

## Use of Immunosuppressants/Immunomodulators in Autoimmune/Inflammatory Dermatologic Diseases during COVID-19 Pandemic—General Recommendation Based on Available Evidence

### Magnitude of the Problem

As of May 16, 2020, there were 44,34,653 confirmed cases of COVID-19 with 3,02,169 reported deaths since its onset in late December 2019 in Wuhan, China.<sup>[1]</sup> Since the human race collectively is not exposed to this novel virus, the protective mechanism is innate immunity to begin with and subsequent development of protective antibodies and/or T-cell mediated immunity.<sup>[2]</sup> Currently, the diagnostic gold standard is real-time polymerase chain reaction (PCR) that involves the reverse transcription of SARS-CoV-2 RNA into complementary DNA (cDNA) strands followed by the amplifications of the specific regions of the cDNA.<sup>[3]</sup> The usefulness of serological tests that can detect IgG and IgM against coronavirus proteins is yet to be established for disease surveillance and epidemiologic research.<sup>[4]</sup>

### Iatrogenic Immunosuppression in Dermatology Patients and COVID-19

It is not yet known whether dermatology patients on immunosuppressive drugs are at an increased risk of acquiring the COVID-19 infection.<sup>[5]</sup> The use of immunosuppressants, however, is fraught with the possibility of severe manifestations of COVID-19 if one acquires COVID-19 infection, though no high-level evidence for this is available.<sup>[5]</sup> This itself may lead to a tendency of discontinuation of immunosuppressive medication, by the patients themselves or upon advice from treating dermatologists. Dermatologists may also be reluctant to start patients on immunosuppression at this time. Rightly so as we are yet to decipher several aspects of the use of immunosuppressive drugs in varied indications across various specialties. Robust data is not available for broad immunosuppressants like ciclosporin, azathioprine, or methotrexate although in previous viral endemic episodes, no significantly increased risk of complications in exposed transplant or other patients on immunosuppressives was noted.<sup>[6]</sup>

The effects of the flare of primary disease on COVID-19 also needs to be considered. A correlation between disease flare of lupus erythematosus (LE) and risk of COVID-19 acquisition has been proposed. This implies that disease activity should be adequately managed to reduce the acquisition of COVID-19 infection in LE patients. In LE, T-cell DNA methylation defects lead to increased expression of methylation-sensitive genes. These genetic expressions are impacted by oxidative stress generated by environmental factors that trigger a lupus flare. The

angiotensin-converting enzyme (ACE) 2 gene that encodes the attachment receptor for SARS-CoV-2, is demethylated and overexpressed in active lupus patients. Therefore, a lupus flare with attendant ACE2 demethylation and overexpression could possibly lead to an increased susceptibility to SARS-CoV-2 infection.<sup>[7]</sup> Further, lupus organ involvement flares including cardiovascular disease, lupus nephritis, central nervous system flares, and interstitial lung disease confer a worse prognosis for COVID-19 patients.<sup>[7,8]</sup>

Another interesting aspect in patients of LE is increased risk of SARS-CoV-2 induced cytokine storm that is characterized by aberrant immune activation and may be triggered by a sudden withdrawal of the immunosuppressive or biologic medication.<sup>[8]</sup> This response akin to macrophage activation syndrome is characterized by elevated cytokine IL-2, IL-6, IL-7, IL-10, interferon- $\gamma$ , and TNF $\alpha$ . This presentation may be with acute respiratory distress syndrome, sepsis, and multi-organ failure. Lupus patients are known to be more prone to viral illness and may also be predisposed to cytokine storm due to their inherent immune dysregulation. In these situations, trials evaluating TNF $\alpha$  inhibitors, Janus kinase inhibitors, anakinra (IL-1 receptor antagonist), tocilizumab (IL-6 receptor antagonist) are underway.<sup>[7]</sup> Interestingly, immunosuppressants and immunomodulators; i.e., steroids, chloroquine and hydroxychloroquine, tocilizumab, etc., are in fact used for management of cytokine storm in COVID-19. The data pertaining to intravenous corticosteroids is conflicting with only one Chinese study reporting reduced death rates in COVID-19 pneumonia with acute respiratory distress.<sup>[9]</sup> The beneficial effect on COVID-19 has also been reported with intravenous immunoglobulin.<sup>[10]</sup>

