

Psoriasis Management During the COVID-19 Pandemic: Recommendations by SIG Psoriasis (IADVL Academy)

Introduction

Most of the psoriasis patients will be worried whether they have to continue the existing therapy, whether discontinuing the existing therapy can worsen their psoriasis during this COVID-19 pandemic or the medications prescribed for psoriasis or the psoriasis disease itself can put them at increased risk of contracting the COVID-19 infection. For the treating physician doubts exist regarding whether systemic medications which have immunomodulatory or immunosuppressive properties and the existing comorbidities can make the psoriasis patients more susceptible to COVID-19 infection.

The COVID-19 pandemic caused by the novel SARS-CoV2 virus has been observed to result in an intense immunological response resulting in a cytokine storm and a systemized inflammatory response resulting in micro thrombi formation in some patients.^[1] Milder forms of psoriasis may not effect a change in treatment strategy, but in patients with moderate to severe psoriasis on systemic treatment with non-biologic agents careful consideration of co-morbidities, risk of COVID-19 infection, and the right measures to control psoriasis is required to decide the management of psoriasis. However, in a psoriatic patient on biologic disease modifying drugs (bDMRDs) or in whom they are being contemplated, the possibility of COVID-19 infection presents as a dilemma. On one hand, the cytokine storm which occurs in COVID-19 patients is to certain extent similar to cytokines worsening psoriasis

and on the other hand biologics which may block the action of these cytokines at the same time can block the protective immunological response against the virus.^[1,2]

Brief Pathophysiology of Sars-CoV 2 (COVID-19)

Understanding of the pathophysiological changes in COVID-19 early in the pandemic was extrapolated from other corona virus infectious syndromes, the middle east respiratory syndrome, and severe acute respiratory syndrome.^[1] SARS-CoV-2 infection activates both innate and adaptive immune response. Corona virus infection results in suppression of interferon (IFN) production early in the disease, followed by a dysregulated, hyper-immune secondary immune response with rise in proinflammatory cytokines interleukin (IL)-6, IL-1 β , IL-2, IL-10, IL-17, and tumor necrosis factor (TNF)- α and a decreased IFN- γ . The excessive pro-inflammatory host response, the so-called "cytokine storm," induces an immune pathology resulting in widespread organ damage due to plasma leakage, vascular permeability, and disseminated vascular coagulation, with severe acute respiratory syndrome in form of pneumonitis, acute respiratory distress syndrome (ARDS), respiratory failure, multiorgan failure, and possibly death.^{[Figure]^[3]} Clinical manifestations range from an asymptomatic phase with apparent recovery or a sudden life-threatening deterioration due to a rapid hyperinflammatory response at the initial stage. Approximately, 80% of

