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Systemic immunobiological, immunosuppressant, and oncologic agents for the treatment of dermatologic diseases during the SARS-CoV-2 (COVID-19) pandemic emergency: A quick review for a quick consultation

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Abstract

The precision medicine era has helped to better manage patients with immunological and oncological diseases, improving the quality of life of this class of patients. Regarding the management of these patients and positivity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), currently, limited data are available and information is evolving. In this quick review, we have analyzed the mechanisms of action and related infective risk of drugs used for the treatment of immune-mediated and oncologic skin conditions during the daily clinical practice. In general, immunosuppressant and antineoplastic agents for dermatologic treatments do not require suspension and do not require special measures, if not those commonly observed. In the case of a coronavirus disease (COVID-19) patient with complications (such as pneumonia, respiratory failure), treatment suspension should always be considered after taking into account the general condition of the patient, the risk-benefit ratio, and the pathophysiology of COVID-19 infection. The COVID-19 emergency pandemic does not imply undertreatment of existing skin conditions, which together with the SARS-CoV-2 infection may jeopardize the patient's life.

KEYWORDS

biologics, COVID-19, dermatologic treatments, immunosuppressants, SARS-CoV-2, skin disease, therapy systemic

1 | INTRODUCTION

In December 2019, a novel and highly pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an outbreak in the city of Wuhan Province of Hubei, China, which soon spread nationwide and spilled over to other countries around the world. The virus was isolated from lower respiratory tract samples of infected patients and the resulting disease was termed as coronavirus disease (COVID-19).[1] Cases of novel SARS-CoV-2 infection have included rapidly progressive lower respiratory tract disease resulting in respiratory failure, development of acute respiratory distress syndrome (ARDS), and prolonged intensive care unit admission. Up to date, only few cases of skin involvement have been reported and the reason for this is probably related to the ability of this virus to bind ACE2 receptor expressed mainly on the pulmonary alveoli epithelium and not on keratinocytes' surface.[2]

In this context, what can be the role of dermatologists for patients that need systemic treatments with immunobiological, immunosuppressant, and oncologic agents? Given the high infectivity of SARS-CoV-2, it is likely that many dermatological patients will be infected; consequently dermatologists will have to manage the possible skin component of the infection and tailor the treatment of possible underlying skin condition accordingly.

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Several dermatological patients are treated with immunobiologic and immunosuppressant therapies as well as with antineoplastic drugs. For this reason, it is important to choose the right way to manage these patients.

The immunologic response to SARS-CoV-2 infection, like many other viruses, is characterized by the robust production of pro-inflammatory cytokines.[3] Several cytokines are involved in the immune response against viral infections, such as interleukin (IL)-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, granulocyte macrophage-colony stimulating factor (GM-CSF), interferon γ (IFNγ), tumor necrosis factor α (TNFα), IP10, MCP1, MIP1A, and MIP1B[4]; among these, several mediators of inflammation are produced by T helper type 17 (TH17) lymphocyte and, at the same time, IL-1β and TNFα promote TH17 responses and vascular permeability and leakage. TH17 cells themselves produce IL-17, GM-CSF (GM-CSF is mainly associated with TH1 cells), IL-21, and IL-22.[5] An important role is played by B-cells and antibodies that are able to reduce the viral load and contribute to the resolution of infection.[6]

The cytokine deregulation in the immune response to SARS-CoV-2 is thought to contribute to the pathogenesis of the infection, but the understanding of the complex interactions of cytokines and SARS-CoV-2 still remains a challenge. The modulation of cytokines' pro-inflammatory effect is important to prevent lung damage, in which cytokine storms play a pivotal role. For this reason, the efficacy of various anti-inflammatory and immunobiologic molecules, such as tocilizumab (anti-IL-6), is being evaluated as treatment for COVID-19 patients with acute respiratory failure.[7]

Several drugs are used for autoimmune and immunomodulated dermatological diseases, and this pandemic prompted us to ask ourselves a question: Is it time to limit treatment with immunosuppressant and immunobiologic drugs? Is it safe to treat patients with oncological drugs for skin tumors? In this quick review, we have analyzed the mechanisms of action and related infective risk of drugs most commonly used during the dermatological daily clinical practice for autoimmune and oncological skin conditions.