It is also important to remember that patients on immunosuppressive medications may have an atypical presentation with SARS-CoV-2 and the index of suspicion should be high. Some authors have also recommended screening by RT-PCR testing twice for the virus before the initiation of biologics especially in high-risk patients.<sup>[11]</sup>

Several dermatologic diseases require the use of immunosuppressants, namely autoimmune bullous diseases, psoriasis, connective tissue diseases, eczemas, severe oral or cutaneous lichen planus, etc., Other diseases with predominant psychological impairment also require immunosuppression like rapidly spreading alopecia areata or vitiligo. In the physicians' perspective, we may prefer to avoid immunosuppressants and manage the later group

of diseases only with counseling and topical medications during the COVID-19 pandemic. However, the patients may still be very keen on being prescribed immunosuppressives for early and effective management. The decision will not be cut-out and shall require several dimensions of consideration.

Not starting immunosuppression or not prescribing appropriate immunosuppression when it is absolutely needed may be life-threatening, e.g., in severe pemphigus with extensive body surface area involvement or severe pustular or erythrodermic psoriasis. Suddenly withdrawing immunosuppression in a patient with the well-controlled disease may jeopardize the control leading to life-threatening disease flare or life-threatening complications of drug withdrawal, the most significant being manifest hypothalamic-pituitary-adrenal axis (HPA) suppression after the sudden withdrawal of long-term systemic corticosteroids. Disease flare shall also lead to unnecessary stress and possibly to frequent travel to a health care facilities, which itself puts a patient at an increased risk of acquiring SARS-nCoV-2 infection. Health care facilities should be kept as much free as possible to deal with COVID-19 patients too.

### Immune Response to SARS-nCoV-2

During the infection, complex immune response- both adaptive and innate, act against the virus.<sup>[12]</sup> Increased neutrophils, reduced lymphocytes, and increased neutrophil/lymphocyte ratio has been observed in severe cases compared to mild ones. Prominent lymphopenia suggestive of impaired immunity occurs in most of the severe cases.<sup>[13]</sup> Lymphopenia is represented by reduced CD4+ T helper cells, CD8+ cytotoxic T helper cells, and regulatory T-cell; helper T-cells and regulatory T-cells are significantly reduced in severe disease patients compared with the milder ones. A reduction in B-cells and NK-T cells is also observed. Taken together, SARS-CoV-2 is an infection marked by immune dysregulation with aberrant chemokine and cytokine response, altered lymphocyte profile leading to tissue damage.<sup>[14]</sup>

Considering complex immune response without a specific pattern, what should be the best choice for immunosuppression when required? Not using any immunosuppression is perhaps the best option, but at the cost of possibly losing a patient to a severe manifestation of primary dermatologic disease and its complications. Practically, a drug that suppresses B- and T- lymphocytes and that acts for a long time after use may preferably be avoided. Even after the drug is stopped because of having active COVID-19, the immunosuppression will continue. Table 1 depicts the commonly used immunosuppressants/immunomodulators, their action on the immune cells and half-life. The half-life of drugs has to be understood in the context of their biological half-life and not on pharmacokinetic half-life.

### Ten Points of General Considerations for Use of Immunosuppressants in Autoimmune/Other Immune -Mediated Diseases

We may see a sudden surge in severe cases of these diseases reporting to the health care facilities after the lock-down is lifted and we should prepare ourselves with the idea of how to manage these groups of patients with disease of varying severity.

The consideration has to be based on the following factors

1. Primary disease
2. The severity of disease- mild, moderate, severe, or in remission
3. Immunosuppression status
  - a. the patient is already on immunosuppression
  - b. the patient is being contemplated for immunosuppression
  - c. a change in immunosuppressant is being contemplated due to inadequate response of the severe disease to existing treatment.
4. Associated comorbidities that already put a patient at increased risk of severe COVID-19 infection like elderly patient, existing cardiovascular disease, lung disease, hypertension, diabetes, etc
5. Occupation
  - a. it involves frequent travel or frequently meeting people
  - b. the patient can be strictly homebound as far as possible.
6. Household status- can or cannot absolutely self-isolate at home
7. Self-care- can or cannot care for self and hence close contact with other relative or caregiver is essential who can-not completely self- isolate too
8. Teledermatology consultation- possible or not possible due to unavailability of access to it or other reasons
9. COVID-19 status
  - a. the patient is COVID-19 positive (admitted patients seen on call)
  - b. there are no symptoms to suggest COVID-19 and there is no risk factor to acquire COVID-19 infection.
10. The general prevalence of COVID-19 in the region of patient's residence/work/travel for other reasons

