## COVID-19: Important Updates and Developments
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# Evidence-based best practice advice for patients treated with systemic immunosuppressants in relation to COVID-19

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**Abstract** The emergence of the COVID-19 pandemic has led to significant uncertainty among physicians and patients about the safety of immunosuppressive medications used for the management of dermatologic conditions. We review available data on commonly used immunosuppressants and their effect on viral infections beyond COVID-19. Notably, the effect of some immunosuppressants on viruses related to SARS-CoV2, including SARS and MERS, has been previously investigated. In the absence of data on the effect of immunosuppressants on COVID-19, these data could be used to make clinical decisions on initiation and continuation of immunosuppressive medications during this pandemic. In summary, we recommend considering the discontinuation of oral Janus kinase (JAK) inhibitors and prednisone; considering the delay of rituximab infusion; and suggesting the careful continuation of cyclosporine, mycophenolate, azathioprine, methotrexate, and biologics in patients currently benefitting from such treatments.
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## Introduction

Infectious diseases continue to pose significant challenges to public health. The first cases of respiratory infections of unknown origin emerged in Hubei province (Wuhan, China) in December 2019. The WHO officially announced on February 11, 2020, that the outbreak is caused by the novel enveloped RNA betacoronavirus that has been named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), and its associated disease has been named "coronavirus disease 2019" (COVID-19).[1] SARS-CoV-2 shares phylogenetic similarities with other coronaviruses, including the one responsible for the severe acute respiratory syndrome coronavirus (SARS-CoV).[2] COVID-19 has quickly turned into a global pandemic, unprecedented in the modern world. As immunosuppressive drugs are prescribed to a greater number of patients, concern exists for increased morbidity and mortality in patients infected with COVID-19 treated with these medications. We review evidence evaluating commonly used immunosuppressants medication in dermatology with regard to viral infections.

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## Cyclosporine

Cyclosporine A (CsA) is a small molecule that binds to members of the cyclophilin family. Cyclophillins are involved in protein folding, and their inhibition results in inhibition of calcineurin and the nuclear factor of activated T cells.[3] CsA has been linked to significant risk of serious infection in psoriasis patients (Relative risk (RR) = 3.12), greater compared with other immunosuppressants, particularly biologics.[4] Similarly, psoriasis patients on CsA are known to have a higher incidence of herpes zoster.[5] In addition, CsA has been shown to decrease immune response to influenza vaccination at high doses.[6] The duration of CsA effects on the immune system is currently unknown; however, *in vivo* animal models found full recovery within 4 days of the last dose.[7]

CsA is known to interfere with replication of diverse viruses, including the human immunodeficiency virus,[8] flaviviruses,[9] and hepatitis C.[10] Intriguingly, CsA has also been shown to inhibit replication of coronaviruses: CsA inhibits replication of MERS,[11] SARS,[12] shuman CoV-229E, CoV-NL-63, feline CoV, and avian infectious bronchitis virus.[13,14] Similar results were seen with nonimmunosuppressive CsA derivatives, such as alispovir,[15] and medications targeting FK506.[16] (p50) More data are needed to evaluate the magnitude of increased risk for viral infections, specifically COVID-19, in patients taking CsA. Similarly, additional data are needed to evaluate whether a possible therapeutic role exists for CsA in patients with COVID-19. Based on limited data, for patients who are not infected with COVID-19 and who have stable control of their dermatologic disease, we suggest not to preemptively discontinue or decrease CsA. Patients on CsA should immediately report any flu or coldlike clinical manifestations to their physicians. For patients with a high degree of suspicion or diagnosed with active COVID-19 infection, we recommend temporary cessation of CsA. In addition, we recommend care when initiating CsA at this time unless there are no other alternatives, taking into account the risk, benefits, and temporary delay of initiation with patients in nonepidemic and epidemic COVID-19 areas.

## Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an FDA-approved immunosuppressant for renal allograft rejection.[3] MMF is a noncompetitive, selective, and reversible inhibitor of inosine monophosphate dehydrogenase,[17] resulting in the inhibition of lymphocyte proliferation and antibody production.[3,18] MMF decreases the immune response to influenza vaccine.[19] Little is known about the time to immune recovery from the last dose of MMF. Given that MMF suppresses the adaptive immune response, important in fighting viral infections, MMF could potentially increase the risk of viral infections; however, MMF inhibits viral genome replication and gene transcription of influenza A and B.[20] Similarly, MMF used in synergy with 6-mercaptopurine and 6-thioguanine can inhibit MERS-CoV

PL(pro), the papain-like protease [PL(pro)] of MERS-CoV.[21] More data are needed to evaluate the magnitude of an increased risk for viral infections, specifically COVID-19, in patients taking MMF. Based on limited data, for patients who are not infected with COVID-19 and who have stable control of their dermatologic disease, we suggest not to preemptively discontinue or decrease MMF. Patients on MMF should immediately report any fever-, flu-, or cold-like clinical manifestations to their physicians, and for patients with a high degree of suspicion or diagnosed with active COVID-19 infections, we recommend temporary cessation of MMF. In addition, we recommend against the initiation of MMF in COVID-19 epidemic and nonepidemic areas.

