

REVIEW ARTICLE

Immunosuppressive agents for dermatological indications in the ongoing COVID-19 pandemic: Rationalizing use and clinical applicability

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Abstract

The ongoing COVID-19 epidemic has brought to the fore many concerns related to use of immunosuppressive agents (ISAs) in dermatology. While it is unclear whether the patients on ISAs for skin conditions are more prone to develop COVID-19, and what impact the ISA may have on the clinical outcome if a patient *does* get infected, rationalizations based on the specific immune effects of each drug, and existing literature on incidence of various infections with each, are possible. In this review, we provide the readers with practically useful insights into these aspects, related to the conventional ISAs, and briefly mention the clinical outcome data available on related scenarios from other patient groups so far. In the end, we have attempted to provide some clinically useful points regarding practical use of each dermatologically relevant conventional ISA in the current scenario.

KEYWORDS

azathioprine, ciclosporine, COVID-19, cyclophosphamide, dermatology, immunology, immunosuppressive, methotrexate, mycophenolate, pathogenesis, steroids

Immunosuppressive agents (ISA) are frequently used in dermatology practice. Increased predisposition to infections and worse outcome when one is contracted, are logical concerns with their use. In the ongoing pandemic of Coronavirus disease 2019 (COVID-19), these concerns are being increasingly discussed and amidst the lack of clarity among dermatologists, dermatology associations across the world are trying to formulate some basic guidelines on continued/new use of ISAs during the pandemic.

The purpose of this review is to analyze the infection predisposition potential of conventional ISAs used in dermatology practice, based on both mechanistic and clinical data, and the outcome data so far available on COVID-19 infection in patients on ISAs, to help the clinicians in making rational decisions for their patients.

The causative agent of COVID-19 is SARS-CoV 2, a novel β -coronavirus, which enters cells using the angiotensin-converting enzyme 2 (ACE2) receptor.^{1,2} The virus most likely originated in bats and has adapted to nonbat ACE2 variants as it crossed species to infect humans.³ ACE2 is expressed in many tissues including nasal mucosa,

bronchus, lung, heart, esophagus, kidney, stomach, bladder, and ileum, which are consequentially vulnerable to SARS-CoV-2.⁴ The initial replication occurs in the mucosal epithelium of the upper respiratory tract where the virus gains entry most likely via respiratory droplets or fomite contact. Further replication occurs in lower respiratory mucosa and possibly in the gastrointestinal mucosa after which a mild viremia develops.^{5,6} The innate immune response is first activated mainly via pattern recognition receptors (PRR) which results in the secretion of type 1 interferons and other inflammatory cytokines. Lymphopenia is a common feature in severe infections with drastically reduced CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells and a reduced percentage of monocytes, eosinophils, and basophils.⁷ The circulating CD4+ and CD8+ T cells are in a state of "excessive activation."⁸ The protective role of SARS-CoV-2 IgM and IgG is unclear, with very high levels reported in severely affected patients, possibly pointing to a role of antibody-dependent enhancement (ADE) of infection.^{9,10} A "cytokine storm" with excessive release of proinflammatory cytokines including IL-6, IL-1 β , IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1,

TABLE 1 Infection risk with use of conventional immunosuppressive agents in dermatology

