Position statement for a pragmatic approach to immunotherapeutics in patients with inflammatory skin diseases during the coronavirus disease 2019 pandemic and beyond

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Abstract
Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, a novel RNA virus that was declared a global pandemic on 11 March 2020. The efficiency of infection with SARS-CoV-2 is reflected by its rapid global spread. The SARS-CoV-2 pandemic has implications for patients with inflammatory skin diseases on systemic immunotherapy who may be at increased risk of infection or more severe infection. This position paper is a focused examination of current evidence considering the mechanisms of action of immunotherapeutic drugs in relation to immune response to SARS-CoV-2. We aim to provide practical guidance for dermatologists managing patients with inflammatory skin conditions on systemic therapies during the current pandemic and beyond. Considering the limited and rapidly evolving evidence, mechanisms of action of therapies, and current knowledge of SARS-CoV-2 infection, we propose that systemic immunotherapy can be continued, with special considerations for at risk patients or those presenting with symptoms.

Received: 7 September 2020; revised: 27 October 2020; Accepted: 12 November 2020

Conflicts of interest
JB has served as an advisor/consultant and received grants and honoraria from AbbVie, Amgen, Celgene, L’Oréal Group, Lilly, Galderma, Janssen, Johnson and Johnson, Leo Pharma, Novartis, Pfizer and Sanofi Genzyme, and served as a speaker for AbbVie, Celgene, L’Oréal Group, Lilly, Janssen, Johnson and Johnson, Leo Pharma, Novartis and Pfizer. KAP has served as an investigator, speaker, advisor/consultant for and/or received grants/honoraria from AbbVie, Akros, Amgen, Anacor, Arcutis, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, LEO Pharma, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Novartis, Pfizer,
Regeneron, Roche, Sanofi-aventis, Sanofi Genzyme, Takeda, UCB, and Valeant. JD has served as an advisor/consultant for AbbVie, Amgen, Bausch, Celgene, Janssen, Leo Pharma, Lilly, Novartis, Sanofi, has received grants and honoraria from AbbVie, Janssen, Corbis, Lilly, and has served as a speaker for Celgene, Janssen. JD is supported by a Senior Scientist Award of the BC Children’s Hospital Research Institute. RV has served as an advisor/consultant and speaker, and received grants and honoraria, from AbbVie, Amgen, Bausch Health, Celgene, Janssen, Lilly, Merck, Novartis, Pfizer and UCB. RG has served as an advisor/consultant for AbbVie, Bausch, Celgene, Janssen, Leo Pharma, Lilly, Novartis, Mallinckrodt Pharmaceuticals, Sanofi, and served as a speaker for Mallinckrodt Pharmaceuticals, Janssen, Sanofi. CC has served as a speaker for AbbVie and Gilead Sciences. PG has served as an advisor/consultant and speaker for Amgen, Eli Lilly, Leo Pharma, Novartis, Pierre Fabre and UCB. MJG has served as an investigator, speaker, advisor and/or consultant for AbbVie, Amgen, Actelion, Akros, Arcutis, Boehringer Ingelheim, BMS, Celgene, Coherus, Dermira, Dermavant, Eli Lilly, Galderma, Glenmark, GSK, Incyte, Janssen, Kyowa Kirin, Leo Pharma, MedImmune, Merck, Novartis, Pfizer, Roche, Regeneron, Sanofi Genzyme, UCB and Valeant. CHH has served as an advisor/consultant/or investigator for AbbVie, Amgen, Arcutis, Bausch Health, Boehringer Ingelheim, Celgene, Dermavant, Dermira, DS Biopharma, Eli Lilly, Galderma, GSK, Janssen, Leo Pharma, Novartis, Pfizer, Sanofi Genzyme, Regeneron and Sun Pharma. CWL has served as an Advisory Board Member, Speaker, Consultant for and/or received honoraria or grants from, AbbVie, Amgen, Bausch Health, Celgene, Eli Lilly, Janssen, GSK, Leo Pharma, Merck, Novartis, Pfizer, UCB and Valeant. CM has served as an Investigator, Advisory Board Member, Speaker, Consultant for, and/or received honoraria or grants from, AbbVie, UCB, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, Leo Pharma, GSK-Stiefel, Janssen, Novartis, Bausch and Pfizer. YP has received grants/honoraria from AbbVie, Amgen, Aquinox, Aralae, Arcutis Biotherapeutics, Baxalta, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermira, DS Biopharma, Eli Lilly, EMD Serono, Galderma, GlaxoSmithKline, Janssen, Leo Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Takeda, UCB Pharma and Valeant. LP has served as an advisor/consultant for AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Fresenius Kabi, Janssen, JS BIOCAD, Leo Pharma, Eli Lilly, Mylan, Novartis, Pfizer, Regeneron, Roche, Sanofi, Sandoz, Samsung Bioepis, Sanofi and UCB, has received grants from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo Pharma, Eli Lilly, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB, and has served as a speaker for Celgene, Janssen, Eli Lilly, Novartis and Pfizer.