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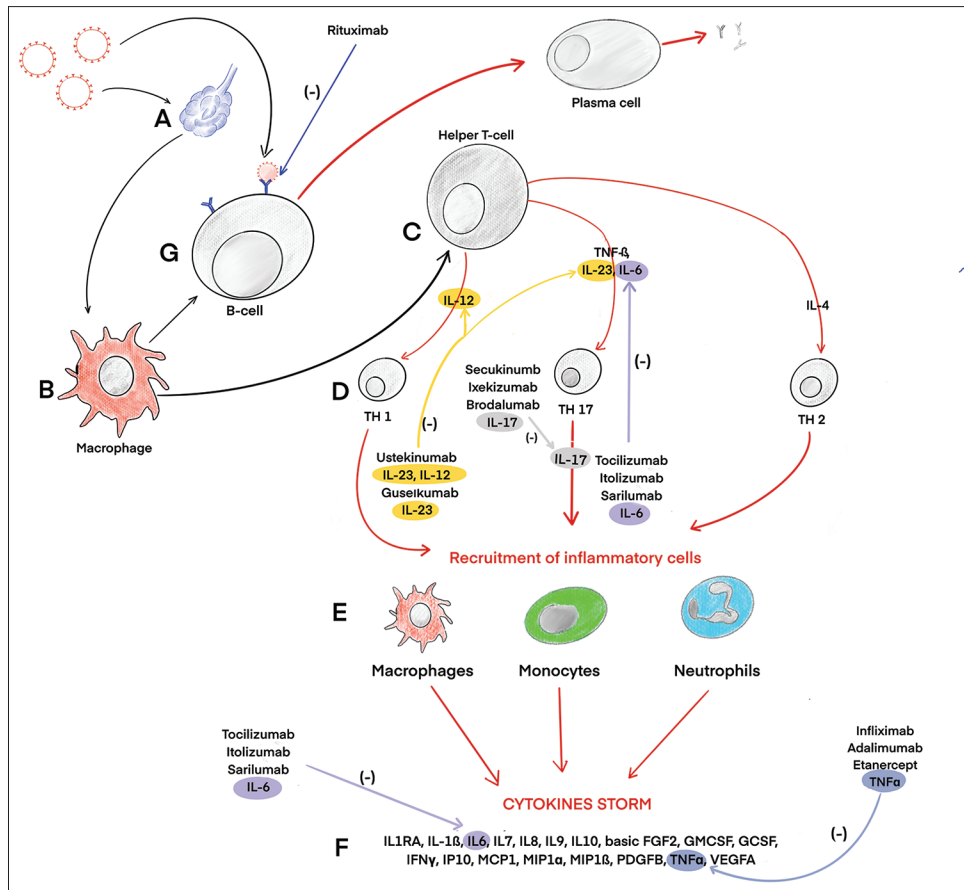


Figure 1: Cytokine flow chart (Diagram credit: Dr Sandeep Arora) SARS CoV2 virion in environment reaches the A. Alveolus where it enters the alveolar cell lining with the help of ACE2 receptor. B. Macrophages process and presenting the viral components to T and B cell C. T cell differentiation leads to activated T cells which induce D. Th1, Th2, and Th17 response E. Cytokines released promote an influx of inflammatory cells: neutrophils, monocytes, and macrophages F. Rapid cytokine release and further recruitment leads the cytokine storm. G. Macrophage also causes activation of B cells causes release of antibodies which help neutralize the virion * Release of ILs (6,12,23,17, TNF cause psoriasis flares. They can also be inhibited by monoclonal antibodies which are used to treat psoriasis. These monoclonal antibodies are marked at specific sites in the figure

COVID-19 patients are asymptomatic or have mild to moderate symptoms, approximately 15% develop severe pneumonia and about 5% develops ARDS, septic shock with multiple organ failure. The common symptoms of COVID-19 are fever, fatigue, and respiratory symptoms, including cough, sore throat, and breathlessness.^[3-5]

The impact of SARS-CoV 2 (COVID-19) on psoriasis and vice versa

The above changes present two dilemmas to the dermatologist treating a patient of severe psoriasis with immunosuppressives, particularly bDMRDs. First the biologics not only have the potential to block the proinflammatory cytokines but also block the host immune response. Emerging data suggest that there is little support to stop biologics in a psoriasis patient only on account of risk of COVID-19 infection and in fact, therapeutic attempts to counter the above mentioned cytokines are being reported with anti-TNF α inhibitors, anti-IL-1,6, 17, and Janus kinase inhibitors in COVID-19 patients [Figure 1]. Associated organ damage, such as viral myocarditis also appears driven by a strong IL-17 response, possibly

resulting in use of anti-IL-17 molecules which can target both psoriasis and COVID-19.^[4,5]

However, it's unclear whether biologics will increase the chances of COVID-19 infection due to attenuation of the initial host response. Anti-TNF- α agents block a central immunological response, so there is a definite risk of increased infections. In contrast, Secukinumab selectively binds to IL-17A, and does not affect other essential Th17 functions, like IL-22 and TNF release. Therefore, Secukinumab carries lower risk of infection compared with anti-TNF- α therapies. On the contrary, Ustekinumab inhibits IL-12 and IL-23. Since IL-12 plays an important role in protection against viral infections, increased susceptibility to viral infections is expected.^[6]

Second, the early clinical manifestations of COVID-19 and side effects of some bDMRDs share the spectrum of upper respiratory tract infection symptoms.

