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Navigating immunosuppression in a pandemic: A guide for the dermatologist from the COVID Task Force of the Medical Dermatology Society and Society of Dermatology Hospitalists



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Dermatologists treating immune-mediated skin disease must now contend with the uncertainties associated with immunosuppressive use in the context of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Although the risk of infection with many commonly used immunosuppressive agents remains low, direct data evaluating the safety of such agents in coronavirus disease 2019 (COVID-19) are scarce. This article reviews and offers guidance based on currently available safety data and the most recent COVID-19 outcome data in patients with immune-mediated dermatologic disease. The interdisciplinary panel of experts emphasizes a stepwise, shared decision-making approach in the management of immunosuppressive therapy. The goal of this article is to help providers minimize the risk of disease flares while simultaneously minimizing the risk of iatrogenic harm during an evolving pandemic. (*J Am Acad Dermatol* 2020;83:1150-9.)

Key words: autoimmune disease; COVID-19; dermatology-rheumatology; immunosuppression; immunosuppressive therapy; medical dermatology; SARS-CoV-2.

In the context of the current coronavirus disease 2019 (COVID-19) pandemic, physicians treating patients with immune-mediated

dermatologic diseases are tasked with challenging decisions when initiating immunosuppressive therapy or altering the existing regimens of their patients.

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Boehringer-Ingelheim, OnQuality, Novartis, ChemoCentryx, UCB Biopharma, and XBiotech. Dr Shinohara has been a principle investigator for clinical trials (Actelion, Soligenix, MIRAGEN). Dr Rosenbach, has served as a consultant for Merck, aTyr, Processa, and Janssen and has received research support from Processa and salary support from *JAMA Dermatology*. Dr Merola is a consultant and/or investigator for Merck, Bristol-Myers Squibb, AbbVie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Celgene, Sanofi, Regeneron, Arena, Sun Pharma, Biogen, Pfizer, EMD Sorono, Avotres, and LEO Pharma. Drs Chen, Fox, Harp, Micheletti, Nambudiri, and Pasioka have no conflicts of interest to declare.

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This article will examine relevant systemic drug safety data obtained from clinical trials, registries, and cohort studies across disciplines to provide expert-derived guidance in the face of much uncertainty.

BASELINE RISK IN IMMUNE-MEDIATED DERMATOLOGIC DISORDERS

Evaluating the baseline infection risk of patients is an important aspect of risk stratification. Several immune-mediated conditions, such as psoriasis and lupus, are associated with increased infection risk irrespective of exposure to immunomodulatory agents.^{1,2} Many of these conditions are further associated with comorbidities known to predict poor outcomes in COVID-19 infection (eg, diabetes and obesity in patients with psoriasis, asthma in patients with atopic dermatitis, and interstitial lung disease with connective tissue disorders).³ Each patient presents a unique set of variables that dictate the approach to their therapy plan. A summary of these considerations is found in [Table 1](#).

LEARNING FROM THE PAST

COVID-19 appears to follow a disease course similar to previous highly pathogenic coronavirus infections (ie, Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), with up to 20% of hospitalized patients progressing to potentially fatal acute respiratory distress syndrome.⁴ Risk factors for poor outcomes during the SARS and MERS outbreaks included older age and the presence of comorbidities such as obesity, diabetes, heart disease, lung disease, and renal disease. Immunosuppression alone was not identified as a significant risk factor for primary infection or death,^{5,6} and several milder or attenuated cases of infection were reported in immunosuppressed populations.^{7,8} Corroborating this, a National Institutes of Health-funded animal study showed that macaques immunosuppressed with cyclophosphamide had significantly lower rates of lung pathology despite active MERS-CoV

infection.⁹ It has been hypothesized that severe pulmonary involvement is likely secondary to an excessive inflammatory response, characterized by macrophage hyperactivation and high levels of proinflammatory cytokines.¹⁰

It is thought that dampening the hyperinflammatory reaction outweighs the risk of temporary impairment in antiviral immunity.

Numerous clinical trials are underway to examine the therapeutic potential of various immunosuppressive and immunomodulatory agents in the treatment of COVID-19 and the potential associated cytokine storm. Existing drug safety data and relevant trial data are presented below.