Funding source
This project was initiated and financially sponsored by the Dermatology Association of Ontario. Unrestricted educational grants have been provided by the following industry partners (listed alphabetically): AbbVie Canada, Amgen Canada, Janssen Canada, Sanofi Genzyme Canada.

Introduction
Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, a new strain of coronavirus that was first identified in the human population in Wuhan, China, in December 2019. Infection with SARS-CoV-2 presents with a broad spectrum of manifestations, ranging from asymptomatic virus shedding to a severe, life-threatening immune-driven inflammatory response often targeting the lungs. Transmission of the virus occurs through droplets and aerosols in closed environments. Infection by autoinoculation (i.e. contact on surfaces followed by subsequently touching mouth, nose or eyes) is a potential but less efficient method of transmission. Of note, skin barrier defects typical of psoriasis and atopic dermatitis should not be of concern for COVID-19 transmission. The efficiency of COVID-19 is reflected by its rapid global spread. The World Health Organization (WHO) situation reports provide regular updates on infection and mortality rates worldwide, based on data received from national authorities (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports).

An area of concern for dermatologists during the COVID-19 pandemic is patients with inflammatory skin diseases, such as psoriasis and atopic dermatitis. Some cohort studies in these populations have indicated increased risk of certain types of infections; however, methodological features raise doubt about the reported effect sizes and these studies are not directly relevant to SARS-CoV-2 infection. Recent literature has raised unsubstantiated concerns regarding immunosuppressive or immunomodulatory effects of systemic immunotherapy for patients with inflammatory skin diseases. There is an ongoing question of whether patients receiving immunosuppressive therapy are at increased risk for SARS-CoV-2 infection, more severe infection, or prolonged course of infection, with no direct evidence supporting these concerns. These knowledge gaps make it challenging for dermatologists to counsel their patients appropriately during and following viral pandemics, such as COVID-19. Several registries have been established to capture clinical data about patients who are on systemic immunotherapies during...
COVID-19; however, the lack of control populations limits the usefulness of this data.

This position paper aims to provide practical guidance for dermatologists managing patients with inflammatory skin conditions on systemic therapies during the current pandemic and beyond. This document is not meant to be an exhaustive review of available literature. Rather, this work is a focused examination of current evidence considering the mechanisms of action of immunotherapeutics in relation to immune response to SARS-CoV-2. Our purpose is to provide a structured framework for discussions on the risks and benefits of systemic therapy for inflammatory skin diseases during a viral pandemic.

Methods

A panel of experts was convened, initiated by the Dermatology Association of Ontario’s guidelines initiative group. This group consists of 11 expert dermatologists who have established expertise in managing inflammatory skin disorders, such as psoriasis and atopic dermatitis, with systemic therapies. Two international dermatologists (LP and PG) from early COVID-19 epicentres (Spain and Italy, respectively) and an infectious disease specialist (CC) were also invited to participate to provide an international and expanded perspective.

The authors were divided into smaller working groups based on expertise and interest, to help address practical aspects of disease management identified by all authors. In place of an exhaustive review, literature searches were performed between 29 and 30 April 2020 focused on review and key articles in PubMed related to high priority topics identified by the committee. Additional articles were added by authors during manuscript development. Most case studies and small case series were excluded from the final publication. Search terms and details are found in the Appendix S1 (Supporting Information). Multiple rounds of content review were undertaken, with special consideration of suggestions provided in Box 1, to reach agreement amongst authors prior to publication.