2 | IMMUNOSUPPRESSANT AGENTS

Currently, there are no data describing the benefits or risks of stopping immunosuppressants during the COVID-19 outbreak. Indeed, understanding the physiology and mechanisms of these agents can aid in the discussion with patients. Concerning patients under treatment with immunobiologic and immunosuppressant agents, the European Academy of Dermatology (EADV) has formed several task forces to assess the security of dermatologic treatments. In general, extra-precautions are being suggested for patients taking immunosuppressant therapies, which should not be suspended.[8] However, the British Association of Dermatologists (BAD) has proposed different recommended behaviors according to the therapy and patient status, with a specific attention for "high-risk" patients as the ones under treatment with rituximab, infliximab, cyclophosphamide, and corticosteroid dose of ≥5 mg plus at least one other immunosuppressive medication or corticosteroid dose of ≥20 mg.[9] The American Academy of Dermatology(AAD) has divided patients whether they are ongoing immunosuppressant therapy or planning immunosuppressant therapy.[10] In the former category, if patients have not tested positive or exhibited signs/symptoms of COVID-19, there is insufficient evidence to recommend discontinuation of systemic immunosuppressive agents. However, for patients on systemic immunosuppressive agents who have tested positive for COVID-19 or exhibit signs/symptoms of COVID-19, the AAD generally recommend to discontinue or postpone the systemic immunosuppressive agents until the patient recovers from COVID-19. In any case, the AAD guidelines generally advice for patients being considered/planning for systemic immunosuppressive agents to always consider the risk vs benefits on a case-by-case basis. The Australian/New Zealand consensus statement highlights that in patients with suspected or confirmed COVID-19 disease, all immunomodulators used for skin diseases should be immediately withheld, with the possible exception of systemic corticosteroid therapy, which needs to be weaned.[11] For patients who develop symptoms or signs of an upper respiratory tract infection, but COVID-19 is not yet confirmed, consider dose reduction or temporarily cessation for 1 to 2 weeks. In otherwise healthy patients, immunomodulators and biologics should be continued.[11] Finally, The National Institute for Health and Care Excellence (NICE) 169 guidelines mainly refer to the BAD guidelines.

In this regard, a good starting point to evaluate immunobiologic and immunosuppressants safety during the daily clinical practice at the time of the COVID-19 pandemic would be the review of the mechanism of action and the evidence from previous studies for each category of drugs. This is to avoid treating patients with such drugs that are at risk of developing important SARS-CoV-2-related complications and also to avoid undertreatment with possible re-exacerbation of the underlying dermatological disease. The related recommendations, listed in the following, should be considered as a starting point for future reviews as new dermatological guidelines are updated.

2.1 | Cyclosporine

Cyclosporine is a calcineurin inhibitor and potent immunosuppressive agent used largely against cellular rejection after solid organ transplantation and for therapy of active and recalcitrant rheumatoid arthritis (RA), psoriasis, atopic dermatitis, and other cutaneous conditions. It has profound immunosuppressive properties, particularly affecting T cells and the cellular immune response. Cyclosporine, acting as a calcineurin inhibitor, produces a decrease in T lymphocytes maturation and a reduction of lymphokine levels, including IL-2.[12] Furthermore, it is able to reduce differentiation and clonal expansion of B-cells, ultimately reducing the production of immunoglobulins.[13] In line with the "EULAR Guidance for patients COVID-19 outbreak," patients already under treatment should not suspend it, in order to avoid an exacerbation of the underlying disease[14] (Table 1). Interestingly, cyclosporine has demonstrated antiviral activity against