### General Recommendations from Other Associations

British Association of Dermatologists has recommended shielding/social distancing based on risk stratification for patients on medication acting on the immune system.<sup>[15]</sup> Shielding or complete self-isolation, wherever indicated, may not be possible for a significant proportion of patients in India. The same document by the British Association of Dermatologists recommends only social

**Table 1: Commonly used immunosuppressives/immunomodulators in India for dermatologic indications with their immune target and biological half lives**

Mechanism/class	Drug	Target	Biological half life
Short acting oral corticosteroid	Hydrocortisone	NFκB inhibition	8-12 h
Intermediate-acting Corticosteroid	Prednisolone	AP-1 inhibition	24-36 h
	Methylprednisolone	Decreased interleukin-1 (IL-1), TNF-α, adhesion molecules, growth factors	
	Triamcinolone		
Long-acting corticosteroid	Dexamethasone	Lymphocyte apoptosis	36-54 h
	Betamethasone	Eosinophil apoptosis Greater effect on T-cells Decreased NK cell activity	
Binds to the cellular protein FK506 binding protein (FKBP)	Tacrolimus	Decreased NFAT, IL-2	12 h
Structural similarity to the endogenous purines	Azathioprine	T-cell-mediated function is depressed Antibody production is diminished in the B cells	5 h
Cell-cycle non-specific drug Acts by DNA cross-linking	Cyclophosphamide	Greater effect upon B lymphocytes than T lymphocytes Greater effect upon suppressor T cells than helper T cells	3-12 h
Inhibition of the intracellular enzyme calcineurin	Cyclosporine	Impaired IL-2 production Affects antigen presenting cells Inhibits production of interferon-γ Downregulates intercellular adhesion molecule 1 (ICAM-1)	5-18 h
Inhibition of inosine monophosphate dehydrogenase	Mycophenolate mofetil	Alters expression and processing of cell surface adhesion molecules Dendritic cells are negatively affected by MMF Inhibits antibody production by activated B-cells	16 h
Competitive antagonist of the enzyme dihydrofolate reductase	Methotrexate	Depression of cutaneous lymphocyte-associated antigen-positive T-cells and endothelial E-selectin Suppress primary and secondary antibody responses	10-27 h
Oral, small-molecule inhibitor of phosphodiesterase 4	Apremilast	Pro-inflammatory innate Th1 immunity components reduced - IL-6, IL-8, TNF-α, macrophage inflammatory protein-1b Systemic Th17 immune response components reduced	6-9 h
Humanized monoclonal IgG1κ antibody selectively binding to IgE molecules	Omalizumab	Prevent mast cell and basophil degranulation	26 days
Chimeric monoclonal antibody against the B-cell surface antigen CD20	Rituximab	B-cell depletion within 2-3 weeks and sustained for 6 months Return to normal levels within the first year after treatment Protective antimicrobial antibodies are produced by long-lived CD20- plasma cells in the bone marrow, autoreactive antibodies are primarily made by short-lived CD20+ plasma cells found in peripheral compartments	21 days
Chimeric TNF-α inhibitor	Infliximab	Reduced IL-20 and IL-23	7 days-9 days
Fully human TNF-α inhibitor	Etanercept	Reduced Th17 cells	4.8 days
	Adalimumab		14 days
Monoclonal antibody	Secukinumab	Anti IL17A	27 days

distancing as is the norm today for those on topical creams and gels (corticosteroids), dapsone, chloroquine/hydroxychloroquine, retinoids, sulfasalazine, and omalizumab.

As per the recommendation of the American Academy of Dermatology for patients on systemic immunosuppressive agents who do not have features of COVID-19 or have not tested positive for it, there is insufficient evidence to recommend discontinuation of systemic immunosuppressive agents at this time.<sup>[16]</sup> For those patients being considered for systemic immunosuppression, the physician should

assess benefits versus risk in those who are low-risk for severe COVID-19 before initiating on immunosuppression in a case to case basis.

