





REVIEW ARTICLE

COVID-19 and immunosuppressive therapy in dermatology

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Abstract

Coronavirus 2019 (COVID 19) was first detected in December 2019 in China. It has become a pandemic. With concern about therapies that may decrease immunity and enhance the severity of an individual's COVID-19 infection, leading to a possibly fatal outcome, use of immunosuppressants has become an important concern. This work focuses on management of various skin diseases individuals lacking immunity to COVID-19 but requiring a systemic immunosuppressant, keeping in view the challenge of the COVID 19 pandemic and that our knowledge of this virus and its effects on the immune system are incomplete including knowledge as to an individual's immunity after COVID-19 infection.

KEYWORDS

COVID 19, dermatology, immunosuppressive therapy

1 | INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2)-infection, delineated as COVID 19, was first detected in December 2019.^{1,2} On March 11, 2020 World Health Organization (WHO) declared COVID 19 as pandemic.^{3,4} There have been many proposed theories on the effect of this SARS-Cov-2 virus on the human immune system. In general, low immunity allows rapid viral replication and delays viral clearance from the body. The amount of viral load is likely directly proportional to the damage to the organs, specifically lungs (Ref). However, there is much to be learned about this specific virus and its effect upon and interaction with the immune system. We do know that many millions worldwide will get COVID-19, a tiny percentage representing a huge number of individuals will have a fatal outcome while the world awaits effective therapy or vaccination or the development of herd immunity.

Various risk factors contributing to severe damage and mortality in COVID 19 patients include old age, obesity, diabetes mellitus, cancer, and cardiovascular co-morbidities.⁵ Many diseases in dermatology require immunosuppressants for treatment. They are usually given with proper monitoring of different blood parameters regularly. However, in the current scenario of COVID 19 pandemic, there have been a dilemma among dermatologists how to tackle the dermatological problems requiring immunosuppressive therapy because of the effects of drugs on immunity and the difficulty in regular monitoring blood parameters due to movements restrictions and safety concerns.

The immunosuppressants have been categorized according to risk profile of COVID 19, taking into account their effect on body immunity.⁶ The drugs with low risk are sulfasalazine, apremilast and hydroxychloroquine, whereas methotrexate and azathioprine have intermediate risk. High-risk drugs include cyclophosphamide, cyclosporine, leflunomide, mycophenolate mofetil, prednisolone, and biologics.³ The immunosuppressive drugs azathioprine, cyclosporine,

cyclophosphamide and mycophenolate mofetil take 3 months for wash out from body.⁷ Details of pharmacokinetics of biologic and nonbiologic drugs have been discussed in Tables 1 and 2.

In various studies regarding live vaccination in rheumatology patients on immunosuppressive therapy, recommendations have been made regarding delay of live vaccination depending on specific immunosuppressant.⁸⁻¹⁰ According to the recommendation, live vaccines should be delayed for at least:

- 5 half-lives after the administration of biological agents or disease-modifying drugs (3-12 months),
- 4 weeks after high-dose corticosteroid therapy (≥ 20 mg/day prednisone or equivalent, for longer than 2 weeks),
- 4 weeks after etanercept and 3 months after other TNF inhibitors (infliximab, adalimumab),
- 4 to 12 weeks after the doses of ≥ 0.4 mg/kg/week or ≥ 20 mg/week of methotrexate
- 6 to 12 months after rituximab
- 2 years after leflunomide.

Low-dose immunosuppressive therapy has been found to be relatively safe without increasing infection risk.^{8,9} Low-dose immunosuppressive therapy is defined as follows:

- Low-dose corticosteroid (< 20 mg/day of prednisone or equivalent, short or long term or alternating days),
- Low-dose methotrexate (< 0.4 mg/kg/week or < 20 mg/week),
- Low-dose azathioprine (< 3 mg/kg/day),
- Low-dose 6-mercaptopurine (< 1.5 mg/kg/day)

The above recommendations for live viral vaccines and immunosuppressive treatment can be co-related with live viral infection of COVID 19 in the absence of any specific data and guidelines. By evaluating immunosuppressive status, treatment of dermatological

diseases can be done weighing risk benefit ratios. Biologics used to cause long-term immunosuppression might best be avoided.