TABLE 1 Immunobiological and immunosuppressive agents

Drugs	Target	Rationale	Risk of infection	Immune hyper-activation	Recommendation[a]
Cyclosporine	CNI	↓ LT, IL-2	+/–	–	No evidence for a preventive suspension[d]
Metotrexate	DHFR	↓ LT	+	–	PTT advised. No evidence for a preventive suspension.[d]
Mycophenolate Azathioprine	DNA DNA	↓ WBC ↓ WBC	+ +	– –	PTT advised. No evidence for a preventive suspension.[d] PTT advised. No evidence for a preventive suspension.[d]
Adalimumab Etanercept Infliximabb Golimumab Certolizumab	TNFα TNFα TNFα TNFα TNFα	↓ TNFα	+	–	PTT advised, above all for Infliximab.[b] No evidence for a preventive suspension.[d]
Ustekinumab	IL-12/23	↓ IL-12/23	–	–	No specific recommendations. No evidence for a preventive suspension.[d]
Secukinumab Ixekizumab Brodalumab	IL-17A IL-17 IL-17RA	↓ IL-17 ↓ IL-17 ↓ IL-17	–	–	No specific recommendations. No evidence for a preventive suspension.[d]
Guselkumab Tildrakizumab	IL-23 IL-23	↓ IL-23 ↓ IL-23	–	–	No specific recommendations. No evidence for a preventive suspension.[d] Due to lack of data compared with ustekinumab, greater care must be taken.
Apremilast	PDE-4	↑c-AMP, IL-10 ↓ cytokines	–	–	No specific recommendations No evidence for a preventive suspension.[d]
Dupilumab	IL-4Rα	↓ JAK–STAT ↓ IL-4, IL-13	–	–	No specific recommendations No evidence for a preventive suspension.[d]
Tofacitinib Ruxolitinib	JAK1-3 JAK1-2	↓ IL-17A/F, IL-15, IL-22 ↓IL-6, IL-12, IL-23	+/– +	–	PTT advised. No evidence for a preventive suspension.[d] PTT advised. No evidence for a preventive suspension, however, closer monitoring of patients compared with tofacitinib is appropriate.
Omalizumab	FcεRI	↓ activation basophils and mast cells	–	–	No specific recommendations. No evidence for a preventive suspension.[d]
Colchicine	Tubulin	↓ neutrophil and lymphocyte function	+/–	–	No specific recommendations. No evidence for a preventive suspension.[d]
Dapsone	Dihydrofolic acid	↓ MPO, folate	–	–	No specific recommendations No evidence for a preventive suspension.[d]
IVIG	Fc receptor	↓ IAb; cytokines; chemokines; metalloproteinases	–	–	No specific recommendations No evidence for a preventive suspension.[d]
Leflunomide	DNA/RNA	↓ DHODH	+/–	–	No specific recommendations. No evidence for a preventive suspension.[d]
Corticosteroids[c]	GR	↓ inflammation ↑ gluconeogenesis	+	–	Start in necessary and selected cases. High dosages, long-term therapy and a concomitant other immunosuppressive treatment may increase the risk of infection. No evidence for a preventive suspension.[d]
Hydroxychloroquine	Lysosomal pH in APCs	↓ TLR9	–	–	No specific recommendations. It has shown to reduce the SARS-CoV-2 viral load and prevent COVID19 complications (alone or with azithromycin)

(Continues)

TABLE 1 (Continued)

Drugs	Target	Rationale	Risk of infection	Immune hyper-activation	Recommendation[a]
Isotretinoin[e] Acitretin[e] Alitretinoin[e]	RXR, RAR RXR, RAR RXR, RAR	↓ Htert, MMP-9 ↑ apoptosis	–	–	No specific recommendations. No evidence for preventive suspension.[d] Due to the continuous hand-wash and use of disinfectant gels, the use of moisturizers is highly recommended.

