The paradox of immunosuppressants and COVID-19

Guang-Shing Cheng[1] and Scott E. Evans[2]

[1]Clinical Research Division, Fred Hutchinson Cancer Research Center and Division of Pulmonary Critical Care and Sleep Medicine, University of Washington School of Medicine, Seattle, WA, USA. [2]Dept of Pulmonary Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Corresponding author: Guang-Shing Cheng (gcheng2@fredhutch.org)

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Lessons learned from a large registry analysis show worse COVID-19 outcomes for patients previously exposed to glucocorticoids https://bit.ly/306rNrk

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For millions of people, taking immunosuppressive medication to control or prevent disease is a daily reality [1]. Rheumatological disease, inflammatory lung disease, organ transplantation and graft-*versus*-host disease are but a few of the immune dysregulation syndromes that may require short- or long-term immunosuppressive therapy (IST). Patients taking ISTs are frequently regarded as immunocompromised, sharing risks of increased infection susceptibility with cancer patients receiving chemotherapy, those with profound neutropenia from haematological malignancies, and individuals living with HIV. In the context of the immune-mediated respiratory failure associated with coronavirus disease 2019 (COVID-19), an apparent paradox arises: can ISTs both promote and protect against severe COVID-19?

As typical of viral infections, an adaptive T-cell-mediated immune response to SARS-CoV-2 infection is required for pathogen clearance. However, an unchecked, overexuberant host response characterised by elevated interleukin (IL)-6 and other pro-inflammatory cytokines appears to be responsible for many severe manifestations of COVID-19 and their associated poor outcomes [2–4]. The subsequent hypothesis that suppressing this immunopathological response could improve the course of disease has been substantiated by high-quality randomised, controlled trials showing survival benefits for critically ill COVID-19 patients receiving dexamethasone or tocilizumab, an IL-6 receptor blocking antibody [5–7]. Baricitinib, an oral JAK1/2 kinase inhibitor, was also shown to accelerate clinical improvement in hospitalised patients [8], including those requiring mechanical ventilation [9]. Pursuing this strategy, no fewer than 400 clinical studies of repurposed anti-inflammatory agents for COVID-19 have been registered at clinicaltrials.gov since the onset of the pandemic [10].

While attenuating the immunopathological response in severe SARS-CoV-2 disease appears to improve patient outcomes, it is recognised that patients on ISTs for chronic conditions may lack adequate immune responses to clear the virus, potentially placing them at high risk for disease progression due to uncontrolled viral propagation. The concern that immunocompromised individuals are at elevated risk for viral acquisition and severe disease outcomes has prompted policy decisions that prioritise delivery of resource-limited interventions, such as vaccinations and monoclonal antibody treatments, to patients receiving ISTs. Congruently, when feasible, ISTs are typically de-escalated in the context of active infections, as has been empirically recommended for solid organ transplant recipients and patients with rheumatological conditions in the setting of SARS-CoV-2 infection [11–14].

In this issue of *European Respiratory Journal*, Ward *et al.* [15] examine the impact of ISTs on outcomes of SARS-CoV-2 infections in a large Danish registry cohort during the first months of the pandemic. To assess this, they determined from a national database which PCR-positive SARS-CoV-2 patients had been exposed to ISTs in the 120 days prior to the infection, and compared their outcomes to SARS-CoV-2 patients who were not exposed to ISTs. Over a six and a half month period starting in March 2020, 527 patients (1.4%) of the nearly 37 000 patients with a positive SARS-CoV-2 PCR test met the definition for

exposure to IST. They used a propensity score-weighted model to account for potential confounding by baseline demographics and the underlying medical conditions that required IST. The primary analysis considered all IST agents in aggregate and found the adjusted relative risk of IST exposure for hospitalisation and intensive care unit admission was not statistically significant. However, the risk of death was increased 56% compared with non-IST-exposed individuals. A subgroup analysis revealed that the elevated risk of death was principally driven by the exposure to glucocorticoids. The investigators looked at three categories of ISTs: 1) targeted immunosuppressants, including sirolimus, JAK-inhibitors and novel biologics such as interleukin inhibitors; 2) calcineurin inhibitors, azathioprine, methotrexate and conventional disease-modifying anti-rheumatic agents, including hydroxychloroquine; and 3) systemic glucocorticoids. They found that the first two classes of IST did not increase risk for severe outcomes, whereas glucocorticoid exposure was associated with 34% greater risk of hospital admission and 138% greater risk of death compared to unexposed patients. Moreover, the relative risk of severe outcomes increased with greater cumulative exposure to glucocorticoids in the 120 days prior to a positive SARS-CoV-2 diagnosis.