Immune response to SARS-CoV-2

Human coronaviruses (CoVs) are enveloped, single-stranded positive-sense RNA viruses. SARS-CoV-2 is a betacoronavirus that is closely related to SARS-CoV-1 and Middle East Respiratory Syndrome (MERS)-CoV.7 Similar to SARS-CoV-1 infection, infection by SARS-CoV-2 is initiated by binding to the angiotensin-converting enzyme 2 (ACE2) receptors of host cells. Tissues having high ACE2 expression, including lung, heart, kidney, brain, gut, some hematopoietic cells and endothelium in general, are targets for infection.9-12 The median incubation period is 5.1 days, with most symptomatic patients developing symptoms within 11.5 days of infection.13 Viral loads are similar in both symptomatic and asymptomatic patients.14

The immune response to SARS-CoV-2 in highly symptomatic patients occurs in multiple progressive phases, with an initial viral response phase, followed by a hyperinflammatory phase with lymphocyte depletion or exhaustion in individuals lacking a competent T-cell-adaptive response.15,16 It is estimated that about 80% of those infected are asymptomatic to moderate in severity, whereas 15% progress to severe pneumonia and 5% develop severe symptoms.17 However, the proportion of asymptomatic and mild patients may be higher. Risk factors for severe COVID-19 and death include male gender18 and older age,19 likely related to immunosenescence.20 When viral clearance is not successful, less specific defence mechanisms such as monocyte and macrophage activation occur resulting in a cytokine storm.21

The innate immune system is the first line of defence against all pathogens, including SARS-CoV-2. An optimal response suppresses the infection at the site of inoculation by lysing infected cells and initiating the adaptive response. Similar to patients with severe MERS and SARS, patients with severe COVID-19 have shown diminished systemic levels of type I interferons (IFNs), a key part of the innate immune response during early viral infection.22,23 Like other human RNA viruses, coronaviruses circumvent the initial innate antiviral immune response and their evasion strategies include interference with the induction of early- and late-phase IFN, IFN signalling and antiviral action of interferon-stimulated gene products.23,24 IFNs also act as modulators of adaptive immunity, thus promoting antigen presentation and cellular immune response to coronavirus infection.23

In a small percentage of patients with an unfavourable course, the later phase of COVID-19 involves an exuberant and less targeted response of the host immune system. Excessive
inflammation at the site of infection, often the lungs, is the result of desperate and extraordinary production of pro-inflammatory cytokines resulting in a cytokine release syndrome or ’cytokine storm’. IL-6 production is postulated as one of the primary instigators of the cytokine storm. The storm results in an uncontrolled cycle of self-immune amplification and multiorgan failure. Patients with severe COVID-19 have higher serum levels of many cytokines and chemokines, including interleukin (IL)-1β, IL-1Ra, IL-2, IL-6, IL-7, IL-10, IL-17, granulocyte colony-stimulating factor (G-CSF), IFN-γ and tumour necrosis factor-α (TNF-α).

Immune pathways targeted in managing inflammatory skin conditions

Systemic therapies used to treat inflammatory skin disorders, such as psoriasis and atopic dermatitis, target immune pathways to varying degrees of specificity, by directly modifying cellular responses or targeting specific cytokines or their receptors. It is unknown whether these treatments impact the severity of coronavirus symptoms, but it is possible to estimate their impact. The immune system is a complex of inter-related and redundant regulatory pathways. Cytokines have pleiotropic effects working synchronously, synergistically or antagonistically with other cytokines. These complex interactions mask many aspects of cytokine modulation. There are limited clinical data on the risk of worse outcomes associated with COVID-19 in patients with psoriasis, atopic dermatitis or other inflammatory skin conditions who are on systemic immunotherapy. Rates of serious and opportunistic infections reported in clinical trials provide mechanism specific guidance when analysed carefully; however, these data are not relevant when considering susceptibility to coronavirus infection. With the exception of systemic steroids as mentioned below, case series and cohorts to date do not suggest a significant increase in risk of COVID-19-related hospitalization and mortality in patients with immune-mediated skin diseases on systemic immunotherapy: small sample sizes lack sufficient comparative power to draw meaningful conclusions. To further complicate these interactions, systemic immunotherapies may influence immune responses to SARS-CoV-2 differentially depending on the stage and course of the infection. Here we summarize the main systemic therapies used to treat psoriasis, atopic dermatitis and selected other inflammatory skin diseases (Table 1) and review clinical considerations during a SARS-CoV pandemic.