Note: Among immunosuppressant agents, only BAD guidelines cite mesalazine and sulfasalazine (both rarely used in dermatology practice), suggesting no specific indications and recommendations, but only social distancing.

Abbreviations: APCs, antigen-presenting cells; c-AMP, cyclic adenosine monophosphate; CNI, calcineurin inhibitor; DHFR, dihydrofolate reductase; DHODH, dihydroorotate dehydrogenase; FcεRI, high-affinity IgE receptor; GR, glucocorticoid receptor; hTERT, telomerase reverse transcriptase; IAb, idiopathic antibodies; IVIG, intravenous immunoglobulin; JAK, janus kinase/signal; LT, T-cell lymphocytes; MMP-9, metalloprotease (gelatinase); MPO, myeloperoxidase; PDE-4, phosphodiesterase-4; PTT, pre-therapy screening with SARS-CoV-2 test and evaluate risk-benefit of the treatment; RXR, retinoid X receptors; RAR, retinoid A receptors; WBC, white blood cells.

[a]Always in association with the basic recommendations to the general population according to the WHO.

[b]High-risk patients according to BAD guidelines.

[c]BAD guidelines define as high-risk patients, the ones under corticosteroid dose of ≥5 mg plus at least one other immunosuppressive medication or under corticosteroid dose of ≥20 mg.

[d]Except in case of COVID-19 patients with complication (such as pneumonia, respiratory failure), treatment can be suspended, always taking into account the general condition of the patient and the risk-benefit ratio and also the pathophysiology of the worsening of the COVID-19 infection.

[e]Although these drugs are not immunomodulatory drugs, they are reported for their wide use in the daily clinical practice in inflammatory dermatologic diseases.

Hepatitis C Virus (HCV) and can block the replication of nidoviruses (arteriviruses and coronaviruses),[15] but there are no reports about a possible activity against SARS-CoV-2.

2.1.1 | Methotrexate

Methotrexate inhibits dihydrofolate reductase, preventing the reduction of dihydrobiopterin (BH2) to tetrahydrobiopterin (BH4), leading to nitric oxide synthase uncoupling and increased sensitivity of T cells to apoptosis, thereby diminishing immune responses. It also inhibits activation of nuclear factor-κB (NF-κB) by increasing both adenosine release and activation of adenosine receptor A_{2a} and by inhibiting the reduction of BH2 to BH4. Methotrexate is generally the first-line therapy for RA, psoriatic arthritis, cutaneous psoriasis, and other forms of inflammatory arthritis, and it enhances the effect of most biologic agents in RA.[16] Since methotrexate is an antimetabolite, its action is carried out by reducing the differentiation and clonal expansion of lymphocytes. Patients scheduled for methotrexate and at risk for exposure per local public health guidance should be screened for SARS-CoV-2 prior to the initiation of therapy in order to guide for a correct decision-making (Table 1). While for patients already under treatment there is no evidence supporting the suspension of treatment, which could cause an exacerbation of the underlying dermatological pathology.[14] In case of COVID-19 infection, the decision of a possible suspension must assess the risk-benefit ratio, based on the severity of the COVID-19 infection and the risk of exacerbation of the underlying dermatologic disease.

2.1.2 | Mycophenolate mofetil and azathioprine

Mycophenolate mofetil and azathioprine inhibit the purine pathway and consequently diminish cell proliferation.[17] Both drugs play a pivotal role in the treatment of various autoimmune diseases, including lupus nephritis and cutaneous immune-mediated diseases. Their action, similarly to methotrexate, is carried out by reducing the differentiation and clonal expansion of lymphocytes. Also in this case, there is no evidence to suspend the treatment in case of COVID-19 infection. Any eventual decision of a possible suspension must be made based on the risk-benefit ratio of both the severity of SARS-CoV-2 infection (eg, pneumonia, respiratory failure) and the possible reactivation of the underlying dermatologic disease (Table 1). A pre-therapy screening with SARS-CoV-2 test is advised, at least during the COVID-19 pandemic emergency.