## Prednisone

Glucocorticoids result in decreased production of proinflammatory cytokines, such as interleukin-1, interleukin-6, tumor necrosis factor, prostaglandins, and leukotrienes, but increasing anti-inflammatory cytokines[22,23] and decreasing inflammatory cytokines.[24] Infections are a well-characterized complication of steroids. A meta-analysis evaluating 71 controlled trials found significantly increased infection rate in patients receiving corticosteroids.[25] In addition, although a dose less than 20 mg daily is not considered sufficiently immunosuppressive to preclude live vaccinations, treatment discontinuation of 1 to 3 months is recommended before live vaccinations for patients on higher daily doses.[26] Although there is no clear evidence of the effects of prednisone on SARS-CoV-2, prednisone has been linked to unfavorable clinical outcomes in other viral infections; for example, prednisone was found to result in significantly higher incidence of severe acute respiratory infections in patients with pH1N1 as well as an increased risk of subsequent critical illness or death. Patients who were given corticosteroids after the onset of severe acute respiratory infections did not have worse outcomes.[27] Prednisone is known to be beneficial in the management of some viral infections: for example, prednisone used with acyclovir decreases pain in herpes zoster.[28] Use of steroids in herpes zoster patients has been shown to lead to decreased level of interleukin-6,[29] an inflammatory cytokine known to be significantly upregulated and a possible therapeutic target in COVID-19.[30,31] Recent presentations have examined the use of glucocorticoids in COVID-19. Although observational studies failed to provide sufficient evidence for use of steroids in treatment of COVID-19–associated lung injury, there are reports of positive clinical experience with SARS and COVID-19.[32,33] Based on available data, for patients who are not infected with COVID-19 and who have stable control of their dermatologic disease, we suggest that the preemptive discontinuation of prednisone be considered. Patients on prednisone should immediately report any fever-, flu-, or cold-like clinical manifestations to their physicians, and for patients with a high degree of suspicion or diagnosed with active COVID-19 infections, we recommend immediate cessation of their prednisone.

Given the limited data available at this point, we recommend limiting oral prednisone only to the most severe clinical scenarios where its use is well established and cannot be substituted with other medications.

## Azathioprine

Azathioprine (AZA) is a moderately potent immunosuppressive agent. AZA and its active metabolite 6-thioguanine, a purine analog, suppresses T-cell function and B-cell antibody production.[18] AZA has been uncommonly associated with opportunistic infections.[3] Although the duration of AZA effects on the immune system is unclear, hematopoietic recovery was observed after at least 40 days from last dose in CD-1 mice.[34] Use of AZA at dosage ≤3 mg/kg is not sufficiently immunosuppressive to preclude live vaccines,[26] and AZA does not interfere with mounting antibody response to influenza vaccine.[35] Data are limited about coronavirus susceptibility in patients treated with AZA; however, patients with systemic lupus erythematosus treated with AZA have higher rates of herpes zoster.[36] Although an increased rate of infection in transplant patients on AZA compared with MMF has been reported,[37] no increased risk of major infections has been found with AZA in systemic lupus erythematosus and HIV.[38,39] Based on limited data, for patients who are not infected with COVID-19 and who have stable control of their dermatologic disease, we suggest not to discontinue or decrease AZA preemptively. Patients on AZA should immediately report any fever-, flu-, or cold-like clinical manifestations to their physicians, and for patients with a high degree of suspicion or who are diagnosed with active COVID-19 infections, we recommend temporary cessation of their AZA or the initiation of AZA inhibitors in COVID-19 epidemic and nonepidemic areas.