#### *Autoimmune bullous diseases*

European Academy of Dermatology and Venereology task-force on autoimmune bullous diseases<sup>[17]</sup> enlists the immunosuppressive drugs that increase the risk for more severe COVID-19 as follows

- rituximab, within the last 1 year
- azathioprine

- mycophenolate mofetil
- mycophenolic acid
- methotrexate
- cyclosporine
- cyclophosphamide
- prednisolone (>10 mg/kg/day).

The profound and prolonged B- cell depletion induced by rituximab is especially a cause of concern and significantly, it may also reduce the immunological memory following SARS-CoV-2 infection, thereby making patients susceptible to reinfection.<sup>[18]</sup>

The same recommendation enlists the following drugs for autoimmune blistering diseases that are unlikely to increase the risk for infection or more severe COVID-19:

- dapsone
- sulfapyridine
- antibiotics (e.g., doxycycline, tetracycline)
- antihistamine

High-dose intravenous immunoglobulin also is unlikely to have a significant immunosuppressive effect. IVIg has been proposed as a potential treatment option for COVID-19.<sup>[19]</sup> Consideration has to be given to an added risk of thromboembolism in COVID-19 positive patients.

For those positive for COVID-19, all immunosuppressants may have to be stopped except long-term prednisolone, which has to be maintained at least 7.5–10 mg/day or its equivalent to avoid manifestations of adrenal insufficiency. There is no clear guidance on restarting treatment after one is cured of COVID-19 and the decision has to be taken on a case to case basis.

The safe treatment option for common autoimmune bullous diseases in India during COVID-19 is suggested below as per disease severity. For those patients of pemphigus who do not have a new lesion for more than 2 weeks and 80% of their lesions are healed, the prednisolone dose has to be tapered. The adjuvants may be considered to be stopped. Those with the disease under remission with minimal treatment, the adjuvant they are on may be considered to be stopped. By definition,<sup>[20]</sup> they receive up to 10 mg per day of prednisolone that may be considered to be tapered. Clinical activity monitoring, preferably by teleconsultation, is required for those who are in remission off treatment.

Patients with severe COVID-19 may have a hypercoagulable state. Active bullous pemphigoid may be independently associated with a prothrombotic state and at an increased risk of venous thromboembolism.<sup>[21,22]</sup> One study has suggested that the treatment of bullous pemphigoid with systemic corticosteroids acts also on the coagulation system by a reduction in inhibition of fibrinolysis.<sup>[21]</sup> Adequate disease control with the approach

as suggested below may be aimed at. Though routine anticoagulation is not recommended in the management of bullous pemphigoid, since high dose intravenous immunoglobulin also leads to a prothrombotic state, a caution for the development of venous thromboembolism may be exercised.

### Pemphigus

Mild- topical corticosteroids ± oral prednisolone (up to 10 mg/day, if sufficient to control disease activity) ± dapsone.

Severe- High dose intravenous immunoglobulin wherever possible (affordability and availability) ± oral prednisolone (up to 10 mg/day, if sufficient to control disease activity).

### Bullous Pemphigoid

Since these patients are elderly with comorbidities and often not able to self-care, they are inherently at an increased risk of severe COVID-19. They may, on the other hand, be amenable to strict home isolation.

Mild disease- topical corticosteroids ± oral prednisolone (up to 10 mg/day, if sufficient to control disease activity) ± doxycycline/tetracycline ± dapsone

Severe disease- topical corticosteroids ± oral prednisolone (up to 10 mg/day, if sufficient to control disease activity) ± dapsone ± doxycycline/tetracycline ± intravenous omalizumab (300 mg once per month) ± high dose intravenous immunoglobulin.

### Mucous Membrane Pemphigoid

Mild disease- topical corticosteroids ± oral prednisolone (up to 10 mg/day, if sufficient to control disease activity) ± doxycycline/tetracycline ± dapsone ± colchicine

Severe disease- topical corticosteroids ± oral prednisolone (up to 10 mg/day, if sufficient to control disease activity) ± doxycycline/tetracycline ± dapsone ± colchicine ± high dose intravenous immunoglobulin.