In conclusion, each drug's mechanism of action, route/frequency of administration, and pharmacokinetics/pharmacodynamics are important to consider when discussing the immunosuppressant agents. These drugs have a short half-life and in case of infection are easier to manage, but nevertheless their action is not specific and less targeted than biological drugs; thus they generally increase the risk of viral infection. In the prevention of SARS-CoV-2 infection and the management of patients with mild symptoms, there are currently no indication for a preventive suspension of these treatments,[14] since possible reactivation of the underlying dermatologic disease may occur. In case of severe COVID-19 patients with related complications (such as pneumonia, respiratory failure), the treatment can be suspended, always taking into account the patient's overall condition and the risk-benefit ratio.

2.2 | Immunobiological agents

2.2.1 | Anti-TNFα

TNFα is a bioactive cytokine responsible for the pathogenesis of inflammation and pain. The rationale of inhibiting TNF-mediated pathways to decrease the inflammatory response has been applied in the treatment of different autoimmune conditions. TNFα inhibitors are most effective for inflammatory bowel disease, RA, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis and ankylosing spondylitis.[18] TNFα inhibitors (eg, adalimumab, etanercept, infliximab, golimumab, and certolizumab) are also immunosuppressive and their chronic use increases the risk of infections,[19] including bacterial pathogens (ie, tuberculosis—except patients treated with etanercept),[20] fungal infections, and viral infections (especially herpes zoster and human papillomavirus).[19] Severe to fatal cases of HBV reactivation have been linked to several anti-TNFα agents.[19] The anti-TNFα inhibitors have little or no effect on HCV levels and have been used safely in patients with chronic hepatitis C.[21]

Biologics have generally a long half-life and can be immunogenic, with the risk that interruption and subsequent restart induces the formation of anti-drug antibodies.[22]Concerning the *Coronaviridae* subfamily, the only superimposable model is that of the H1N1 influenza virus. Overall, the risk of H1N1 influenza in patients receiving anti-TNFα therapy appears similar to that of the background population, with at most a modest theoretical increase in risk of infection or developing severe disease.[23,24] Levels of TNFα have been shown to correlate with symptoms in human,[25] and with the extent of fever and lung disease.[26] On the one hand, viral replication within lung epithelial cells is strongly inhibited by TNFα; on the other hand, this cytokine is a key player in the "cytokine storm" driving the ARDS in severe pneumonia. This last point suggests that anti-TNFα agents might actually be beneficial in the treatment of COVID-19-related severe pneumonia.[27] As of today, there is no evidence for the preventive suspension of anti-TNFα treatments. In the case of COVID-19 patients with complications, such as pneumonia, respiratory failure, treatment can be suspended, once the general condition of the patient, the risk-benefit ratio and also the pathophysiology of COVID-19-related ARDS have been assessed. A pre-therapy screening for SARS-CoV-2 test is always recommended, at least during the COVID-19 pandemic emergency (Table 1).

2.2.2 | Anti-IL-12/23, anti-IL-17, and anti-IL-23

IL-12, IL-23, and IL-17 are crucial for host response to infections and tumors. The drugs targeting these cytokines are widely used in dermatology specially to treat psoriasis. IL-17A is produced by memory effector $CD4^+$ and $CD8^+$ T lymphocytes and is a crucial lymphokine of TH17 cells, which are pivotal for autoimmune inflammatory and immunological processes. In addition, the IL-23/TH17 cell pathway is critical for protective immunity against bacterial and mycotic infections.[28]

Ustekinumab is a fully human IgG1 monoclonal antibody that binds with high affinity to the p40 subunit of IL-12 and IL-23 cytokines, neutralizing their activity and consequently blocking their downstream effects. Current evidence suggests that ustekinumab carries a low risk for serious and opportunistic infection in patients with psoriatic arthritis and can be safely used.[29] There are no specific recommendations regarding SARS-CoV-2 infection and patients should be evaluated as the general population (Table 1).