Biologic therapies (TNF-α inhibitors, interleukin inhibitors)

Biologics used to treat inflammatory skin diseases do not impact infectivity and have no opportunity to engage in early innate immune response to SARS-CoV-2. Modulating cytokine levels as part of the routine treatment of inflammatory skin diseases could be net neutral, increase risk, or provide a net benefit in COVID-19, depending on the stage of disease. Equally important is the effect size cytokine modulation may have in altering risk. Cytokine inhibitors have been postulated to inhibit the cytokine storm in the hyperinflammatory phase of COVID-19, and clinical trials are ongoing to investigate theoretical benefit of IL-6 inhibitors tocilizumab (ChiCTR2000029765) and sarilumab (NCT04315298), TNF-α inhibitor adalimumab (ChiCTR2000030089), and IL-17 inhibitor ixekizumab (ChiCTR2000030703). At present, registries and observational studies of patients on biologics have shown no increased risk of severe COVID-19 while on these therapies. Given the small and selective samples in registries, they have insufficient power to provide meaningful analyses.

Biologic therapy (ANTI-CD20 antibody)

Rituximab has specific risks based on its mechanism of action; however, it has not shown additional risk of acquiring infection in patients with rheumatoid arthritis or bullous diseases. A low-dose regimen (500–1000 mg × 2) used in dermatology may result in fewer infections than the standard dose used in haematology (375 mg/m² weekly × 4). There is a risk of reactivation of chronic viral infections (e.g. hepatitis B, JC virus, cytomegalovirus). B-cell depletion does not appear to impact initial immune response to SARS-CoV-2 infection but may impact the adaptive, antibody-mounting immune response. Additionally, rituximab may inhibit efficacy of response to influenza vaccine, and concerns have been raised about a blunted vaccine response which may warrant dose interruption to allow for effective vaccination against SARS-CoV-2 when a vaccine is available.

Targeted small molecules (phosphodiesterase-4 inhibitors, Janus kinase inhibitors)

Small molecules tend to affect multiple pathways to varying degrees, and the risk of their use during COVID-19 is unknown. Apremilast, a phosphodiesterase-4 (PDE4) inhibitor, is generally perceived as safe in the long term, with low incidence of infection. Apremilast affects several cell types and blocks multiple intracellular signals in a manner that is less specific than Janus kinase (JAK) inhibitors. JAK inhibitors may block intracellular signalling more precisely but with greater variability depending on cell type and JAK pairing. JAK inhibitors are thought to have an immunosuppressive mechanism of action through pleiotropic inhibition of many cytokines and may be protective in severe COVID-19. Baricitinib and ruxolitinib were proposed as theoretical therapeutic options for COVID-19 since they block clathrin-mediated endocytosis of coronaviruses. Some cytokines whose signalling relies on JAKs, specifically IFN-γ and IL-4, have demonstrated antiviral activity against SARS-CoV-1 in vitro through inhibition of host ACE2 expression.