While the effects of glucocorticoids on severe outcomes are robust, it is somewhat surprising that no significant effect was demonstrated with other classes of ISTs. It is possible that the low number of exposures and the low frequency of severe outcomes limited the ability to discern a significant effect of IST groups on survival. Another challenge, supported by the sensitivity analysis, is that the effect of underlying disease may in some cases overwhelm the outcome effects of the IST in isolation. Further, while the authors made great effort to include a very comprehensive list of potentially immunosuppressive therapies, the wide range of IST mechanisms may also limit the ability to detect significant outcomes effects when aggregated into inhomogeneous groups. The possibility remains that some categories of IST have no impact or even play a protective role against COVID-19, while others confer harm. A recent US cohort study failed to demonstrate a negative impact of non-glucocorticoid IST on COVID-19 outcomes when considered in broad categories. On further analysis by specific IST mechanistic categories, JAK-inhibitors were significantly associated with severe outcomes [16]. The COVID19-Global Rheumatology Alliance reported similar findings in their cohort of rheumatological patients: tumour necrosis factor antagonists were not associated with worse outcomes, whereas use of glucocorticoids was [17]. Taken together, these findings support the important notion that not all ISTs equally influence SARS-CoV-2 susceptibility and survival.

Based on currently available evidence, it seems prudent to err on the side of caution by considering patients with recent IST exposure, including non-glucocorticoids, as “high risk” individuals when prioritising distribution of COVID-19 treatments and vaccinations, as currently recommended by most public health guidelines. This study enhances our confidence that high doses of antecedent glucocorticoids contribute to worse COVID-19 outcomes. The effect of cumulative glucocorticoid exposure is consistent with fundamental principles that overall immunosuppression portends poor outcomes for infections. The poorer outcomes in patients exposed to glucocorticoids may relate to impaired viral clearance, increased risk for secondary infections, metabolic consequences of chronic steroid exposure, poor overall physiological reserve and/or other unknown mechanisms. Further, glucocorticoids may potentiate infectious complications of other ISTs. Persistent SARS-CoV-2 viral replication and mutagenesis have been documented in immunocompromised hosts receiving high dose steroids and immunochemotherapy [18, 19].

Glucocorticoids are used ubiquitously as first-line therapy for inflammatory conditions. In pulmonary medicine, prednisone remains widely recommended for management of COPD and asthma exacerbations. First-line treatment of acute exacerbations of idiopathic pulmonary fibrosis consists of 3 days of high-dose methylprednisolone or the equivalent. Steroids are used unsparingly for acute drug-induced pneumonitis, which now is more relevant than ever with the rise in immune-mediated pneumonitis from checkpoint inhibitor cancer therapy. Conventional treatment of cryptogenic organising pneumonia requires a minimum of 4–6 months of prednisone.

The potential harms due to glucocorticoids do not generally negate their immediate salutary effects. Glucocorticoids—nonselective, powerful, and inexpensive—are the blunt instrument that the physician reaches for to rapidly reverse a deteriorating situation. The immediate risks of glucocorticoid exposure are largely negligible relative to the immediate risk of death from diseases they are intended to treat. Yet one should not underestimate the profound effects of exogenous corticosteroids on immunity and overall health, especially as these effects become more pronounced with higher doses and longer exposures. Ironically, the COVID-19 pandemic has brought to the fore the bevy of selective and targeted immunomodulatory agents that already exist or are in advanced development. Of the many lessons learned during this pandemic, one is a reminder that alternatives to glucocorticoids exist. Studies such as that of

WARD *et al.* [15] suggest the need to better understand whether steroid-sparing approaches may provide therapeutic benefits in inflammatory conditions without potential complications of glucocorticoid exposures. For example, in diseases such as organising pneumonia or iatrogenic pneumonitis, it may be possible to rapidly taper the high doses of steroids that are used for initial disease control, replaced by more selective anti-inflammatories that may confer less susceptibility to infection.

In the evolving understanding of how manipulation of the host response to SARS-CoV-2 contributes to patient outcomes, the work by WARD *et al.* [15] both highlights the inhomogeneity of effects of many types of ISTs on infection susceptibility and emphasises that even ubiquitously used agents like glucocorticoids can contribute to substantial harms. Further, studies such as this should galvanise investigators to enhance the mechanistic understanding of how ISTs contribute to the pathogenesis of infections, so they can be properly deployed to protect our patients with disorders of immune dysregulation.

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