DATA REGARDING INFECTION RISK AND COMPLICATIONS OF IMMUNOSUPPRESSIVE

AND IMMUNOMODULATORY AGENTS

Glucocorticoids

Evidence linking systemic corticosteroids to increased infection risk comes from a meta-analysis of 71 clinical trials, which found an increased overall rate of infection in patients receiving systemic corticosteroids (relative risk [RR], 1.6; 95% confidence interval [CI], 1.3-1.9).¹¹ The risk was dose-dependent and minimal with daily doses <10 mg.^{11,12} Similarly, observational data from the large Corrona registry (Corrona, LLC, Waltham, MA) also found increased overall infection risk with prednisone >10 mg/d in patients with rheumatoid arthritis (incidence rate ratio, 1.30; 95% CI, 1.1-1.5).¹³

Therapeutic potential in COVID-19. Data evaluating the use of systemic corticosteroids in COVID-19 are limited. Recently, the preliminary results of a large randomized controlled trial (RCT) conducted in the United Kingdom revealed reduced 28-day mortality and hospital length of stay in oxygen requiring or ventilated patients treated with dexamethasone 6 mg daily for 10 days as compared with usual care.¹⁴ Conversely, data from the SARS and MERS epidemics are conflicting and many studies have revealed no mortality benefit, delayed viral clearance, and evidence for harm.¹⁵⁻¹⁷ A similar lack of benefit and potential for harm has been noted in other viral pneumonias, including influenza and respiratory syncytial virus.^{18,19}

CAPSULE SUMMARY

- This article adds to the limited literature on coronavirus disease 2019 (COVID-19) and immunosuppression. It provides expert opinion based on existing drug safety data and recent COVID-19 outcome data in patients with immune-mediated dermatologic disorders.
- The goal is to facilitate management of immunosuppressive drugs and minimize potential for harm in this patient population.

Abbreviations used:

CI:	confidence interval
COVID-19:	coronavirus disease 2019
IL:	interleukin
MERS:	Middle East respiratory syndrome
OR:	odds ratio
RR:	relative risk
SARS:	severe acute respiratory syndrome
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2
TNF:	tumor necrosis factor
URI:	upper respiratory tract
VTE:	venous thromboembolism

Conclusions. There is evidence for harm without a clear mortality benefit when systemic corticosteroids have been used to treat MERS and SARS-associated pneumonia. Existing safety data also indicates that daily doses of systemic corticosteroids >10 mg of prednisone equivalent are associated with an increased susceptibility to overall infection. Recently however, preliminary evidence from a large RCT suggests that the use of dexamethasone reduces mortality in hospitalized COVID-19 patients. Further data are needed to define the optimal use and potential complications of systemic corticosteroid use in the setting of COVID-19.

Methotrexate

In clinical trials, methotrexate increased infection risk in patients with rheumatoid arthritis (risk ratio, 1.25; 95% CI, 1.01-1.56), compared with placebo, but not in those with other immune-mediated conditions, including psoriasis, psoriatic arthritis, ankylosing spondylitis, and scleroderma.²⁰ Robust data for adverse events related to methotrexate come from a recent clinical trial evaluating the efficacy of low-dose methotrexate for the treatment of atherosclerosis in patients with cardiovascular disease. Mild infections were slightly increased (hazard ratio, 1.15; 95% CI, 1.01-1.30), but there was no statistically significant increase in upper respiratory tract (URI) or influenza infections.²¹

Conclusions. A modestly increased risk of infection associated with methotrexate has been suggested in some studies. Further data are needed to understand the impact of methotrexate on SARS-CoV-2 infection.