Another aspect of psoriasis management in the background of COVID-19 pandemic is the need for frequent visits to health care facilities by psoriasis patients for follow-up

and investigations, especially those on systemic therapy like methotrexate, cyclosporine, etc., and consequently the higher risk of exposure to COVID-19.

General measures

1. In the present scenario of COVID-19 pandemic, patients with psoriasis should take common sense measures and precautions to lower the risk of becoming infected with SARS-CoV-2, (COVID-19) illness.
1. They should always wear face coverings/masks in public places, maintain physical distancing, and wash hands regularly with soap and water and use hand sanitizers frequently.^[3,7] If a psoriasis patient has had close contact with COVID-19 infected person and/or experiences signs or symptoms of COVID-19 infection, then the patient is advised to stay home (14 days of home quarantine for contacts at present, subject to direction of the public health authorities) without going out and should seek medical attention without fail.^[7]
2. Although there are no specific evidences available about non-pharmacological interventions like weight reduction, lifestyle modification, psychotherapy, stress reduction techniques in psoriasis patients in relation to COVID-19, these are likely to have a beneficial effect for psoriasis as well as for the immune status because of improvement is the status of co-morbidities and hence recommended.
1. It is not clear whether patients with psoriasis and/or psoriatic arthritis are at increased risk of contracting SARS-CoV-2 or having a worse course of COVID-19 illness.^[7]
2. Psoriasis patients on immunosuppressives should practice use of masks and social distancing as recommended. Psoriasis patients on immunosuppressives and with multiple risk factors like advanced age and cardiovascular conditions should practice “shielding” a step ahead of social distancing where they should avoid going out in public places altogether.
2. The major cause of serious health outcomes and death from COVID-19 illness is due to advanced age (65 years or more) and having comorbidities (underlying major medical conditions like diabetes, high blood pressure, bronchial asthma, or obstructive pulmonary disease, chronic kidney disease, chronic liver disease, organ transplant recipient, obesity, heart failure, coronary artery disease, or cardiomyopathies, use of immunosuppressive medications, etc.). It is to be noted that several of these risk factors are components of metabolic syndrome, a known association of psoriasis.^[3,7]
3. Psoriasis patients are not immunocompromised *per se* unless the patient was on prolonged duration of systemic steroids or immunosuppressive medications.
4. In general, patients need not stop their biologic or oral therapies for psoriasis if they do not have any serious comorbidities and if their hematological and biochemical test results like complete blood picture, liver function tests, lipid profile, kidney function tests, etc., and also chest X-ray are normal.^[3,7] For most patients, the benefit of continuing treatments for psoriasis outweighs the hypothetical risks of poor COVID-19-related outcomes.
5. It is recommended that Individuals in high-risk groups should consult/have a conversation with their treating doctors and clear their doubts about whether it is recommended to continue the therapy or alter the therapy.^[3,7]
6. Type of treatment should be guided by the treating doctor considering the patient’s age, sex, disease severity, and underlying medical conditions or comorbidities.^[3]
7. The treating doctor and the psoriasis patient should understand that individuals with newly diagnosed psoriasis and/or psoriatic arthritis and who are not receiving treatment are at increased risk of having serious impact on physical and emotional health, and in case of psoriatic arthritis, permanent joint damage, and disability.^[7]
8. While it is generally advised to hold immune-modulating treatment during an infection, in the case of COVID-19, several different immune-modulating treatments used for psoriasis especially the biologics are being studied in experimental placebo controlled trials to treat or prevent severe COVID-19 illness.^[1]
3. If biologic or oral systemic medication is stopped, then the decision to restart treatment should be made in conjunction with the health care provider keeping in mind the age and sex of the patient, the severity of the disease, the impact of the disease on his physical and mental health, joint involvement, and the presence of comorbidities. Psoriasis may be further exacerbated by the stress that is brought on by the pandemic, and there are also reports of psoriasis flares associated with COVID-19 illness.^[7,8]