Commonly encountered diseases in daily practice requiring immunosuppressives are atopic dermatitis/eczema, psoriasis, and pemphigus. In addition, some dermatologic emergencies, such as severe drug reactions (SJS/TEN, DRESS syndrome), dermatomyositis and erythroderma, may require immunosuppressive therapy. Considering the risk of COVID infection in an individual not known to have immunity to COVID-19 and disease severity, dermatologists must take decision for treatment in different scenario.

1.1 | Psoriasis

The treatment options for psoriasis are broad. Topical and systemic treatments often depend upon the severity of disease. Conventional systemic treatment options are methotrexate, topical PUVA, retinoids, cyclosporine, fumaric acid esters, and hydroxyurea.¹¹ Among all methotrexate, cyclosporine, and retinoids are widely practiced by dermatologists. Recently different biologicals targeting different pathways of disease are in market. Apremilast is the only oral biological approved for psoriasis; others are either given subcutaneously or intravenously.¹¹ Looking at current COVID 19 pandemic the treatment of psoriasis is individualized in different scenarios.

1.1.1 | Scenario 1: Chronic plaque psoriasis: Localized and $< 10\%$ BSA involved

- a. New case: Start with topical corticosteroid or calcipotriol along with emollients.
- b. Old case on systemic immunosuppressive: Stop systemic treatment and maintain on topicals and emollients. Advise the patient

TABLE 1 Pharmacokinetics and approximate duration of immunosuppression of biologics

Family	Biologic	Target	Half life	Duration of immunosuppression after stoppage
TNF-inhibitors	Adalimumab	TNF- α	10-20 days	3-6 months
	Etanercept	TNF- α	4.2 days	1 month
	Certolizumab pegol	TNF- α	14 days	3-6 months
	Golimumab	TNF- α	11-12 days	3-6 months
	Infliximab	TNF- α	7.7-14.7 days	3-6 months
	Mepolizumab	IL-5	16-22 days	3-6 months
	Secukinumab	IL-17A	27 days	6-12 months
	Ixekizumab	IL-17A	13 days	3-6 months
	Ustekinumab	IL-12,IL-23	15-32 days	6-12 months
	Nemolizumab	IL-31RA	12.6-16.5 days	3-6 months
B-cell inhibitor	Rituximab	CD20	20.8 days	6-12 months
	Belimumab	BAFF	12.5-19.4 days	6-12 months
Co-stimulatory modulator	Abatacept	CD80,CD86	13.1-16.7 days	3-6 months

TABLE 2 Pharmacokinetics and approximate duration of immunosuppression of nonbiologic drugs

Family	Drug	Half life	Duration of immunosuppression after stoppage
Folate antagonist	Methotrexate	<30 mg/m ² -3 to 10 hours ≥30 mg/m ² -8 to 15 hours	4-12 weeks: with doses of ≥0.4 mg/kg/week or ≥ 20 mg/week
Purine analog	Azathioprine	5 hours	3 months: with >3.0 mg/kg/d
Inosine monophosphate dehydrogenase inhibitor	Mycophenolate mofetil	17.9 hours for mycophenolic acid	3 months
Glucocorticoid	Prednisolone	2-4 hours	1 month: ≥20 mg/day prednisone or equivalent, for longer than 2 weeks
Alkylating agent	Cyclophosphamide	7 hours	3 months
Isoxazole	Leflunomide	14 days	2 years
Calcineurin inhibitor	Cyclosporine	18 hours	3 months

to stay at home for at least 3 months without any outside movement. Maintain proper hand hygiene.

1.1.2 | Scenario 2: Chronic plaque psoriasis >10% BSA/ disabling psoriatic arthritis

Discuss the risk and benefits of before starting treatment. If no contact history with COVID 19, healthy young adult without any other comorbidities can be started with apremilast with or without hydroxychloroquine and symptomatic treatment with NSAIDs for joint pain at least 3 months. The patient can be in touch over phone to avoid frequent visit to medical office or hospital.

1.1.3 | Scenario 3: Pustular psoriasis and rupoid psoriasis

Systemic acetretin with emollients

1.1.4 | Scenario 4: Psoriatic erythroderma

The patient usually needs to be admitted for intravenous fluid support. Treatment may commence with acetretin/apremilast or a combination of these. If there is no response considering the disease severity patient can be shifted to cyclosporin/methotrexate after discussing the risk and benefits with the patient. Patient should use normal surgical mask 24 hour including the health care workers. Proper hand hygiene should be maintained by the patient. After discharge patient should stay confined in home or home quarantine for at least 3 months.