Drug	Effects on host immune response	Literature regarding infection risk
Methotrexate	<ul style="list-style-type: none"> Induces apoptosis of activated T cells Modulates cytokine secretion from T-helper cells: increasing IL-4, IL-10 and reducing INF-γ and IL-2 (reduction in Th1 response) Inhibits production of pro-inflammatory cytokines (TNF-α, IL-6) and enhances production of anti-inflammatory cytokines (IL-10) Increased adenosine release also increases secretion of anti-inflammatory cytokine IL-10 and inhibits production of TNF-α, IL-6, and IL-8¹⁴ 	<ul style="list-style-type: none"> Observational studies: inconsistent results; none¹⁵ to increased risk¹⁶⁻¹⁸ Systematic meta-analysis: Small but significant increased risk of all infections (but not serious infections) in RA, but <i>no increased risk of infections</i> in non-RA indications (psoriasis and psoriatic arthritis [PsA], ankylosing spondylitis [AS], systemic sclerosis [SSc], and Crohn's disease)¹⁹ <i>No increased risk of total or serious infections in non-RA inflammatory rheumatic diseases including psoriasis</i>¹⁹
Ciclosporine	<ul style="list-style-type: none"> Selective action on T lymphocytes (mainly helper and suppressor subsets)²⁰ Decreased IL-2 production Reduced activity of NK cells Reduced INF-γ production¹³ 	<ul style="list-style-type: none"> <i>Low dose ciclosporine (mean 2.6 mg/kg/day) for dermatological indications: no serious infections</i>²¹ <i>Psoriatic cohort of 2845 patients: risk of infections higher than Methotrexate</i>²² <i>No infections reported on use as a single agent in a cohort of recalcitrant urticaria</i>²³ Associated with increased risk of viral warts and Epstein Barr Virus (EBV) reactivations in transplant patients on ciclosporine based regimens²⁴ Increased risk of CMV infection reported in transplant recipients and ulcerative colitis (reactivation) receiving ciclosporine^{25,26} Other infections reported with use in ulcerative colitis (high dose intravenous administration \pm other ISAs): Pneumocystis carinii pneumonia, aspergillus infection, Nocardia lung abscess²⁷
Cyclophosphamide	<ul style="list-style-type: none"> Noncell cycle specific antimetabolite Rapid immunosuppressive action Depressive action on both humoral and cell-mediated immunity^{28,29} Toxicity to immune cells: B cells > T suppressor cells > T helper cells^{30,31} B cells remained low at 1 year following 6 cycles of pulsed IV cyclophosphamide³¹ 	<ul style="list-style-type: none"> Opportunistic infections may develop without leukopenia, although incidence <i>increases with increasing severity and the duration of leucopenia</i> (increased risk with TLC \leq 3000/μl)³² Infections noted with use <i>in immunobullous disorders (as adjuvant to oral steroids)</i> <i>Common</i>: bacterial infection of involved skin, transient oral candidiasis, upper respiratory tract infections <i>Less common</i>: intravenous line infection, community-acquired pneumonia, viral pneumonitis, septic bacterial bursitis, uni/multi dermatomal herpes zoster, candidal balanoposthitis, vaginal candidiasis, reactivation of tuberculosis^{33,34} Nonsignificant increase in incidence of infections (minor) with intravenous pulse cyclophosphamide combined with oral steroids for pemphigus vulgaris³⁵ In lupus nephritis patients, addition of cyclophosphamide to steroids does not increase risk of infections over use of steroid alone, except for localized herpes zoster^{36,37} Pulse cyclophosphamide, when used without daily oral cyclophosphamide, has been associated with lower risk of leukopenia and infections³⁸
Azathioprine	<ul style="list-style-type: none"> Suppresses function of T cells, B cells, antigen presenting cells, and natural killer cells¹⁴ 	<p>Infections reported with <i>dermatological use as adjuvant to steroids</i>: Herpes zoster, oral candidiasis, dermatophytoses, cellulitis, upper respiratory infections, pneumonia, tuberculosis³⁹</p> <p><i>As an isolated agent</i>:</p> <ul style="list-style-type: none"> No infections reported in a cohort of 40 cases treated for urticaria 12 of 46 patients of airborne contact dermatitis developed skin infections (furunculosis-7, herpes labialis-1, herpes zoster-1, scabies-1, tinea corporis-2) and one developed tuberculosis²³ <p>Inflammatory bowel disease cohorts: nonsignificant difference in infections compared with controls (Viral: CMV, EBV, Varicella zoster; Bacterial: <i>E. coli</i> osteomyelitis, <i>Listeria monocytogenes</i>, Nocardia, Salmonella, and Staphylococcal, pneumonia, urinary tract infection, and sepsis)^{40,41}</p> <p>Lymphopenia <600/μl increases the risk for development of infection⁴²</p>

TABLE 1 (Continued)