Specific Recommendations in COVID-19 Pandemic

There is very little scientifically proven data on the effect of COVID-19 disease on psoriasis and treatment of psoriasis, in general and specifically in special situations like pregnancy or childhood psoriasis and some clinical types like pustular and erythrodermic psoriasis. Limited data in other conditions where similar molecules are used for treatment may be extrapolated to our practice.^[9] Therefore, the recommendations are based on the data available on the treatment options for psoriasis with respect to viral upper respiratory tract infections and other corona virus infections, and early experiences reported in literature since onset of the pandemic, and recommendations of other professional bodies.[Table 1]^[2,3,10-12]

Table 1: Summary of recommended treatment according to types of psoriasis

Type of psoriasis	Recommended treatment in non COVID-19 patients	Recommended treatment in COVID-19 positive patients
Chronic plaque psoriasis	Topicals, acitretin, apremilast, phototherapy/ photochemotherapy, biologics [Figure 1] For- Methotrexate/ cyclosporine- to perform a risk/benefit analysis and if possible decrease the dose/taper	Topicals, acitretin, apremilast Stop methotrexate/ cyclosporine Biologics To be stopped. However in severe psoriasis cases decision regarding continuation to be taken by treating doctor after assessing the risk:benefit ratio, can consider reduction in dose and frequency
Psoriatic erythroderma	To achieve control with cyclosporine/methotrexate and to shift to acitretin/biologics as early as possible	Biologics/acitretin
Generalized pustular psoriasis	Acitretin	Acitretin
Nail psoriasis	Contraindications or poor response- cyclosporine/ methotrexate/biologics	Topical formulations, retinoids
Psoriatic arthropathy	Topical formulations, intralesional injections, retinoids Biologics after risk-benefit analysis	Topical formulations, retinoids
Childhood psoriasis	Biologics, apremilast	Apremilast, biologics- decision by treating doctor after assessing the risk:benefit ratio
Psoriasis in pregnancy	Topicals+ NBUVB After risk-benefit analysis- cyclosporine	Topicals For biologics- decision by treating doctor after assessing the risk:benefit ratio

Psoriasis in COVID-19 Negative Patients

Risk of COVID-19 infection

1. If a psoriasis patient is not taking an immunosuppressive treatment and is free from other underlying diseases, then there may be “minimal additional risk” of them contracting SARS-CoV-2 relative to the rest of the population.
2. Individuals over the age of 60 years and/or patients with comorbid conditions including smokers, cardiovascular diseases, diabetes, hepatitis B, chronic obstructive pulmonary disease, chronic kidney diseases, and cancer have a higher risk for developing a more serious course of the illness after infection with COVID-19. This is important as many of these comorbidities are independently associated with psoriasis.^[3]
3. Patients with severe psoriasis on immunosuppressive therapies and those with other medical conditions are probably are at a higher risk of infection and have increased risk of severe COVID-19 infection.
4. Hydroxychloroquine should preferably be avoided for COVID-19 prophylaxis in psoriasis patients.^[7]

Decision on continuation of treatment

1. It is not recommended that psoriasis patients stop their treatment unless they have an active infection.^[3]
2. Psoriasis patients in high risk groups should consult

their health care provider about whether to continue or alter therapy.

3. Factors to be taken into account for all psoriasis management decisions in consultation with the patient:^[3]
 - a. The specific treatment/biologic being used
 - b. The age, disease characteristics, and co-morbidities of the patient
 - c. Chances of exposure of the patient to COVID-19.
 - d. Patient’s specific situation and concerns.