Colchicine is under trial to prevent the complications of COVID-19 (ClinicalTrials.gov Identifier: NCT04326790) and counteracting inflammation in COVID-19 pneumonia (ClinicalTrials.gov Identifier: NCT04322565)

For any of the above diseases, case-to-case modification shall be required and use of higher dose of prednisolone or any other significant immunosuppressive drugs shall require discussion with the patient about the increased risk of severe COVID-19. Strict home isolation should be enforced for a prolonged period of time, depending on the biological half-life of drugs as listed in Table 1.

## Dermatitis Herpetiformis

Gluten-free diet ± dapsone ± topical corticosteroids.

## Follow-up and Monitoring

Monitoring investigations need to be done as per protocol for prescribed drugs and follow-up should be done by using telecommunication as much as possible and practically feasible.

## Lupus Erythematosus

Treatment of LE is aimed at achieving remission or minimal disease activity and preventing organ damage and improving the quality of life.<sup>[7,23]</sup>

Hydroxychloroquine, one of the 4 approved drugs for LE, is the backbone of lupus treatment and has also been shown to have an anti-viral effect on SARS-CoV-2. It is associated with a reduction in lupus flares, organ damage, and improved overall survival. The reduction in lipids and of thrombosis due to antiplatelet effects helps in the prevention of cardiac disease. Therefore, it should be initiated or continued in all patients, and given its recommendation in SARS-CoV-2 prophylaxis, the importance of drug adherence should be emphasized.<sup>[23]</sup> If indicated, angiotensin-converting enzyme inhibitors should also be continued in recommended doses.<sup>[7]</sup>

It is imperative that glucocorticoids should be used at the lowest effective dose and should not be abruptly stopped regardless of suspicion of COVID infection status.<sup>[7]</sup> In COVID negative patient, other steroid-sparing drugs like methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine may be continued, especially in patients with a history of vital organ-threatening rheumatic disease.<sup>[7,8]</sup>

Belimumab is approved for LE for extrarenal disease with continuing disease activity or flares despite standard therapy.<sup>[23]</sup> Though not available in India, the cutaneous, musculoskeletal, and serological manifestations demonstrate the most significant improvement. Belimumab administration may be considered currently by a subcutaneous route as compared to the intravenous infusion to minimize hospital visits.<sup>[8]</sup> Rituximab is currently used off-label, in patients with severe renal, hematological, or neuropsychiatric disease refractory to therapy. A recent report described a severe and life-threatening form of COVID-19 in a patient of granulomatosis with polyangiitis on rituximab with corticosteroids. The authors concluded that glucocorticoids and rituximab may have limited the cytokine storm but cautioned about the use of these drugs during the COVID-19 pandemic.<sup>[18]</sup>

In these times, the follow-up visit for monitoring and investigation reviews maybe deferred/conducted by telemedicine. The protocol for investigative review should

be adhered to and if a personal visit is required appropriate personal protective equipment should be used by the patient.

Stress is a well-recognized trigger for LE and physicians should include the addressal of the psychological, social, and economic impact of COVID-19 pandemic and promote drug adherence.<sup>[7]</sup> This in addition to advanced social distancing and initiation of registries reporting treatment outcomes will help in synthesizing effective disease management strategies. This shall be helpful during the ongoing pandemic or possibly future ones with a coronavirus.

## Treatment Recommendations<sup>[24]</sup>

### *In recently diagnosed LE (including cutaneous LE)*

Topical agents: corticosteroids, calcineurin inhibitors, sunscreen, and photoprotection

Systemic agents: hydroxychloroquine sulphate; dapsone especially for bullous LE, vasculitis; acitretin, and thalidomide for cutaneous LE

### *Severe disease or vital organ-threatening disease*

#### *COVID -19 negative*

Add high-dose glucocorticoids, immunosuppressive (methotrexate, mycophenolate mofetil, and azathioprine) and if not controlled/life-threatening, add rituximab, high dose intravenous immunoglobulin.

#### *Patients on therapy for LE with exposure to COVID-19/ become COVID 19 positive*

Hydroxychloroquine sulphate may be continued and biologics and immunosuppressive agents should be withheld pending 2 negative test results for COVID-19 or until symptoms become absent/resolve for 2 weeks.