1.1.5 | Scenario 5: Psoriasis patients on biologics

It is believed that proactive biologic discontinuation could lead to treatment failure via formation of anti-drug antibodies. Psoriasis,

being a chronic disease, needs long-term treatment and hence stoppage of biologic treatment would cause worsening of disease, increase the hospital visits and have negative psychological effects in COVID pandemic time. Psychological stress will again aggravate the disease. Due to chance of failure of biologic because of anti-drug antibody formation, the cost of treatment will increase in future due to of biologic switching.¹² Also, it is hypothesized that stoppage of biologic will lead to higher proinflammatory states and could worsen the cytokine storm in COVID 19 affected patients.¹³ Therefore, discontinuation of biologics to prevent COVID 19 infection should be personalized.

1.2 | Pemphigus vulgaris

Pemphigus vulgaris produces painful oral and skin erosions that can be sources of entry to infectious organisms. If the patient is not treated, the severity of pemphigus may increase, making the patient more vulnerable to secondary infection and possible sepsis. Currently the CDC is advising maintenance of proper hand hygiene, avoidance of fomite contact to prevent transmission of COVID 19. However eroded skin being as a risk factor for COVID 19 is unknown. To prevent disease progression and possible sepsis, pemphigus patients need treatment with options mostly immunosuppressive. Systemic corticosteroids are considered first line drugs. Others medications useful are rituximab, cyclophosphamide, azathioprine, and mycophenolate mofetil. Intravenous immunoglobulin and plasmapheresis can also be tried.¹⁴ The treatment of pemphigus vulgaris will vary depending upon the situations. However, it is advised to maintain immunomodulatory therapy when needed since unjustified withdrawal could lead to uncontrolled disease activity resulting in high morbidity and mortality.¹⁵

1.2.1 | Scenario 1: New case with extensive skin erosions and oral mucosa erosions

The patients need to be admitted. Proper skin care with barrier dressings. In addition to oral corticosteroids at 1 mg/kg/day, intravenous

immunoglobulin can be considered rather than starting conventional immunosuppression. If CDA is achieved, slow tapering of the GCD may proceed. Where IVIG is not available, conventional immunosuppression such as MMF may be given as well. Under pre-COVID-19 times, rituximab would have been the first choice but given its irreversible long-term immunosuppression and precautions around viral infections, it is not advised to be started at present.¹⁶ Patients need to use masks 24 hours during hospital stay and at home. After discharge patients need to remain home-quarantined for 3 months and follow up with tele dermatology, ideally. The only visits to the hospital should be if the disease flares up.

1.2.2 | Scenario 2: A chronic pemphigus case without skin lesions but on dexamethasone cyclophosphamide pulse

If no skin lesions, DCP can be withheld during the COVID 19 pandemic and the patient can be started with prednisolone <20 mg/day. Oral cyclophosphamide also needs to be stopped because the combination of oral steroid and cyclophosphamide will cause more immunosuppression.

1.2.3 | Scenario 3: A chronic relapsing pemphigus patient on daily oral glucocorticoid with controlled/uncontrolled disease

Once the disease is controlled taper prednisolone rapidly to ≤ 20 mg/day prednisolone. Ideally, avoid other immunosuppressants. If the disease remains uncontrolled IVIg can be added if feasible. If disease is not controlled on <0.2 mg/kg/day, consider entry into a phase 3 RCT which is enrolling globally with a short acting reversible BTK inhibitor vs placebo, the PEGASUS trial (NCT02704429). BTK inhibitor PRN1008 works via reversible covalent binding and therefore has a self-limited immunomodulatory effect.