Topical Therapy and Non-Biologics

1. Topical therapies can be continued.
2. In contrast to immunosuppressive and anti-metabolites like methotrexate, cyclosporine, azathioprine, mycophenolate mofetil etc., retinoids like acitretin and isotretinoin appears to be safer.
3. Narrow band UVB therapy (NBUVB) and psoralen UVA (PUVA) therapy appear to be safe. However, there are practical difficulties of using the same chamber for multiple patients, which requires disinfection of the chamber, after every patient, in addition to the risk of infection due to frequent visits to the health care facility.^[7] Therefore, oral PUVASOL will be a safer option for patients with more than 10% body surface area (BSA) involvement after careful counseling regarding feasibility during the first visit. Hand-held NBUVB devices for use in

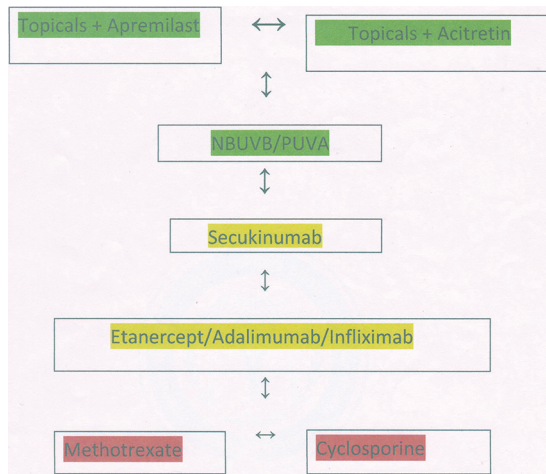


Figure 2: Algorithm for treatment of psoriasis vulgaris patients not infected with COVID-19 (only biologics available in India have been included and since infliximab is an infusion, admission/day care is needed with associated risk of COVID-19 infection due to frequent and prolonged visit to health care facilities)

home can be considered for patients with less than 10% BSA if there is insufficient response to topical therapy alone. Patients who are unable to afford a hand-held NBUVB device can be counseled for topical PUVASOL.

4. Apremilast has been proven to be safe in the setting of viral infections like HIV, hepatitis B, hepatitis C. Inhibition of phosphodiesterase 4 results in high levels of cyclic AMP, which in turn decreases inflammatory cytokines like TNF α . Similarly, animal experiments have shown IL-6 inhibition by apremilast. Therefore, this anti-inflammatory activity of apremilast could be helpful to prevent the dreaded “cytokine storm” of COVID-19 infection.^[13] Although data specific to COVID-19 are still limited, apremilast has shown the best safety profile among systemic treatments for psoriasis in patients infected with COVID-19, as well as lowest infection rate among susceptible psoriasis patients. Apremilast does not affect B cells, T cells, IgG, or IgM and long-term safety studies have shown that it has a lower risk of infection and infestations.^[14] Therefore, along with acitretin, apremilast appears to be the very safe for treatment of psoriasis in the present scenario, even in patients infected with COVID-19, and could even inhibit “cytokine storm.”
5. Nonbiologic medications, including small molecule inhibitors and immunosuppressants, are easier to stop and restart due to shorter half-life.^[15]
6. Hydroxyurea has been used as a second line drug for psoriasis to be used in patients with contraindications to first line drugs. The main side effect of hydroxyurea is myelosuppression. It has been recommended in HIV positive psoriasis patients and is being used in sickle cell anemia patients to reduce their need for blood transfusion in the backdrop of COVID-19 pandemic.^[16,17] Therefore, based on available evidence,

it should be safe to use hydroxyurea to treat psoriasis during COVID-19 pandemic.

7. Others therapies: There are few reports of effectivity of other non-traditional medicines like systemic curcumin, a turmeric derivative, omega 3 fatty acids, and vitamin D in the treatment of psoriasis.^[18-20] As the evidence of efficacy of these treatments are limited, these can be considered as adjuvant therapy in psoriasis. As these are not immunosuppressants and in fact, there are speculations of beneficial effect of these compounds for COVID-19, these can be deemed to safe to use in the current scenario.