## Psoriasis

Psoriasis is a relatively common dermatosis that affects almost 3% of the population. Moderate to severe disease necessitating systemic therapy may be required in up to 15% of cases.<sup>[25]</sup> The broad immunosuppressives, methotrexate, and cyclosporine have been extensively and successfully used in moderate to severe psoriasis. Biologics targeting TNF $\alpha$ , IL12, IL17, and IL 23 have also proven efficacy. Therefore, it is expected that the management of psoriasis would be severely impacted by the cessation of immunosuppressive therapy.

The cytokines targeted by biologics may have a key role in an immune response against many bacteria, viruses, and fungi and potentially there may be an increased risk of respiratory tract infections with use of these biologics. For

example, IL-17 is important for mounting a mucosal immune response, and IL-17 targeting biologics could increase respiratory tract infections. A recent meta-estimate from phase 3 trials of secukinumab and ixekizumab found that there was an increased risk of respiratory tract infections of any etiology in IL-17 group versus placebo (Odds ratio 1.56, 95% confidence interval).<sup>[26]</sup> Ustekinumab may also have a slightly increased risk due to IL-12 blockade as IL-12 has a vital role in mounting a protective immune response against viruses.<sup>[27]</sup> However, in the clinical setting, the withdrawal/denial of biologics for the treatment of psoriasis because of this possible risk of infection is debatable. Indeed, data from phase III clinical trials of anti- TNF $\alpha$  agents in psoriasis have reported similar rates of nasopharyngitis and upper respiratory tract infections as the placebo.<sup>[28]</sup> Further, data from registries and pharmacovigilance indicates that biologics acting against IL-17 and IL-23, fumaric acid esters, apremilast, and methotrexate have no additional risk for viral infections.<sup>[6]</sup>

The decision to stop or modify the drug regimen could be guided by the disease severity, presence of psoriatic arthritis, comorbid conditions conferring higher risk for COVID-19, and the risk of exposure to COVID-19 based on community prevalence.<sup>[29]</sup> Therefore, patients with erythrodermic, pustular, extensive psoriasis, or psoriatic arthritis with no risk factors for COVID-19 may be initiated on immunosuppressive therapy after informed consent and counseling for necessary precautions.

Most current recommendations are for cautious initiation of cyclosporin, methotrexate, and TNF $\alpha$  inhibitors in psoriasis patients from areas with high COVID-19 prevalence and all immunosuppressives and biological therapy may be withheld if exposure to a confirmed COVID-19 case occurs.<sup>[30]</sup> Interestingly, the target binding protein for cyclosporine, cyclophilin, is also required for viral replication. Therefore, cyclosporine has been shown to inhibit influenza A virus, hepatitis C virus, and coronavirus including the severe acute respiratory syndrome (SARS) and has been postulated to have a possible beneficial effect during the COVID-19 outbreak. In a recent series of adult patients treated with cyclosporine for psoriasis ( $n = 114$ ) or atopic dermatitis ( $n = 16$ ), no deaths or hospitalization due to COVID-19 were reported and only 2 patients of psoriasis developed the mild disease, thereby indicating that cyclosporine did not increase the severity of SARS-CoV-2 infection.<sup>[31]</sup>

The impact of biologics on COVID-19 was analyzed in a retrospective multicenter, observational, Italian study in patients with chronic plaque psoriasis ( $n = 5,206$ ) on biologic therapy. Patients who had been hospitalized or died from COVID-19 between February 20<sup>th</sup> and April 11<sup>th</sup>, 2020 were analyzed. No mortality was reported and 6 patients on biologics like guselkumab, adalimumab, ustekinumab, secukinumab, and etanercept had COVID-19 positivity and 4 required hospitalization (3 had comorbidities). The

authors concluded that while psoriatic patients are known to have higher associated metabolic and cardiovascular comorbidities and this cohort was on immunosuppressive/immunomodulating agents, there was no increased risk of hospitalizations or deaths from COVID-19.<sup>[32]</sup> Moreover, unnecessary biologic discontinuation would lead to a disease worsening and lower biologic efficacy when it is reinstated.