Antimetabolites and calcineurin inhibitors

Azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF) and cyclosporine A (CsA) are used to treat
| Drug class          | Mechanism of action                                                                 | Overall infection risk                                                                 | Immunological considerations                                                                                                                                 |
|---------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Biologics**       |                                                                                      |                                                                                        |                                                                                                                                                                |
| TNF-α inhibitors    | Bind and neutralize tumour necrosis factor (TNF)                                      | Minimal to negligible\(^{6,85}\) (Risk of non-serious, viral, respiratory tract infections may be increased. May increase herpes reactivation.) | May induce type 1 IFN and be useful against virus. TNF-α works synergistically with IFN-γ, innate response at site of infection.                                |
| IL-inhibitors       | Blocks cytokine signalling (IL-4/IL-13, IL-17A, IL-12/23, IL-23)                    | Minimal to negligible\(^{6,4,86}\)                                                   | Blockage of these cytokines is not thought to be crucial to mounting a host immune response to viral infections. Theoretical benefits in later stages of severe COVID-19, trials in progress. |
| Anti-CD20 antibody  | FcγR mediated B-lymphocyte depletion                                                  | Minimal (Increased risk of infection in rituximab is well documented, but minimal at the low doses used clinically for inflammatory skin diseases) | B-cell lymphopenia (depletes mature and type I B cells) occurs with modest impact on adaptive response that may be associated with worse outcomes, use caution. Inhibition of antibody response to vaccination is documented. |
| **Targeted small molecules** |                                                                                    |                                                                                        |                                                                                                                                                                |
| JAK inhibitors      | Inhibit one or more Janus kinases interfering with the JAK-STAT signalling pathway   | Minimal to negligible\(^{67}\)                                                       | Block type I IFN (α/β) and type II IFN (γ) signalling to a modest degree. Given the role of JAK-STAT dependant IFNs in antiviral immunity, withholding JAK inhibitors in early infection may be beneficial\(^{41,87}\). May be beneficial against COVID-19 cytokine storm, trials ongoing\(^{51}\). |
| PDE4 inhibitors     | Inhibition of phosphodiesterase-4 (PDE4) resulting in accumulation of cyclic adenosine monophosphate (cAMP) and protein kinase A activation\(^{86}\) | Minimal to negligible\(^{50}\)                                                       | Blocks activity of numerous intracellular signalling processes, may weakly block T-cell receptor signalling. Intracellular PDE4 blockade has pleiotropic changes to many cytokines including IL17α/f, IL22, TNF-α, IFN-γ. |
| **Immunosuppressants** |                                                                                    |                                                                                        |                                                                                                                                                                |
| Azathioprine        | Purine analogue that inhibits nucleic acid synthesis                                 | Minima\(^{67,58}\) (based on data in rheumatoid arthritis and lupus nephritis)      | May inhibit establishing immune memory.                                                                                                                                                                                   |
| Cyclosporine A      | Blocks calcineurin, which is involved in disparate immune and metabolic processes Inhibits T-cell activation and cytokine production, primarily IL-2 and IL-4\(^{89,90}\) | Minima\(^{60,63,64}\)                                                              | Inhibits coronavirus replication. Will inhibit establishing immune memory\(^{64,59,60}\).                                                                                                                                 |
| Methotrexate        | Multiple mechanisms of action. Inhibits dihydrofolate reductase, involved in RNA/DNA synthesis and repair. Acts in part as folic acid antagonist with demonstrated polyamine inhibition\(^{91}\), adenosine release, and JAK2 inhibition in vitro\(^{92}\) | Minima\(^{65,67,68,93}\)                                                              | May inhibit establishing immune memory.                                                                                                                                                                                   |
| Mycophenolate mofetil | Prodrug of mycophenolic acid (MPA) that inhibits inosine-5’-monophosphate dehydrogenase and depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation\(^{94}\) | Minima\(^{72}\) (based on data in lupus nephritis)                                  | Antiviral activity against MERS-CoV in vitro\(^{97}\). May inhibit establishing immune memory.                                                                                                                                 |

Table 1  Overview of common immunomodulators used to treat inflammatory skin conditions and potential risks and treatment considerations for COVID-19
Corticosteroids

Table 1

| Drug class  | Mechanism of action                                                   | Overall infection risk | Immunological considerations |
|-------------|----------------------------------------------------------------------|------------------------|------------------------------|
| Prednisone  | Synthetic glucocorticoid whose mechanism alters DNA replication within the nucleus | Modest to minimal – dose-dependent | May suppress viral clearance. Prednisone may be continued. Consider lower dose (≤10 mg/day) if possible Dexamethasone confers survival advantage in hospitalized patients with COVID-19 receiving respiratory support. |

COVID-19, coronavirus disease 2019.

Based on a registry of 525 patients with inflammatory bowel disease, chronic corticosteroid use was a risk factor for severe COVID-19 outcomes (aOR: 6.9, 95% CI: 2.3–20.5), but causation cannot be attributed. This was also noted in a registry of patients with rheumatic diseases. Small sample size, absence of a control population, and collider bias amongst other inadequacies questions the reliability of correlated observations.