Biologics

1. Biologics have a longer half-life. Treatment interruption of some biologics can result in loss of response when reintroduced or result in the formation of antibodies to the discontinued biologic.^[3,15,21]
2. Compared to traditional immunosuppressive agents, biologics tend to be more targeted and do not cause global immunosuppression.^[3,15]
3. Among biologics, for tumor necrosis factor blockers, overall infections and upper respiratory infections were increased by up to 7% compared with placebo, except for etanercept (showed no increase).^[21]
4. IL-17 blockers showed increases in overall infections of up to 11%, but majority of those were candidial infections. Upper respiratory infections were increased slightly for secukinumab.^[21]
5. Ustekinumab showed a small increase in overall infections but not in respiratory tract infections.^[21]
6. Literature available at present shows that biologics did not increase the risk of SARS-CoV-2 infection among psoriasis patients and in psoriasis patients infected with SARS-CoV-2 did not increase the severity of illness.^[22]
7. Treatments administered orally or subcutaneously rather than IV infusion will minimize the contact of the patient with health care facilities and minimize chances of exposure to infections [Figure 2].

Initiation of new treatment

1. The benefit-to-risk ratio of any new immunosuppressive treatment for psoriasis patients with comorbidities should be carefully decided on a case-to-case basis.

COVID-19 Positive Psoriasis Patients

4. For psoriasis patients diagnosed with COVID-19 disease, immunosuppressive medications like methotrexate and cyclosporine should be stopped, whereas retinoids and apremilast^[14] can be continued along with topical therapy. Retinoids and acitretin can be administered in the recommended dosage. Cyclosporine is an immunosuppressive and most of the recommendations advice cautious initiation of cyclosporine, in psoriasis patients from areas with high COVID-19 prevalence

and stopping cyclosporine in the event of exposure to a confirmed COVID-19 patient. However, the primary molecular target of cyclosporine is cyclophilin, which is needed for replication of many virus. So, cyclosporine has been shown to inhibit influenza A virus and hepatitis C, hence could be having beneficial effect during COVID-19 infection. Recent evidence showed that cyclosporine did not increase the severity of COVID-19 infection.^[23] Although there is lack of specific data regarding biologics in COVID positive patients, a cautious approach is warranted and biologics should be stopped. However, in severe cases of psoriasis, the decision regarding continuation of biologics can be taken depending upon the severity of illness by the treating physician including in dose and frequency.^[3]

5. A preliminary analysis of the first 200 cases out of the 488 cases reported so far in PsoProtect (Psoriasis Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection), most of them from Europe, shows that for majority of the psoriasis patients the severity of psoriasis remained unchanged during COVID-19 infection. More than 50% of them were on biologics at the time of COVID-19 infection. Out of the patients on biologics, for 55% of those patients biologic medications were stopped. Only 0.03% of the psoriasis patients succumbed to COVID-19^[24]
6. Systemic steroid is being used in the treatment of COVID-19 illness, for patients with moderate to severe disease and with persistently raised inflammatory markers. Steroid withdrawal is known to be associated with psoriasis flares. However, since for majority of COVID-19 patients the duration of systemic steroid therapy is short the risk of rebound flare is small.^[7] However, if steroid therapy is prolonged for COVID-19 in a patient of moderate to severe psoriasis, slow tapering of steroid is recommended with simultaneous administration of systemic medications for psoriasis as mentioned above.
7. Hydroxychloroquine should preferably be avoided in psoriasis patients with COVID-19.^[7]

Different Morphological Types and Special Scenarios

Psoriatic erythroderma- Since this is a type of severe psoriasis treatment has to be initiated with cyclosporine/methotrexate after a risk-benefit analysis and effort should be made to quickly bring the disease under control and maintain the patient on acitretin/biologics. In these patients the comorbidities of the patient have to be carefully evaluated and taken into account for decisions related to treatment.^[13,25]

Generalized pustular psoriasis- Acitretin is effective as a monotherapy in generalized pustular psoriasis. In case of contraindications or poor response cyclosporine/methotrexate/biologics can be considered after a risk-benefit

analysis and consideration of co-morbidities.^[3] Systemic steroids can be used in life-threatening generalized pustular psoriasis for quick control of the disease but it should be always be given under cover of above-mentioned systemic treatments and tapered very slowly to prevent disease flares.