If a reduction in the immunosuppressive treatment is decided on, the options could be cessation of the immunosuppressive drug or biologic, reduction in drug dosage or biologic administration frequency, transition to an alternative safer drug or biologic, reduction or discontinuation of concomitant immunosuppressant drugs with the biologic.<sup>[30]</sup> To prevent disease flare, this should be supplemented with stress reduction and continuation or augmentation of topical agents including liberal emollients, topical corticosteroids, vitamin D analogs for limited areas or home phototherapy. This therapeutic approach may also be preferred in patients with limited psoriasis involvement. In case of extensive, severe, or unresponsive disease, drugs with known efficacy in psoriasis like acitretin or small molecules like apremilast that have a shorter half-life as compared to most biologics may be preferred.<sup>[8,29]</sup> Hydroxychloroquine sulphate used for prophylaxis and treatment of COVID-19 may potentially cause disease exacerbation in patients with psoriasis. The exact risk of psoriasis induction or exacerbation with antimalarials is unknown.<sup>[33]</sup> In conclusion, as the COVID-19 virus is a novel pathogen with increased mortality in patients with comorbidities, a cautious approach is warranted.<sup>[29]</sup>

### *Atopic dermatitis*

Children, who comprise the majority of patients of atopic dermatitis (AD), have not featured prominently in COVID-19 pandemic. Data from China suggests children below 10 years of age account for only 1% of cases, though it can affect infants as well. They frequently do not have a significant disease and can be a facilitator of transmission.<sup>[34]</sup>

The European Taskforce on Atopic Dermatitis recommends to continue all immunomodulatory treatment including immunosuppressives since disease exacerbation may have a significant negative impact on patients' immunity.<sup>[35]</sup> The immunomodulatory drugs used for management of AD also takes care of comorbidities, i.e., asthma, chronic obstructive pulmonary disease, etc., and sudden termination of such agent in a patient with the stable disease will exacerbate skin condition and systemic comorbidities.

As stated above, the effects of cyclosporine on coronavirus other than SARS-CoV2 have been studied. Cyclosporine has been shown to reduce the in-vitro replication of Middle East respiratory syndrome coronavirus (MERS-COV) and SARS-COV. However, no data is available on the effect of cyclosporine on SARS-CoV-2.<sup>[36]</sup>

Targeted treatment directed against type 2 inflammation as seen in AD, like dupilumab, is not considered to increase

the risk of viral infections.<sup>[37]</sup> Availability and cost may restrict its use in India. It may be safer than cyclosporine, but the theoretical benefit is not established by robust clinical data.<sup>[35]</sup>

### Miscellaneous Conditions

Erythema multiforme and acute generalized exanthematous pustulosis like eruption have been reported as a cutaneous manifestation of COVID-19.<sup>[38-41]</sup> In an appropriate clinical setting, coexisting COVID-19 has to be ruled out. Other severe adverse cutaneous drug reactions, like Stevens Johnson syndrome- toxic epidermal necrolysis may require the use of immunosuppression/immunomodulation. This shouldn't be a great cause of concern, however, as they are generally short-lasting after the prompt withdrawal of triggering agents. They can be managed with cyclosporine and high dose intravenous immunoglobulin.

In India, reactions of leprosy may be common and may require immunosuppression. The reader can peruse the recently published recommendations.<sup>[42]</sup>

### Conclusion

Patients with autoimmune/immune-mediated skin diseases necessitating immunosuppressive therapy can continue their treatment even during the current COVID-19 outbreak, thereby preventing disease flares resulting in a poor quality of life, sequelae, and increased need for health care usage. Initiation of a therapeutic regimen including immunosuppressives should be based on informed consent, benefit-risk-analysis, and detailed patient evaluation.<sup>[30]</sup> Counseling to enforce the practice of good infection prevention measures such as hand hygiene and respiratory etiquettes, social distancing, and the use of telehealth resources should be provided.

### Disclaimer

Our understanding of COVID-19 is rapidly evolving. So is the use of immunosuppressives in dermatologic and other indications during COVID-19 pandemic. The general recommendations here are based on available evidence. The evidence may change over time and the reader need to keep self-updated on developments. The reader may apply clinical judgment in treating patients.

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