Treatment considerations for systemic therapy during coronavirus pandemic

In the treatment of plaque psoriasis, interrupted biologic therapy results in worse outcomes compared to continuous therapy. Stopping most biologics will result in a progressive slow return of disease, with possibility of increased disease requiring aggressive therapy. Stopping a biologic may also result in loss of response or development of anti-drug antibodies, leading to poor recapture of drug efficacy. In making treatment decisions, drug half-life could be considered. Biologics with a longer half-life could be delayed by a month or more (i.e. guselkumab, risankizumab, tildrakizumab and ustekinumab), whereas those with shorter half-life could be delayed by 2–4 weeks, without marked problems and disease reoccurrence. There is also the question of risk of combination biologic therapy with methotrexate or apremilast. There are no data about whether combination therapy increases the overall patient risk for severe COVID-19. Prior to the pandemic, studies of combination therapy involving methotrexate with either etanercept, adalimumab or ustekinumab showed no significant safety differences than the biologic alone. See Table S1 (Supporting Information) for a detailed consideration of biologic treatment half-lives, risk of disease flare, loss of response when stopped, combination therapy considerations and comorbidity contraindications.

As there is limited direct evidence assessing risks associated with continuing immunosuppressive treatment during a pandemic, our approach is to consider potential risks in a stepwise manner. Risks associated with continuing treatment were framed by reviewing drug mechanism of action and the potential impact on immune response to infection. Not surprisingly, several small
molecules inhibit RNA virus replication.\textsuperscript{52,61,67} Although it is likely that some of these agents (e.g. TNF-alpha antagonists) may modify innate immune response to viral infections, successful infection by SARS-CoV-2 effectively aborts anti-viral directed innate response.\textsuperscript{23,24} Less certain is whether or not these agents may modify innate immune response to viral infections, success- likely that some of these agents (e.g. TNF-alpha antagonists) may modify innate immune response to viral infections, success- likely that some of these agents (e.g. TNF-alpha antagonists) may modify innate immune response to viral infections, success-

Although patient or clinician preference may prompt delayed initiation or stopping of systemic therapies, physicians should consider multiple factors including the individual’s risk of untreated or undertreated inflammatory skin disease based on severity and impact on quality of life (Table 2). In general, initiation or maintenance of systemic therapy should not be withheld. Physicians should consider whether the patient is at high risk of exposure to SARS-CoV-2 (e.g. occupation as a front-line health care worker in an area with many active cases), is showing symptoms of COVID-19, as well as the stage or severity of infection. Contraindications as per label may also be considered. In asymptomatic or mild COVID-19 cases, there is little evidence to suggest that systemic therapy should be withheld, or dose reduced. Given the uncertainty and potential severity of COVID-19 in symptomatic patients, discontinuation of non-life-preserving therapies in symptomatic patients could be considered. In select cases, the physician might consider the risk of a poor outcome with COVID-19, for example, in patients with underlying comorbidities and older age (over 65 years of age). Increased risk of developing severe COVID-19 is often correlated to the presence of comorbidities including hypertension, type 2 diabetes, obesity or chronic obstructive pulmonary disease.\textsuperscript{81–83} Patients with moderate to severe psoriasis and other inflammatory skin conditions may have multiple comorbidities that increase their risk of severe COVID-19. Physicians should prioritize screening these patients for comorbidities and factor this into treatment decisions. In moderate to severe COVID-19, risks and benefits should be weighed on an individual basis while addressing both patient and physician concerns.