Nail psoriasis- Topical formulations and intralesional injections can be continued. Among non-biologic treatment retinoids and apremilast are safe, whereas it will be preferable to avoid immunosuppressives like methotrexate. Administration of biologics should be undertaken after a risk-benefit analysis taking into account the severity of nail involvement and urgency of treatment.^[26]

Psoriatic arthropathy- As biologics and apremilast are more targeted and do not cause global immunosuppression, they are safer than methotrexate.^[14,15,27] Among the biologics etanercept appears to be safer.^[20] Chronic administration of systemic corticosteroids should be avoided for psoriatic arthritis as in such patients COVID-19 infection is associated with worse outcome.^[7]

Childhood psoriasis-Mild psoriasis in children should be managed with topical treatment. NBUBV for children with moderate to severe psoriasis can be considered after careful assessment of the risks of frequent hospital/clinic visits. Hand-held NBUBV devices can be considered for children with less than 10% BSA involvement if there is insufficient response to topical therapy alone. Methotrexate/retinoids/cyclosporine/biologics can be considered for children with psoriasis who cannot be managed on topical treatment alone, but the target should be achieving quick control and remission of the disease. Among biologics, adalimumab (≥ 4 years), etanercept (≥ 6 years) is recommended.^[28]

Psoriasis in pregnancy: Pregnant ladies could be at a higher risk of severe illness after infection with COVID-19.^[29] Mild psoriasis in pregnancy can be managed with topical therapy. Narrow band UVB therapy for pregnant patients with extensive but stable chronic plaque psoriasis could be offered after a careful consideration of the risks of frequent hospital/clinic visits. Cyclosporine should be considered in severe unstable psoriasis or in pustular psoriasis on a case to case basis after detailed counseling of the patients and considering the risk-benefit ratio.^[28] Methotrexate, acitretin, isotretinoin are contraindicated in pregnancy. Biologics are pregnancy category B drugs and British and European guidelines recommend discontinuing biologics prior to conception.^[30] However, if at all biologics are used in psoriasis patients in pregnancy TNF- α blockers should be preferred because of availability of relatively more long-term data and among TNF- α blockers, etanercept has the advantage of less placental transfer and lesser contact with health care facility due to subcutaneous administration.^[31] Even then, it will be preferable to stop biologic therapy in the second

or third trimester to minimize fetal exposure and limit the risk to the newborn. However, biologics can be restarted or continued during breastfeeding.^[28]

COVID-19 vaccine and biologics: Although there are several candidate vaccines for COVID-19, none are approved at present. Live vaccines are contraindicated for patients on biologic therapy and biologic therapy should be stopped 6-12 months before giving a live vaccine. This has to be taken into account for psoriasis patients on biologics as and when a COVID-19 vaccine becomes available.^[28]

Role of teledermatology in psoriasis patients during COVID-19 pandemic.

Telemedicine has been given legal validity in light of the COVID-19 pandemic and Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) has come forward with a directive on teledermatology services.^[32] In general, teledermatology is more suitable for follow-up of patients rather than management of new patients.^[32] Since a large number of psoriasis patients have metabolic syndrome, which can result in worse prognosis in the event of COVID-19 infection, teledermatology can be an excellent tool to follow-up psoriasis patients on treatment, to make minor changes in their treatment regimen without exposing them to the risk of infection inherent in a physical consultation. Even, teledermatology can be used to triage some new patients, and in provisionally diagnosed cases with mild psoriasis, topical treatment can be prescribed as a temporary measure till a physical consultation is feasible.^[7]

Significant knowledge gaps exist regarding several aspects of COVID-19 pandemic caused by novel SARS-CoV2 virus and even after almost 10 months since the onset of the pandemic, there is limited specific clinical data. This has resulted in rapidly changing guidelines and recommendations, as new data becomes available. So, the above-mentioned recommendations are based on our knowledge at present and subject to revision.

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Conflicts of interest

There are no conflicts of interest.

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