Drug	Effects on host immune response	Literature regarding infection risk
Mycophenolate mofetil	Inhibits T and B lymphocyte responses, including mitogen and mixed lymphocyte responses	As <i>adjuvant to steroids in pemphigus</i> (dose 2-3 g), infections reported include: Candidal mucocutaneous infections (10%), herpes (2%), molluscum (2%), tinea (3%), upper/lower respiratory tract(5%/3%), urinary tract infection (5%), skin and soft tissue infections (5%), viral (2%) (at least one infection in 21% patients) ⁴³ An <i>increased susceptibility to viral infections</i> , especially herpes, has been noted: herpes zoster occurs with incidence figures of 2% to 10% in psoriasis, ⁴⁴ 20% in atopic dermatitis ⁴⁵ and 6% in liver transplant recipients, ⁴⁶ although the viral infections noted have not been of increased severity or duration ^{44,46}
Corticosteroids	Profound effects on both innate and adaptive immune response. Immune cells suppressed: all subsets of lymphocytes (B cells at higher doses than T cells), mast cells, monocytes, eosinophils, basophils, neutrophils, macrophages, antigen presenting cells Repressed signal transduction pathways (NFKB, AP-1) leading to reduced production of various cytokines and inflammatory mediators	Risk of <i>some bacterial, viral, and fungal infections 2- to 6-fold higher</i> in those on oral glucocorticoids compared to age, gender, and the underlying disease matched controls ⁴⁷ Large population-based cohort study: baseline steroid use associated with increased long-term risks of community-acquired infections and sepsis (adjusted OR for sepsis-2.11) ⁴⁸ Increased risk of serious bacterial infections with <i>as low as 5 mg prednisolone equivalent</i> for 1 week ⁴¹ Infection risk is <i>dose and duration dependent</i> with stepwise increase in the risk of serious bacterial infections with increasing dose and duration Risk of serious bacterial infections higher for current exposure to corticosteroids compared with other DMARDs ⁴⁹ Risk for Lower Respiratory Tract Infection and local candidiasis highest during the first week of exposure and decreases thereafter while the risk remains stable throughout exposure for herpes zoster, bloodstream infections, and cellulitis ⁴⁷ Increased risk of <i>opportunistic infections</i> including <i>Pneumocystis jiroveci</i> pneumonia, aspergillosis, nontuberculous mycobacterial disease, candidiasis, cryptococcosis, strongyloidiasis ⁵⁰ Risks of infection increases with <i>age</i> and is higher in <i>diabetics</i> , with <i>higher doses</i> , and lower plasma albumin level ⁴⁷

MIP1 α , and TNF occurs in severe cases causing extensive tissue damage in lungs and other organs.^{11,12} Thus, an uncontrolled activation of the innate immune response, along with an impaired adaptive immune response, characterize severe disease.⁷

The antiviral host response largely depends on cytotoxic T lymphocytes, NK cells, antibody-dependent cellular cytotoxicity and certain cytokines, prominently interferons. NK cells mediate immunity to viral pathogens directly through the cytolysis of virally infected tissues or indirectly by elaborating inflammatory cytokines, such as interferons (IFNs).¹³ The major ISAs used in dermatology act on various aspects of the host immunity, and mainly on adaptive immune responses. It is theoretically plausible that the "cytokine storm" that occurs in severe COVID-19 cases may be mitigated by some ISAs, although clinical relevance of this is pending trials. Further, the concern of mitigating viral replication by effective host immune response takes precedence over the ameliorating the cytokine storm that may only arise in a small proportion of cases. Before we delve further into which drugs may be potentially more harmful than the others, it is pertinent to recapitulate the immune effects of the major ISAs used in dermatology and their infection risk (Table 1).

Broadly, oral glucocorticoids extensively affect the various immune pathways and cells, and can precipitate a broad spectrum of bacterial,

fungal and viral infections in those on chronic treatment, and even with short term use of low doses.⁵¹ Steroids have been used to suppress the "cytokine storm" occurring in severe SARS CoV-2 infection, however, the safety, utility, and timing of administration are not clearly defined.⁵² Cyclophosphamide is a rapidly acting immunosuppressive suppressing both cellular and humoral immunity. The drug, at low doses, preferentially depletes T regulatory cells while enhancing effector T cell function mainly CD8+ cytotoxic T lymphocytes. The NK cell response is also augmented by cyclophosphamide.⁵³ Thus, antiviral responses may not be affected at low doses. The risk of infective complications probably increases with development of leucopenia, although the infections reported in dermatological literature are mostly non serious¹³ (Table 1). It is notable that the risk of leucopenia and infective complications is lower with pulsed cyclophosphamide than with daily oral cyclophosphamide.⁵⁴ However, in dermatological conditions, pulse cyclophosphamide is generally combined with daily oral cyclophosphamide (given in between the pulses), thus offsetting any advantage of pulse cyclophosphamide on that account.³⁰