Antimalarial drugs

When used for their immunomodulatory properties, antimalarials have not been associated with infectious complications in systemic autoimmune disease,^{22,23} and some studies even suggest their

use may help prevent serious infections in systemic lupus erythematosus.²

Therapeutic potential in COVID-19. Antimalarial drugs were at the forefront of the COVID-19 pandemic based on some early, uncontrolled, and small case series suggesting potential efficacy in the treatment of SARS-CoV-2 infection. Although in vitro data suggest chloroquine and hydroxychloroquine both inhibit coronavirus,^{24,25} available clinical data do not suggest any benefit for the treatment of patients critically ill with COVID-19.²⁶⁻³⁰

Conclusions. The current data show no significant risk of infection or infectious complications when antimalarials are used for the treatment of immune-mediated disease and therefore suggest low potential for harm in COVID-19 infection. However, data supporting the use of antimalarials for prevention or treatment of COVID-19 are lacking at present, and use of antimalarials outside of a hospital or clinical trial is cautioned against.³¹

Oral small molecules (azathioprine, mycophenolate mofetil, and cyclosporine)

Using claims data, Schneeweiss et al³² examined the 6-month risk of serious and opportunistic infections in patients with atopic dermatitis. Compared with methotrexate, cyclosporine A had a 58% higher risk of overall infection (adjusted RR, 1.58; 95% CI, 1.17-2.15). In the same study, azathioprine had double the infection risk (RR, 1.78; 95% CI, 0.98-3.25), whereas mycophenolate mofetil tripled the risk (RR, 3.31; 95% CI, 1.94-5.64). A separate study comparing patients with systemic lupus erythematosus newly treated with mycophenolate mofetil or azathioprine found no differences in rates of serious infections.³³ Studies that examined the incidence of viral infections found that herpes zoster virus infections are increased with azathioprine^{34,35} and that cytomegalovirus infections are increased with mycophenolate mofetil,³⁶ although the latter appears to be limited to patients who have received a transplant.

Therapeutic potential in COVID-19. Some authors have suggested the use of cyclosporine in the treatment of COVID-19³⁷ based on its ability to inhibit coronavirus replication in vitro.^{38,39} That said, its clinical efficacy has not been proven, and there are no ongoing clinical trials in patients with COVID-19.

Conclusions. Azathioprine, mycophenolate mofetil, and cyclosporine A increase the risk of infection relative to reference agents such as methotrexate, warranting increased caution and discussion with patients regarding starting or continuing therapy.

Table I. Summary of key considerations in the shared decision-making process concerning immunosuppressive and immunomodulatory therapy during the coronavirus disease 2019 pandemic

1. The severity of the underlying disease, with special consideration given to a history of flares with medication changes and potential need for emergency care.
2. The patient's underlying risk factors (eg, comorbidities).
3. Contextual factors impacting patient risk (eg, high-risk occupation, caregiver roles, at-risk individuals in the home or work environment, etc).
4. The patient's preferences and level of risk tolerance.
5. The level of exposure to health care settings dictated by the need for monitoring laboratory tests or administration of the drug (eg, infusions), or both.
6. The relative level of immunosuppression attributed to a given therapy or combination of therapies based on available information.

Apremilast

Long-term safety data from open-label extension studies in psoriasis and psoriatic arthritis do not show an increased risk of serious infections compared with placebo.^{40,41} Similarly, URI and nasopharyngitis rates were comparable in the placebo-controlled phases of these studies.

Conclusions. The available data suggest a low risk of infection associated with the use of apremilast and, therefore, low potential for harm in COVID-19 infection.

Janus kinase inhibitors

The bulk of the safety data regarding Janus kinase (JAK) inhibitors comes from the use of tofacitinib in rheumatoid arthritis. Analysis of the most recent tofacitinib data from randomized controlled trials and long-term extension studies in rheumatoid arthritis reveals serious infection rates of 2.4 per 100 patient-years,⁴² comparable to the event rates reported for biologic disease-modifying antirheumatic drugs^{43,44} and baricitinib.⁴⁵ A particular concern with JAK inhibition is the risk of varicella zoster virus reactivation and antiviral immunity. This appears to be a class effect due to impairment of the interferon antiviral response. It has been noted across all indications and occurs at an increased rate with both selective and nonselective JAK inhibitors.⁴⁶⁻⁴⁸

Therapeutic potential in COVID-19. Ruxolitinib (NCT04362137) and baricitinib (NCT04280705) are currently being evaluated in phase III clinical trials for potential therapeutic effect in patients critically ill with COVID-19. It is suggested that preferential inhibition of JAK1 and JAK2 significantly down-regulates the production of interleukin (IL) 6 and interferon- γ , both of which are implicated in the hyperinflammatory state seen in patients critically ill with COVID-19.^{10,49} Moreover, unlike tofacitinib, baricitinib and ruxolitinib have demonstrated

antiviral activity via inhibition of receptor-mediated endocytosis of SARS-CoV-2 viral particles.⁵⁰