Secukinumab is a human IgG1κ monoclonal antibody selectively targeting and neutralizing IL-17A; ixekizumab is a humanized IgG subclass 4-kappa (IgG4-κ) anti-IL-17A monoclonal antibody; and brodalumab is a fully human IgG2 anti-IL-17RA monoclonal antibody, which binds with high affinity to human IL-17RA, with consequent inhibition of the IL-17 pathway (in the specifics, brodalumab inhibits the activity of IL-17A, IL-17F, IL-17A/F heterodimer, IL-17C, and IL-25 molecules). All these treatments are effective for both psoriasis and psoriatic arthritis,[30] showing low risk of serious and opportunistic infections. Therefore, to date, there are no specific recommendations regarding SARS-CoV-2 infection, but the World Health Organization (WHO) recommendations for the general population should be always applied (Table 1).

IL-23 is primarily produced by antigen-presenting cells and induces and maintains differentiation of TH17 and TH22 cells, which produce pro-inflammatory cytokines (eg, IL-17 and IL-22).[31] IL-23 is composed of subunits p19 and p40 that bind to the IL-23 receptor (IL-23R) and IL-12 receptor b1 (IL-12Rb1), which results in activation of pro-inflammatory JAK2, TYK2, and signal transducer and activator of transcription (STAT) signaling molecules.[31] IL-23 antagonism blocks downstream effector cytokines observed in psoriasis such as IL-17A, IL-17F, IL-22, and TNF secreted by T cells, natural killer cells, type 3 innate lymphoid cells, neutrophils, and mast cells.[32] Guselkumab is a fully human IgG1 lambda monoclonal antibody that binds to the p19 subunit of IL-23 and inhibits the IL-23-specific intracellular and downstream signaling. Guselkumab is a safe and effective drug for psoriasis as it carries a low risk of serious and opportunistic infection; thus it can be safely used.[33,34] However, although data on the safety of ustekinumab (IL-12 and IL-23 inhibitor) in the setting of HBV infection are available,[34] currently there are little data about guselkumab and tildrakizumab (IL-23 subunit p19 inhibitors). Accordingly, greater care should be taken in patients taking anti-IL-23 inhibitors, although, at the moment, there are no specific recommendations and no evidence supporting preventive suspensions (Table 1).

2.2.3 | Apremilast

Apremilast is a small molecule, which inhibits the enzyme phosphodiesterase-4 (PDE-4). PDE-4 is responsible for the degradation of cyclic adenosine monophosphate (cAMP), which is an important step in the inflammatory signaling of immune effector cells including T lymphocytes, monocytes, and macrophages. Apremilast therapy has been shown to decrease the level of circulating pro-inflammatory cytokine with a concurrent rare occurrence of

tuberculosis reactivation and severe infections.[35] Recently, apremilast has been suggested to be a safe and effective therapeutic option in HIV- and HBV-positive patients with psoriatic arthritis.[36] Accordingly, there are no specific recommendations to suspend or to not initiate a treatment with apremilast. As for the other biologic treatments, in case of COVID-19 patients with complication (such as pneumonia, respiratory failure), treatment can be suspended, always taking into account the general condition of the patient and the risk-benefit ratio and also the pathophysiology of the COVID-19 infection (Table 1).

2.2.4 | Dupilumab

Dupilumab is a human monoclonal antibody targeting IL4Rα that inhibits the signaling of TH2 cytokines, IL-4, and IL-13, thereby inhibiting receptor signaling downstream the JAK-STAT pathway.[37] It is currently approved for the treatment of atopic dermatitis, moderate to severe asthma, and chronic rhinosinusitis with nasal polyposis. Eosinophilic infiltration and production of TH2 cytokines are critical drivers of these diseases.[37] Despite atopic patients being characterized by an increased risk of respiratory comorbidities and cutaneous infection, this drug is safe and effective. Dupilumab can switch TH2 to TH1 phenotype and this condition could increase response to viral infection.[38] Targeted treatment selectively interfering with type 2 inflammation is not considered to increase the risk of viral infection and might be prescribed without specific recommendation and/or restrictions (Table 1).