## Rituximab

Rituximab is an immunoglobulin-G1 monoclonal antibody that targets CD20 antigen, a protein expressed on the surface of most B lymphocytes, causing depletion of B lymphocytes. Rituximab can cause B-cell depletion via (1) Fc receptor gamma-mediated antibody-dependent cytotoxicity and phagocytosis, (2) complement-mediated cell lysis, (3) growth arrest, and (4) B-cell apoptosis.[40] In addition, rituximab may also result indirectly in substantial but reversible depletion of CD4+ T cells.[41] Rituximab is avoided in patients with chronic hepatitis B, hepatitis C, or HIV. Based on international guidelines, and experience with increasing risks of other types of infections, use of rituximab is being cautioned in the setting of this pandemic, as it may increase the risk of worsening consequences of SARS-CoV-2 infection; for example, according to the Multiple Sclerosis International Federation, patients currently receiving treatment with rituximab should take all measures possible to isolate to reduce their risk of infection (msif.

org, last accessed March 18, 2020). Currently, given the novelty of COVID-19, there is no study specifically examining the effect of rituximab on the risk of developing infection with COVID-19 in any cohort of patients. In addition, there is no study to our knowledge looking at the risk of acquiring other types of coronavirus that have emerged previously (SARS-CoV, MERS-CoV, etc.). Based on limited data, for patients who are not infected with COVID-19 and who have stable control of their dermatologic disease, we suggest not to preemptively discontinue or decrease rituximab. Given that rituximab can decrease the number of B cells for over 6 months,[42] physicians and patients should discuss the possibility of delaying rituximab injections based on individual cases. Patients on rituximab should immediately report any fever-, flu-, or cold-like clinical manifestations to their physicians, and for patients with a high degree of suspicion or diagnosed with active COVID-19 infections, we recommend temporary cessation of their rituximab. In addition, we recommend against the initiation of rituximab in COVID-19 epidemic and nonepidemic areas.

## Methotrexate

Methotrexate (MTX) is a dihydrofolate reductase inhibitor that inhibits DNA synthesis, resulting in antiproliferative and anti-inflammatory effects.[3] Serious side effects of MTX have mostly been reported in the rheumatology literature: bone marrow suppression, liver fibrosis, pulmonary fibrosis, and increased risk of infections. The lower dermatologic dose of MTX (5-15 mg/week) is also thought to carry an increased risk and severity of infection, especially compared with biologics.[43] Although duration of MTX immunosuppression after its last dose is unclear, RA patients showed improved immunogenicity of influenza vaccination 2 weeks after MTX cessation.[44] Regarding viral infections, MTX is known to increase the incidence of herpes zoster in RA patients.[45] In addition, reactivation of hepatitis B upon withdrawal of low-dose MTX in RA patients has also been reported, leading to the screening practice for viral hepatitis before initiation of MTX.[46] Despite evidence of increased infection risk, there is no evidence about the impact of continuing or withholding MTX during an infection on outcomes. Intriguingly, *in vivo* studies demonstrated that MTX inhibits replication of RNA viruses, such as dengue virus and Zika via inhibition of purines and pyrimidines synthesis.[47,48] There are no data on possible effects of MTX on COVID-19. Based on limited data, for patients who are not infected with COVID-19 and who have stable control of their dermatologic disease, we suggest not to preemptively discontinue or decrease MTX. Patients on MTX should immediately report any fever-, flu-, or cold-like clinical manifestations to their physicians, and for patients with a high degree of suspicion or diagnosed with active COVID-19 infections, we recommend temporary cessation of their MTX. In addition, we recommend against the initiation of MTX in COVID-19 epidemic and nonepidemic areas.

## JAK inhibitors

Interferons (IFN) play a crucial role in the immune response to viruses. Binding of type I IFN to its receptor leads to activation of JAK kinases, which then activate the STAT transcription factors to upregulate antiviral immunity.[49] Selective JAK inhibitors (JAKi), including ruxolitinib and tofacitinib, are now being used in dermatology. A protective role for IFN-1 against coronaviruses, including SARS-CoV, has been previously elucidated *in vitro*[50] and *ex vivo*.[51] Of particular concern, STAT-1–deficient mice are more susceptible and develop more severe and disseminated infection when exposed to SARS-CoV compared with wild-type mice.[52,53] A possible role of IFN in the treatment of SARS has been previously suggested.[54] The potent immunosuppressive effects of tofacitinib were also shown by the almost double rate of herpes zoster among RA patients treated with tofacitinib compared with those treated with biologics.[55] In addition, tofacitinib has been shown to decrease response to pneumococcal vaccination.[56] Interruption of tofacitinib for 2 weeks improves response to vaccination.[56] There are no data on effects of JAKi on COVID-19. Based on available data, for patients who are not infected with COVID-19 and who have stable control of their dermatologic disease, we suggest discontinuing oral JAKi. Patients on oral JAKi should immediately report any fever-, flu-, or cold-like clinical manifestations to their physicians, and for patients with a high degree of suspicion or diagnosed with active COVID-19 infections, we recommend immediate cessation of their oral JAKi. In addition, we recommend against the initiation of oral JAKi in COVID-19 epidemic and nonepidemic areas.