Additional concerns in COVID-19. A high rate of venous thromboembolism (VTE) has been noted in COVID-19, occurring in up to one-third of critically ill patients, despite prophylactic anticoagulation.^{51,52} Because JAK inhibitors carry a "black box warning" of increased VTE risk, there is reasonable concern that their use may increase the likelihood or severity of VTE when used in patients with COVID-19.⁵³

Conclusions. The use of JAK inhibitors is associated with an increased risk of serious infection, herpes zoster virus reactivation, and VTE. However, recent studies show potential direct antiviral and anti-inflammatory effects in COVID-19, seemingly unique to ruxolitinib and baricitinib. Taken together, there are insufficient data at this time to fully characterize the risk of harm or benefit in SARS-CoV-2 infection.

Anticytokine biologic therapy

Data from BIOBADADERM (Spanish Registry of Adverse Events for Biological Therapy in Dermatological Diseases), a Spanish registry designed to study the safety of systemic therapy in psoriasis, showed an increased risk of overall infection with tumor necrosis factor (TNF) inhibitors compared with ustekinumab and nonbiologic drugs (acitretin, cyclosporine, and methotrexate). Of all TNF inhibitors, infliximab had the highest risk of infection (adjusted risk ratio, 1.71; 95% CI, 1.1-2.65).⁵⁴ Similarly, data from the large Psoriasis Longitudinal Assessment and Registry (PSOLAR) indicated a higher risk of serious infections with adalimumab and infliximab compared with nonbiologic drugs.⁵⁵ Conversely, no increased risk of serious infections was noted when ustekinumab and

Table II. Summary of large case series and registry data of autoimmune disease patients infected or exposed to SARS-CoV-2

Characteristics*	Studies		
	Haberman et al ⁷¹	Gianfrancesco et al ⁷²	Brenner et al ⁷³
Total number of patients [†]	86	110	525
Confirmed cases of COVID-19	59 (69)	110 (100)	525 (100)
Age, mean y	46	N/A [‡]	43
Female sex	49 (57)	79 (72)	243 (46.3)
Most common diagnosis	PsA: 21 (24)	RA: 40 (36)	CD: 312 (59.4)
Other diagnoses	RA: 20 (23) CD: 20 (23) UC: 17 (20) Psoriasis: 14 (16) AS: 9 (10)	PsA: 19 (17) SLE: 19 (17) Other: 17 (15) [§] AS: 7 (6) Vasculitis: 7 (6) SjS: 5 (5)	UC: 203 (38.7) IBD unspecified: 7 (1.3)
Medications			
Biologic drugs	TNFi: 38 (44) IL-17i: 6 (7) IL-12/23i: 6 (7) IL-23i: 3 (3)	Unspecified: 49 (45)	TNFi alone: 176 (33.5) IL-12/23i: 55 (10.5) TNFi + DMARD: 52 (9.9) α -Integrin: 50 (9.5)
JAKi	6 (7)	5 (5)	8 (1.5)
csDMARD	MTX: 17 (20)	69 (63)	110 (21)
Hydroxychloroquine	8 (9)	N/A	0
Hospitalization	14 (16)	39 (35)	161 (31)
Deaths	1 (1)	6 (5)	16 (3)

AS, Ankylosing spondylitis; CD, Crohn's disease; COVID-19, coronavirus disease 2019; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; IL, interleukin; JAK, Janus kinase inhibitor; MTX, methotrexate; N/A, not available; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; TNFi, tumor necrosis factor- α inhibitor; UC, ulcerative colitis.

*Data are shown as number (%) or as indicated otherwise.

[†]Includes both confirmed and highly suspected cases of COVID-19.

[‡]20% of patients were aged >65 years.