Ciclosporine has a more specific action on T lymphocytes but also shows some depression of innate response via effect on NK cells.¹³ It inhibits both T-helper cells and precursors of cytotoxic T lymphocytes, while sparing the T suppressor cell induction.⁵⁵ The inhibition of both

TABLE 2 Summary of literature regarding patients on chemotherapeutic/immunosuppressive/immunomodulatory medications who developed COVID-19

Rheumatology			
Authors	Patient profile	Drugs	Outcome of COVID-19
Monti et al ⁶³	Chronic arthritis RA-3, SpondyloArthritis (SpA)-1	Methotrexate: 2 Leflunomide: 1 Etanercept: 2 Abatacept: 1 Low dose steroids: 2 (<5 mg/day prednisolone equivalent) Tofacitinib: 1	Hospital admission required: 1
Oncology			
Authors	Patient profile (patients on active treatment for cancer at the time of COVID diagnosis)	Drugs	Outcome of COVID-19
Liang et al ⁶⁴	Four—Lung adenocarcinoma One—Chromophobe renal cell carcinoma One—Papillary thyroid microcarcinoma (age range: 47-63 years)	Two on chemotherapy for advanced cancer Two on targeted therapy One on TSH inhibition therapy One—recurrence, on immunotherapy (further details not mentioned)	Severe disease in two of six (one on chemotherapeutic drugs and one on immunotherapy) (Ages: 58 and 63 years)
Yu et al ⁶⁵	Five patients of non-small cell lung cancer	Combinations of: Carboplatin, Pembrolizumab, Pemetrexed, Docetaxel, Cisplatin, Osimertinib, Sintilimab	Severe disease—one (on pemetrexed, cisplatin, and radiotherapy) (Age not mentioned)
Transplant recipients			
Authors	Patient profile	Drugs	Outcome of COVID-19
Gandolfini et al ⁶⁶	Two renal transplant recipients (75 and 52 years of age)	Tacrolimus Mycophenolate mofetil Steroids	Survived—One Died—One
Huang et al ⁶⁷	One renal transplant patient (58 years of age) One Bone marrow transplant recipient (51 years of age)	Mycophenolate mofetil Steroids Ciclosporine	Died Died

NK cells and cytotoxic T cells is perhaps a reason for viral infections developing with ciclosporine use. Animal models have demonstrated an inability to mount an effective immune response to viral infections including Cytomegalovirus (CMV), influenza, and Herpes Simplex Virus-2 (HSV-2) with administration of ciclosporine although paradoxically the drug has been shown to inhibit MERS-CoV replication in cell culture.^{20,56} Also, viral infections with cyclosporine are largely reported with its use in nondermatological indications, mainly in transplant recipients and ulcerative colitis. Mycophenolate mofetil has a more profound effect on effector T cells than ciclosporine and also suppresses NK cells, possibly accounting for the high incidence of cutaneous viral infections with mycophenolate mofetil, although the drug has a low infection risk otherwise.^{57,58} Azathioprine has also demonstrated in vitro activity against NK cells and has a substantial effect on antibody-dependent cell-mediated cytotoxicity, thus interfering with antiviral immune responses.⁵⁹ Although, when used alone

for dermatological indications, the drug has mainly been associated with cutaneous bacterial and viral infections and infestations mainly (Table 1).

Interestingly, mycophenolic acid and 6-thioguanine have been found to have potent activity against coronaviruses in in vitro assays. The clinical implication of this is, however, not clear.^{60,61} Methotrexate (MTX) has a good safety record with robust literature support on lack of any significant infection risk for use in nonrheumatoid arthritis (RA) indications. The respiratory adverse effects of MTX have been a cause of concern, especially in RA patients. However, MTX related pneumonitis is rarer than previously thought and importantly, MTX use in psoriasis and psoriatic arthritis is not associated with any significant increase in respiratory adverse events as per a recent meta-analysis.^{38,62}