## Biologics

Biologics revolutionized the management of numerous dermatologic conditions. With the COVID-19 pandemic, many patients and providers are understandably concerned about the immunomodulatory effects associated with injectable biologics.[57] In Table 1, we compare the overall upper respiratory tract infection on published data from pivotal trials in FDA package inserts. Although it is challenging to infer clinical decision making from these data in regard to COVID-19, it may be used to decide whether or not to continue injectable biologics during this pandemic. As shown in Table 1, biologic injectables seem to carry minimal increased risk of infection. In addition, it is important to consider that discontinuation of some biologics may result in loss of efficacy and formation of autoantibodies[58–60]; thus for patients who are not infected with COVID-19 and who have stable control of their dermatologic disease, we suggest not to preemptively discontinue or decrease biologic injectables. Patients on biologics should immediately report any fever-, flu-, or cold-like clinical manifestations to their physicians, and for patients with a high degree of suspicion or diagnosed with active COVID-19 infection, we recommend temporary cessation of their biologic injectables. In addition, we recommend careful initiation of biologic injectables at this time unless there are no other alternatives taking into account and after careful discussion of risk, benefits, and temporary delay of initiation with patients in nonepidemic COVID-19 areas.

## Conclusions

COVID-19 presents an unprecedented challenge to our modern society. A common concern is the continuation of immunosuppressants for dermatologic conditions. We reviewed the mechanism of action and evidence of increased infection associated with commonly prescribed immunosuppressants. Without specific data in the context of COVID-19, we have recommended considering discontinuation of oral JAKi and prednisone and careful continuation of other medications in patients currently benefitting from such treatments (Table 2). Available evidence of potential worsening of viral diseases with oral JAKi and prednisone exists, although no clear data

**Table 1** Infection rates of biologic injections per FDA package inserts

|  | Biologic | Upper respiratory tract infection for placebo, % (n) | Upper respiratory tract infection for drug, % (n) | Raw difference, % |
|---|---|---|---|---|
| TNF-α | Infliximab (Remicade) | 14*ˣ (41) | 15*ˣ (135) | +1 |
|  | Etanercept (Enbrel) | 13* (25) | 13* (51) | 0 |
|  | Adalimumab (Humira) | 4 (14) | 7 (59) | +3 |
|  | Certolizumab (Cimzia) | 5*ˣ (5) | 7*ˣ (24) | +2 |
| IL-12/23 | Ustekinumab (Stelara) | 5*ˣ (30) | 5*ˣ (64) | 0 |
| IL-17 | Secukinumab (Cosentyx) | 1*ˣ (3) | 3*ˣ (36) | +2 |
|  | Ixekizumab (Taltz) | 3*ˣ (12) | 3*ˣ (51) | 0 |
|  | Brodalumab (Siliq) | 6 (40) | 5 (112) | −1 |
| IL-23 | Tildrakizumab (Ilumya) | 3*ˣ (9) | 2*ˣ (25) | −1 |
|  | Guselkumab (Tremfya) | 5* (19) | 5* (41) | 0 |
|  | Risankizumab (Skyrizi) | 2 (4) | 5 (28) | +3 |

IL, interleukin; TNF, tumor necrosis factor.
* Data collected from pivotal phase III trials reported as mean. *x Combined doses reported as mean.

**Table 2** Recommendations on initiation and continuation of immunosuppressants

| Medication | Infection status | | | |
|---|---|---|---|---|
| | Not infected | | Infected/high suspicion | |
| | Initiation | Continuation | Initiation | Continuation |
| Cyclosporine | Consider delay | Yes | No | No |
| Mycophenolate mofetil | No | Yes | No | No |
| Prednisone | No | Consider cessation | No | No |
| Azathioprine | No | Yes | No | No |
| Rituximab | No | Consider delay | No | No |
| Methotrexate | No | Yes | No | No |
| Janus kinase inhibitors (JAK) | No | Consider cessation | No | No |
| Biologics | Consider delay | Yes | No | No |

are available for CVOID-19. We also recommend careful consideration of delaying rituximab infusion on a case-to-case basis, given that rituximab can lead to prolonged decreased number of circulating B cells. In general, reinstitution of any immunosuppressant should be considered only after a negative COVID-19 test and complete resolution of all COVID-19–related clinical signs and clinical manifestations. It is unclear at this time whether anti–COVID-19 immunoglobulin-G could be used to safely reinstate or initiate immunosuppressants in COVID-19 epidemic and nonepidemic areas.

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