[§]Other included (all with n < 5): inflammatory myopathy, ocular inflammation, other inflammatory arthritis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, osteoporosis, psoriasis, isolated pulmonary capillaritis, gout, and autoinflammatory disease.

etanercept were compared with nonbiologic drugs.⁵⁵

Recently, Murrell et al⁵⁶ reviewed data from pivotal clinical trials in psoriasis and found that URIs were increased with TNF inhibitors compared with placebo but that URI rates were comparable between placebo and IL-17, IL-12/23, and IL-23 inhibitors. A different group also reviewed the clinical trial data for all 11 biologic therapies approved in psoriasis and found no significant increase in URI or influenza infection rates compared with placebo.⁵⁷ In contrast, Wan et al⁵⁸ recently published a meta-estimate of pivotal clinical trials with 3 IL-17 inhibitors and found an increased risk of viral and nonviral URIs compared with placebo (odds ratio [OR], 1.56; 95% CI, 1.04-2.33).

Conclusions. Taken together, these data suggest a low risk of harm with IL-12/23 or IL-23 inhibition. Further data are needed regarding any potential increased risk of viral and nonviral URIs associated with IL-17 inhibition. The data presented indicate

higher rates of overall infection and URIs with TNF inhibitors; however, ongoing trials investigating the therapeutic potential of adalimumab in the COVID-19–related cytokine storm are still underway, and this precludes any definitive comments relating to the safety of TNF inhibitors in COVID-19.

Rituximab

Reactivation of chronic viral infections, such as hepatitis B and cytomegalovirus, is a rare yet well-reported adverse effect of rituximab.⁵⁹ Other viral illnesses, such as URIs and nasopharyngitis, are frequently reported, but clinical trial data in rheumatoid arthritis suggest similar overall rates of infections when rituximab is compared with methotrexate plus placebo.^{60,61} Long-term observational studies also show that this risk remains stable with repeated infusions.^{62,63} Data in the dermatologic literature are limited, but a randomized controlled trial in pemphigus vulgaris showed a similar rate of infections in the rituximab plus

Table III. Guidance statements for management of immunosuppression during the coronavirus disease 2019 (COVID-19) pandemic*

Patients well-controlled on maintenance therapy	<p>We suggest continuing immunosuppressive/immunomodulatory therapy at the lowest necessary effective dose, because immunosuppression alone does not appear to predict poor COVID-19 outcomes.</p> <p>We do note the following exceptions:</p> <ol style="list-style-type: none"> Long-term systemic steroids should be tapered to daily doses <10 mg prednisone equivalent, if safe to do so. Patients on recurrent rituximab dosing may benefit from immunoglobulin level testing. If hypogammaglobulinemia exists, consider altering/delaying dose or initiating immunoglobulin therapy, or both.
Patients requiring initiation of treatment	<p>We suggest the following:</p> <ol style="list-style-type: none"> On the basis of disease severity and baseline risk, consider favoring low-risk immunomodulatory agents (eg, apremilast, hydroxychloroquine, methotrexate) over immunosuppressive agents with a higher known or suspected risk of infection (see Table II). When medically appropriate, opt for short courses of low to moderate doses of systemic corticosteroids over high-dose regimens (eg, <20 mg prednisone equivalent daily for <2 weeks); if needed for maintenance therapy, consider doses <10 mg daily. When possible, avoid starting rituximab, due to its prolonged B-cell-depleting effects, if equally efficacious alternative therapies are available; exceptions include mucous membrane blistering disorders. If possible, use alternatives to cyclosporine and other agents requiring intensive toxicity/safety monitoring.
Patients with active COVID-19 infection, including COVID-19 ⁺ testing (even in the absence of symptoms)	<p>Although the potential benefit of immunosuppression is being studied in the context of cytokine storm, we suggest that, if possible, immunosuppressive therapy be held in patients testing positive for COVID-19, even if asymptomatic, with the concern being the complication of bacterial infections and pneumonia. Many systemic immunosuppressive drugs have long half-lives, and temporary cessation of therapy is unlikely to result in disease flare. Individual discussions may be considered for severe flares with potentially organ-threatening manifestations. Treatment can resume after recovery (refer to Centers for Disease Control and Prevention or local health authority for recovery criteria).</p> <p>Exceptions to the above include:</p> <ol style="list-style-type: none"> Systemic steroids may be tapered but not stopped abruptly. Providers should follow recommendations for corticosteroid stress doses in critically ill patients. Drugs with minimal immunosuppressive potential (e.g., apremilast, antimalarials) may be continued after thorough patient assessment (refer to Table I).
Patients with active immune-mediated skin disease	<ol style="list-style-type: none"> When possible, maximize/optimize nonimmunosuppressive therapy, such as topical steroids, immunomodulatory agents (eg, apremilast, antimalarials, and retinoids), and anti-inflammatory medications (eg, tetracycline or macrolide class antibiotics). High-dose systemic corticosteroids should be avoided where possible, and taper plans should be kept to the minimum necessary dose and duration.