1.3 | Atopic dermatitis/Eczema

The first line treatment for atopic dermatitis is topicals. The topical treatments are emollients followed by TCS and TCI.^{17,18} Systemic treatments are sought with severe eczema not responding to topicals. The systemic medications used in AD include cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil, systemic corticosteroids and phototherapy.¹⁷ Cyclosporine A (CsA) is recommended as the first-line therapy in severe cases of chronic AD in adults and used in severe cases of AD in children and adolescents.¹⁹ Methotrexate (MTX), azathioprine (AZA), and mycophenolate mofetil (MMF) are utilized as second line treatment in adult patients with AD, when CsA is ineffective or contraindicated.²⁰ Systemic corticosteroids (CS) are approved for the treatment of AD, mainly in adult patients for up to 1 week, in carefully selected cases of disease exacerbation.¹³ In

COVID 19 pandemic era the systemic treatment for AD should be opted wisely to prevent COVID 19 infection. Dupilumab selectively interferes with type 2 inflammation is not considered to increase the risk for viral infections and might thus be preferred compared to conventional systemic immunosuppressive treatments, in COVID-19 pandemic.²¹

1.3.1 | Scenario 1: Severe AD not responding to topicals requiring systemic therapy

Start with low dose corticosteroid <20 mg/day prednisolone for ≤ 2 weeks followed by stoppage and maintain with topicals. After stopping systemic treatment patients should be supplied with ample topical therapy, and guidance on the amount needed to prevent flares until systemic therapy can be reinstated. Judicious use of emollients and antihistamines. Patients to be in home quarantine for 3 months. Low dose methotrexate <20 mg/week can also be given.

1.3.2 | Scenario 2: Stable AD with acute flare up in severe form

Short course oral corticosteroid for ≤ 2 weeks followed by stoppage and maintain with topicals with judicious use of emollient and antihistamine.

1.4 | Acute emergencies

1.4.1 | Steven Johnson syndrome and toxic epidermal necrolysis

Various treatments including corticosteroids, cyclosporine, tacrolimus, intravenous immunoglobulin and plasmapheresis haven't been tried in SJS/TEN, none of which have proven efficacy,²² with systemic steroids and oral cyclosporine being used most widely.²³ However in the current scenario of COVID 19 pandemic, options are being reevaluated with intravenous immunoglobulin being preferred treatment to arrest the activity of disease. Another promising alternative is plasmapheresis.

1.4.2 | Dermatomyositis

Dermatomyositis may produce severe muscle inflammation or myositis leading to severe muscle pain, weakness and sometimes dysphagia, dysphonia, and dyspnea due to weakened esophageal and respiratory muscles.²⁴ High dose oral prednisone may be initiated early to improve muscle weakness.^{25,26} The dose of prednisolone varies between 0.5 and 2 mg/kg/day for initial treatment.²⁷ In situations where prednisone cannot be used, second-line agents such as methotrexate and azathioprine may be appropriate. Rituximab, intravenous

immunoglobulin (IVIG), and other biologics are useful in those who developed resistance to therapy. In patients experiencing steroid-related toxicity, a steroid-sparing agents such as methotrexate, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, leflunomide, chlorambucil, and tacrolimus can be tried.²⁸

Scenario 1: Acute and severe myositis

Though corticosteroids are first line treatment, to avoid immunosuppression because of risk of COVID 19, intravenous immunoglobulin should be considered first choice. After control of myositis low dose immunosuppressive therapy can be started.

Scenario 2

Stable dermatomyositis with normal muscle enzyme on corticosteroid and another sparing agent.

Corticosteroids need to be tapered off and other immunosuppressive to be stopped.

CONCLUSION

Treatment of dermatologic disorders requiring a long-term immunosuppressant is challenging at this point of time due to COVID 19 pandemic. In the absence of any effective treatment or vaccine for COVID 19 infection, lots of patients are losing their life. Hence, before giving treatment to any disease condition, physicians need to weigh the risk benefit ratio of giving immunosuppressive drug. It is advisable to consider other options. If immunosuppressive treatment is to be given, it should be with low dose and minimum duration. In addition, patients who do not have immunity to COVID 19 should take protection according to CDC guidelines and consider home quarantine as a member of a vulnerable population until there is effective vaccination or treatment or herd immunity has been reached.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

Robert A. Schwartz involved in conceptualization, data curation, and writing-original draft. Swetalina Pradhan involved in investigation, writing-review, and editing. Dedee F. Murrell involved in investigation, writing-original draft, writing-review, and editing. Mohammad Jafferany involved in methodology, supervision, writing-review, and editing. Olga Y. Olisova involved in supervision, writing-review, and editing. Konstantin M. Lomonosov involved in supervision, writing-review, and editing. Torello Lotti involved in supervision, writing-review, and editing. Mohamad Goldust involved in conceptualization, data curation, and writing-original draft.

DISCLAIMER

We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in

this document have been met and that each author believes that the manuscript represents honest work.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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