**Table 2** Physician and patient considerations for stopping, continuing, or starting/switching systemic immunotherapy during SARS-coronavirus pandemic

| Patient concerns: | Physician considerations: |
|------------------|--------------------------|
| • Risk of acquiring COVID-19 | • Comorbidities and risk factors for severe COVID-19 |
| ○ Household transmission, attending in-person appointments, occupation | • Presence of COVID-19 signs/symptoms and severity of infection |
| • Risk of developing severe disease if exposed to SARS-CoV-2 | • COVID-19 test results, household transmission and possible exposure |
| • Flare-up of skin disease without treatment | • Risks of withholding treatment (drug half-lives, disease flare, recapturing efficacy) |
| | • Logistical considerations (e.g. injection training, laboratory tests and monitoring) |

**Table 3** Factors to consider when managing a practice during and after SARS-CoV-2 pandemic

| Considerations during pandemic |  |
|-------------------------------|--|
| **Scheduling visits**\textsuperscript{95,96} | • Consider telehealth (phone or video appointments) where possible |
| • Use telehealth to triage or take history in advance to shorten physical contact |
| • Staggering patient appointments |
| **Office procedures**\textsuperscript{95–98} | • Extra time will be needed for cleaning examination rooms between patients |
| • Request that patients wear a mask when visiting the office/clinic |
| • Minimize the number of people in the office, including staff, medical students and research fellows |
| • No accompanying persons in the clinic where possible |
| **Office design**\textsuperscript{98} | • Reconfigure waiting areas to adhere to public health distancing guidelines, e.g. 2 m distance between chairs, tape on floor |
| • Remove toys, magazines, brochures |
| • Consider a protective barrier such as plexiglass for reception, or position furniture in front of reception to create a 2 m physical distance |
| • Consider signage to remind patients about COVID-19 symptoms and hygiene practices |
| **Screening for COVID-19**\textsuperscript{98} | • Screen patients for COVID-19 before they come to the office and on day of visit |
| • Know your local public health department guidance in diagnosis and reporting of COVID-19, and recommendations on self-isolation and testing in patients who screen positive |
| **Risks vs. need for medical care**\textsuperscript{95,98} | • Prioritize essential services, e.g. melanoma biopsy/surgery during strict stay-at-home restrictions |
| • As stay-at-home restrictions relax, if non-essential care, consider the risk-benefit to the patient of an in-person visit (e.g. age of patient, condition being treated) |

**Clinic management during a SARS-related coronavirus pandemic and beyond**

As a precaution to reduce the spread of COVID-19 in the community, many governments worldwide have closed or limited non-essential services. Accordingly, dermatology clinics and offices have adapted processes to manage a practice virtually.

COVID-19, coronavirus disease 2019.
during COVID-19 (Table 3). As restrictions relax, dermatology clinics need rigorous infection control policies. In terms of personal protective equipment, face masks could result in a large reduction in infection risk ($n = 2647$; aOR: 0.15, 95% CI: 0.07–0.34, RD –14.3%, –15.9 to –10.7; low certainty), with stronger associations for N95 or similar respirators compared with disposable surgical masks or similar. 84 This translates into a reduction in transmission associated with wearing a mask of approximately 65%, albeit with wide confidence intervals. If a patient has no symptoms and is deemed not at high risk for COVID-19, the use of surgical masks and hand hygiene should be routine in the dermatology clinic for patients and staff. Resources such as the American Academy of Dermatology Coronavirus Resource Centre (https://www.aad.org/member/practice/coronavirus) and Canadian Dermatology Association (https://dermatology.ca/dermatologists/covid-19-updates/) offer recommendations for dermatologists and guidance on managing a dermatology practice in a safe and compliant manner.

Conclusion
According to the current limited evidence, most patients with inflammatory skin conditions treated with systemic immunotherapy can continue treatment. There is no expected impact on infectivity or on the innate immune response leading to worse outcomes. Nonetheless, treatment decisions are complex and should be made on a case-by-case basis. COVID-19 considerations (i.e. presence of COVID-19 symptoms, risk of exposure to SARS-CoV-2 and perceived risk factors for severe infection), as well as the small but potential protective benefits of immunosuppressants, should be balanced with the risk of psoriasis flare-ups, loss of therapeutic efficacy, and potential for development of anti-drug antibodies upon reintroduction of some biologic treatments.

Acknowledgments
Anna Czerwonka, H BSc and Jai Sharma, MSc, FUSE Health Inc. (Toronto, ON) provided professional medical writing services in the form of editorial, organizational and librarian support for this manuscript.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Biologic treatment and combination therapy considerations which may guide patient counselling.

Appendix S1. Literature search terms and strategy.