*With limited COVID-specific safety data available on any given treatment, it is challenging to produce firm recommendations on the safety of immunosuppression in the context of the current pandemic. Notably, our guidance statements are based on expert opinion and interpretation of safety data deemed most relevant rather than on formal guidelines derived from high-quality comparative studies. Limitations include the heterogeneity of the safety data encompassing various autoimmune conditions and the limited reports available on the status of immunosuppressed patients affected by COVID-19. The applicability of the information and recommendations provided here are limited by the rapidly evolving nature of the COVID-19 pandemic, in addition to patient-specific and local health care constraints. Decisions should ultimately be individualized to a specific scenario, and reflective of shared-decision making between provider and patient.

short-term steroid group compared with the steroid-only group.⁶⁴ However, it is worth noting that the rituximab group had lower cumulative exposure to prednisone.

An important consideration is the risk of prolonged hypogammaglobulinemia, especially with repeated courses of rituximab.⁶⁵ Cases characterized in the literature reveal an increased risk of URIs,

pneumonias, and viral infections, including fatal instances of enteroviral meningoencephalitis.^{66,67}

Particular concerns in COVID-19. There is evidence to suggest that rituximab may blunt protective immune responses to vaccines. Indeed, impaired antibody responses are seen to both influenza and polysaccharide vaccines, with effects lasting up to 6 months after treatment with rituximab.^{68,69}

Risk	Drug	Comments
Strong	Systemic steroids	Strong dose-dependent risk of infection and existing evidence for harm in critically ill viral pneumonia patients although some preliminary evidence showing potential mortality benefit of dexamethasone in oxygen or ventilator dependent patients
	Rituximab	Prolonged B-cell depletion; consider potential impact on future vaccine immunity to COVID-19
Mixed	Cyclosporine	Frequent monitoring; multiple drug-drug interactions; risk of harm is likely dose-dependent
	Azathioprine and Mycophenolate mofetil	Association with viral infections, including HZV and CMV (transplant data)
	JAK inhibitors	Caution regarding use due to viral infection concern (HZV) and DVT/PE risk Potentially beneficial anti-viral effect with baricitinib and ruxolitinib, but not with tofacitinib
	TNF inhibitors	IFX likely highest risk among anti-TNF; caution with higher doses (e.g., IFX 10 mg/kg dosing)
Low	IL-17 inhibitors	Possible increased URI risk suggested in recent metanalysis of clinical trial data
	Methotrexate	Low overall risk of infections or infectious complications; may be associated with higher risk when used in combination therapy
	IL-12/23 inhibitor	Theoretical role of IL-12 in antiviral response, though not clearly implicated in COVID-19 pathology
	IL-23 (p19) inhibitors	
Not immunosuppressive	Apremilast	
	Dupilumab	
	Hydroxychloroquine	No significant risk of infection or infectious complications; to date, no evidence for benefit in treatment of COVID-19
	Other:	Immunomodulatory agents (e.g. retinoids, dapsone, colchicine, etc.)

■ Evidence suggests harm - avoid if possible
■ Mixed data - proceed with caution
■ Low risk of harm
■ Not immunosuppressive

CMV, Cytomegalovirus; DVT, deep venous thrombosis;
 HZV, herpes zoster virus; IL, interleukin; PE, pulmonary embolus; URI, upper respiratory infection.

Fig 1. Drug safety recommendations in the context of the coronavirus disease 2019 (COVID-19) pandemic. *CMV*, Cytomegalovirus; *DVT*, deep venous thrombosis; *HZV*, herpes zoster virus; *IL*, interleukin; *PE*, pulmonary embolus; *URI*, upper respiratory infection.

