

# Immunosuppression drug advice and COVID-19: are we doing more harm than good?

The National Institute for Health and Care Excellence guidelines advise stopping immunosuppressive drugs for confirmed or suspected COVID-19 patients with autoimmune and inflammatory disorders. This may not be in the patient's best interest, given the potential long-term consequences of not managing chronic conditions, and immunosuppression may even be protective in those affected with COVID-19.

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The National Institute for Health and Care Excellence (2020) has released guidelines on the management of patients known or suspected to have COVID-19 who have autoimmune and inflammatory disorders. This encompasses patients who fall under the care of many specialties including rheumatology, dermatology, respiratory, gastroenterology and ophthalmology. The advice is for these patients to stop taking their immunosuppressive drugs, including disease-modifying antirheumatic drugs, JAK inhibitors and biologics. However, the evidence this is based on is unclear and such advice may be detrimental to the overall health of these patients.

The National Institute for Health and Care Excellence (2020) also recommends the use of corticosteroid injections in patients only if their disease is severe, and NHS guidelines recommend, if steroids are required, that low doses should be used. This advice has been extrapolated from concerns of risks of increased mortality and delayed viral clearance associated with the use of steroids in those with influenza and Middle East respiratory syndrome coronavirus (National Health Service, 2020). However, there is no definitive evidence yet about the risks of steroids in patients with COVID-19 infection.

Current guidelines for COVID-19 patients are therefore based on presumptions about the effects of medications on the pathophysiology of COVID-19. However, stopping these medications could be harmful to these patients. For example, in patients with rheumatological conditions, these drugs are important in reducing or preventing joint damage, pain control, and preservation of the function and structure of joints (Cohen and Cannella, 2020). Their effects take weeks–months to materialise, so stopping these vital medications for a short period may leave the rheumatological disease unmanaged for a long time. In a systematic review, Halpin et al (2020) reported that there is currently no evidence supporting the withdrawal of inhaled corticosteroid medications in patients with asthma or chronic obstructive pulmonary disorder with COVID-19 and that stopping these medications is likely to be harmful. They recommend the continuation of these medications. Steroids, disease-modifying antirheumatic drugs and biologics are used to manage psoriasis and they can take weeks to show their therapeutic effects. Alongside its dermatological effects, psoriasis has significant psychosocial consequences for those affected and thus disease control is paramount for both the physical and psychological wellbeing of these patients (Feldman, 2020). Biologics also play a key role in treating colitis and ensuring remission of disease, so discontinuing this medication will prevent healing of the inflammation in the colon and continue to adversely affect the lives of these patients (Peppercorn and Kane, 2019). Some biologics remain in the system for weeks because of their prolonged half-life, so stopping immunosuppressive medications in patients suspected or confirmed as having COVID-19 may not confer any benefit at all (Dhimolea, 2010).

It is of note that the pathophysiology of infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in those with severe clinical outcomes involves a state of hyperinflammation driven by the 'cytokine storm' (Mehta et al, 2020). During this, the immune system is over-activated, releasing pro-inflammatory cytokines (Spezzani et al, 2020) such as tumour necrosis factor-alpha, interleukins, granulocyte-colony stimulating factor and macrophage inflammatory protein-1 alpha (Misra et al, 2020). These cytokines cause multi-organ and tissue damage, with many patients requiring intensive care management. It is thus hypothesised that patients with COVID-19 who are taking anti-cytokine medications

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such as biologics or disease-modifying antirheumatic drugs may have a better prognosis because they have a weakened cytokine response and hence less mounting of the cytokine storm (Spezzani et al, 2020). Monteleone and Ardizzone (2020) argue that patients with inflammatory bowel disease, for example, may be protected against COVID-19 infection as the cytokines released during the cytokine storm and those released in the pathophysiology of inflammatory bowel disease are alike and hence biologics would be therapeutic against both conditions. They argue that these patients should remain on their immunosuppressive medications as there is no evidence to indicate that COVID-19 occurs more often in patients with inflammatory bowel disease than in the general population. Thus far no inflammatory bowel disease patients with concurrent SARS-CoV-2 infection have been reported from specialist inflammatory bowel disease centres in Wuhan, China.

The COVID-19 Global Rheumatology Alliance (2020) has reported 3181 rheumatology patients with COVID-19 infection as of 16 June 2020, which is only 0.04% of the total COVID-19 cases (n=7941 791) reported by the World Health Organization (2020) on 16 June 2020. Patients with rheumatological conditions do not appear to be disproportionately increasingly affected by COVID-19. Furthermore, emerging evidence suggests that patients with cancer who are taking cytotoxic drugs or other anti-cancer treatment are not at increased risk of mortality (Lee et al, 2020). Experience in ophthalmology indicates that taking immunosuppressives for non-infectious uveitis does not seem to confer an increased risk of developing severe COVID-19 infection (Smith and Lai, 2020).

Preliminary experience from regions with a high incidence of SARS-CoV-2 infection shows that patients taking baseline immunosuppressants (biologics, disease-modifying antirheumatic drugs or JAK inhibitors) do not seem to be at any higher risk of life-threatening complications from SARS-CoV-2 than the general public (Barnard, 2020). For example, Gisoni et al (2020) performed a large retrospective observational study in Italy that looked at the impact of the pandemic on patients with chronic psoriasis taking biologics, and found there was not a significant number of hospitalisations or deaths from COVID-19 in these patients.

Global evidence is emerging that supports the use of immunosuppressive therapies. In an Italian study, the use of high-dose anakinra (an interleukin-1 receptor antagonist) reduced systemic inflammation and improved respiratory function in patients with COVID-19. It also allowed intubation to be postponed or completely avoided in most patients (Cavalli et al, 2020). The use of tocilizumab (an interleukin-6 receptor antagonist) in early clinical trials in China, involving severe or critical COVID-19 patients, showed good efficacy with 75% of patients reducing their oxygen requirement (Zhang et al, 2020).

The authors believe that until there is evidence of immunosuppressant medication causing harm in those infected with COVID-19, these medications should be continued if clinically indicated. Stopping these medications may have unjustifiable withdrawal effects on stable conditions across specialties and may cause more harm than benefit. Moreover, they may even be protective against severe COVID-19 clinical outcomes.

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## Key points

- National Institute for Health and Care Excellence guidelines recommend that patients infected with SARS-CoV-2 should suspend their immunosuppressive therapies such as disease-modifying antirheumatic drugs, JAK inhibitors and biologics.
- However, the evidence this is based on is unclear and such advice may instead be detrimental to the overall health of patients.
- Patients with severe COVID-19 disease exhibit features of hyperinflammation which is driven by a 'cytokine storm', but immunosuppressed patients may be protected from this cytokine storm as a result of a blunted immunological response.
- Global evidence shows that patients with rheumatological conditions do not appear to be disproportionately increasingly affected by the coronavirus pandemic and immunosuppressants may actually be beneficial.
- It may be unnecessary, and potentially detrimental, to ask patients to stop their immunosuppressant medications.

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