Although, the data on incidence of COVID-19 in patients on ISAs and their clinical outcomes is scarce as yet (Table 2), some clarity may

be gained from data on other viral respiratory infections and previous influenza and corona virus epidemics. Use of ISAs was not listed as a risk factor for primary MERS-CoV infection during the outbreak in middle eastern countries.^{68,69} However, persons with chronic medical conditions which included those on ISAs were found to be more vulnerable to clinically defined SARS in the SARS-CoV outbreak in China in 2003.⁷⁰ A large retrospective cohort study involving 46 030 rheumatoid arthritis patients found a higher incidence of influenza in this group but with no effect of disease-modifying antirheumatic drugs—DMARDs (including azathioprine, cyclophosphamide, ciclosporine, and methotrexate) or biologic use on the incidence rate.⁷¹ Similarly, for complications, the incidence rates did not depend on whether or not DMARDs or biologics were being taken. However, systemic steroid use has been shown to be a risk factor for developing severe influenza.⁷² D'Antiga⁷³ shared their preliminary experience among patients in follow-up for cirrhosis, transplantation, autoimmune liver disease, chemotherapy for hepatoblastoma at the Hepatology, Gastroenterology and Transplantation center in the “red zone” of the Italian outbreak, stating that none of their patients developed a clinical pulmonary disease, despite some testing positive for SARS-CoV-2 and suggesting that immunosuppressed patients may not be at increased risk of severe pulmonary disease compared to the general population. However, there is no data yet on the incidence of SARS-CoV-2/other respiratory viral illnesses in cohorts of dermatology patients on ISAs, leaving interpretations to extrapolations from the available literature from other conditions, although dermatology patients on ISAs would generally be overall healthier compared to rheumatological, oncological or transplant patients on ISAs and hence likely far better than the other reported groups.

Interestingly, MTX has been shown *not* to affect the immunogenicity of trivalent influenza vaccine given to RA patients while continuing the drug, though the same is reduced in patients treated with anti-TNF agents.^{74,75} Similarly, no difference in antibody titers, compared with healthy controls, was detected after influenza vaccination among transplant recipients on azathioprine, while response was reduced by ciclosporine and mycophenolate mofetil.^{76,77} This is likely related to the differential effects of these drugs on humoral immune response but is unlikely to be of much significance to the primary host response to the virus during a natural infection.

Lastly, from the scant clinical outcome data on patients on ISAs developing COVID-19 (Table 2), it can be seen that among rheumatological patients on DMARDs, outcome was not different from what is otherwise expected from available literature on COVID-19 so far.⁷⁸ From among oncological and transplant recipients on ISAs infected with COVID-19, severe infection and mortality seems to have occurred especially in older ages patients. Older age has otherwise too emerged as a significant risk factor for severe COVID-19 disease and mortality. Further, transplant and oncology patients are generally on multiple ISA drugs and may have poorer general health status than dermatology patients on ISAs.⁷⁹

To conclude, there is little evidence so far to support a presumption of a higher incidence and greater severity of COVID-19 in dermatological patients on ISAs. Awaiting further data, however, a few

broad points may be taken into consideration to reduce the supposed impact of the disease on dermatology patients requiring ISAs, and these are listed below:

1. Sudden shifts in drugs and doses must be avoided to prevent flare of underlying diseases. In case, a patient on steroids/other conventional ISAs develops laboratory confirmed COVID-19, the decision to reduce dose/withhold the drug must be based on the severity of the underlying dermatological disease. For example, in case of a recalcitrant and severe pemphigus vulgaris patient, sudden interruption of treatment may itself be life threatening. On the other hand, in a stable well-controlled patient of psoriasis, interruption of treatment till recovery of COVID-19 is a practically feasible option. However, oral steroids should never be suddenly interrupted when they have been in use for long.⁸⁰
2. The dose of oral steroids should be kept at a minimum level required for disease control.
3. Keep a close watch on total leucocyte and lymphocyte counts for patients on azathioprine and cyclophosphamide, as infection risk with these has been shown to be associated with lower counts.
4. Methotrexate has strong literature to support its use as there is low infection risk in non-RA conditions. Hence it may be the preferred conventional ISA in these times and can be used in standard dermatological doses.
5. Ciclosporine use has been associated with development of severe viral infections in nondermatological patients and hence cautious use is advised. Drug interactions also need to be considered while using antimicrobials in infected patients already on ciclosporine.
6. Standard measures for prevention of COVID-19 via droplet and fomite contact must be emphasized to patients.

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