Conclusions. The data suggest increased rates of infection and infectious complications associated with the use of rituximab. Together with a long immunologic half-life and prolonged impairment of vaccine immunity, there are significant potential safety concerns, suggesting a need for increased caution during the ongoing COVID-19 pandemic. To minimize harm, evaluation (and potential correction) of rituximab-induced hypogammaglobulinemia may be considered among patients who receive recurrent rituximab dosing.

Dupilumab

A comprehensive evaluation of infection risk with dupilumab was conducted by Eichenfield et al.⁷⁰ Their analysis pooled data from 7 randomized controlled trials in atopic dermatitis, which showed similar infection rates per 100 patient-years in the treatment and placebo groups. Specifically, the rates of viral URIs and influenza infections were lower in the dupilumab groups compared with placebo. Similarly, an observational study by Schneeweiss et al³² found no increase in the rates of serious bacterial or opportunistic infections with dupilumab compared with methotrexate.

Conclusions. Data to date suggest a low risk of infection with the use of dupilumab and a low potential for harm in COVID-19.

DATA FROM THE COVID-19 PANDEMIC

One large case series and 2 registries have reported a combined total of 721 confirmed or highly

suspected cases of COVID-19 in adult and pediatric immune-mediated inflammatory disease populations through May 19, 2020.⁷¹⁻⁷³ The results are summarized in Table II.⁷¹⁻⁷³ Haberman et al⁷¹ noted that those requiring hospitalization were more likely to have rheumatoid arthritis, had more comorbidities, were older, and had greater use of methotrexate, hydroxychloroquine, and corticosteroids. They also reported an overall incidence of hospitalization of 16%, which was comparable to the 26% incidence in patients with COVID-19 in the general population in New York.⁷¹ They concluded that baseline use of biologics was not associated with worse COVID-19 outcomes.

In the inflammatory bowel disease registry, 16 deaths (3%) were identified, with half occurring in patients aged >70 years, whereas no deaths were noted in patients aged <30 years. On multivariate analysis, Brenner et al⁷³ reported a strong association between systemic steroids and the composite outcome of intensive care unit admission, ventilator use, and death (adjusted OR, 6.9; 95% CI, 2.3-20.5). In contrast, no association was seen between TNF inhibitor monotherapy and poor COVID-19 outcomes (adjusted OR, 0.90; 95% CI, 0.37-2.17). Although the authors did not report on the use of IL-12/23 inhibitors, as of May 19, 2020, data from the registry (available for viewing on covidibd.org) revealed 1170 cases, with 9% (100 of 1170) of patients having poor outcomes. Among subgroups, 23% (23 of 98) of steroid users had poor outcomes

compared with only 2% (8 of 337) of patients on TNF inhibitor monotherapy and 3% (3 of 112) of patients on IL-12/23 inhibitors.

With regards to infection risk, a case-control study by Damiani et al⁷⁴ evaluated 1193 patients with psoriasis and identified only 16 cases of COVID-19 from February 21 to April 9, 2020. Compared with the general population of Lombardy, patients on biologics had a higher risk of testing positive for COVID-19 (OR, 3.43; 95% CI, 2.25-5.73) and hospitalization (OR, 3.59; 95% CI, 1.49-8.63).

Conclusion. Most of the patients on systemic immunosuppressive or immunomodulatory therapy included in these studies did not require hospitalization, and death remained a rare outcome. However, systemic corticosteroid use in this patient population appeared to increase the risk of poor outcomes in COVID-19.

DISCUSSION AND RECOMMENDATIONS

We believe a patient-centered approach, with shared decision making informed by the data presented here, will help mitigate risk to our patients. Factors to consider are summarized in Table I. Our interpretation of the literature based on the highest quality of evidence available to date is found in Table III. The overarching principles are that immunosuppressive and immunomodulatory therapy can be safely initiated or continued in most patients. Physicians should alter and optimize regimens in favor of lower-risk options where possible, and as outlined more specifically in Table III and Fig 1.

Further data regarding the safety of these agents are needed and constitute a key unmet need for our patients.

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