacy of the mRNA vaccines against SARS-CoV-2 will also be decreased in patients treated with corticosteroids. Consequently, the immunogenicity and protection efficacy of the SARS-CoV-2 mRNA vaccines in patients who concurrently receive corticosteroids must be urgently investigated. In the meantime, we should consider postponing COVID-19 mRNA vaccination in patients currently receiving high doses of corticosteroids. Corticosteroids induce immunosuppression by interfering with the signaling of nuclear factor κB (NF-κB) and activator protein 1 (AP-1), which results in a decreased expression of pro-inflammatory cytokines and chemokines.[11] Moreover, corticosteroids are widely used for acute and chronic inflammations, including severe allergies, asthma, rheumatoid arthritis, inflammatory bowel diseases, skin diseases, and multiple sclerosis.[11] For example, in the UK, 1% of the total adult population and 2.5% of the elderly between 70 and 79 years of age took oral corticosteroids in the year 2000.[12] Finally, it is possible that other immune suppressive drugs, such as cyclosporine and methotrexate, could also prove detrimental to the vaccination efficacy of mRNA vaccines.

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