2.2.5 | Tofacitinib/ruxolitinib

Tofacitinib is an oral/topical inhibitor of JAK1 and JAK3, which are tyrosine kinases involved in both hematopoiesis and immune response. In the latter case, by blocking the downstream components of the pro-inflammatory signaling pathways, tofacitinib suppresses cytokine-/growth factor-mediated gene expression and the abnormal activation of the inflammatory cascade. In the specifics, tofacitinib suppresses the expression of IL-23 receptor, IL-17A, IL-17F, IL-15, and IL-22.[39] While ruxolitinib acts by inhibiting JAK1 and JAK2 pathways through the block of STAT3 phosphorylation due to IL-6, IL-12, or IL-23, finally resulting in the suppression of pathogenic TH17 cells differentiation.[39] Additionally, ruxolitinib leads also to a dose-dependent decrease in production of IL17, IL-20, and IL-22, also reducing IFN-γ expression.[40] A meta-analysis showed that (based on phase II and III studies, where tofacitinib was administered together with methotrexate or as monotherapy) tofacitinib may increase the risk of infections, including upper respiratory tract infections and nasopharyngitis, with pneumonia and herpes zoster being the most common adverse events causing a discontinuation of treatment.[40] In contrast, a meta-analysis showed that serious infections are not significantly more frequent in tofacitinib-treated patients than in placebo.[41]

Finally, in a study regarding the use of tofacitinib for alopecia areata, mild clinical infections, including paronychia and upper respiratory tract infection, were reported in 25% of patients and only one patient with previous atopic dermatitis and history of herpes zoster experienced uncomplicated dermatomal zoster after 2 months of tofacitinib.[42] Therefore, a pre-therapy screening with SARS-CoV-2 test should be proposed to patients before starting the treatment with tofacitnib. Patients under treatment with tofacitinib should continue the therapy, also in the case of mild COVID-19 infection. Tofacitinib should be suspended in patients with COVID-19-related complications (such as pneumonia, respiratory failure), always taking into account the risk-benefit ratio and a possible exacerbation of the underlying dermatologic disease.

A large phase IV postmarketing study regarding patients under treatment with ruxolitinib reported herpes zoster (8.0%) as the most frequent infection, followed by bronchitis (6.1%) and urinary tract infections (6.0%). In published case reports, the most frequent infections were tuberculosis, HBV reactivation and *Pneumocystis jirovecii* infection.[43] Published data suggest a relevant, increased risk of infection for patients in treatment with ruxolitinib, thus the same recommendations as for tofacitinib should be applied, paying more attention (Table 1).

2.2.6 | Omalizumab

Omalizumab, a recombinant humanized monoclonal IgG antibody targeting free IgEs, is an effective and well-tolerated treatment for patients with chronic spontaneous urticaria. This antibody has an additional plethora of effects aiming at dampening allergic inflammation: decrease expression of high-affinity IgE receptors(FcεRI) on mast cells and basophils, increased eosinophil apoptosis, and decreased antigen presentation to T cells.[44] In conclusion, omalizumab is not associated with an increased risk of infections; instead treatment with omalizumab decreased the duration of rhinovirus infections, viral shedding, and the risk of illness.[45] Therefore, no specific recommendations are needed for patients under treatment with omalizumab (Table 1).

2.3 | Antimalarial agents

During the COVID-19 pandemic emergency, this class of treatment is widely discussed by the International Scientific Community based on the good clinical response of some COVID-19 patients to hydroxychloroquine (HCQ) alone or in combination with azithromycin and low molecular weight heparin.

2.3.1 | Cloroquine/hydroxycloroquine

Cloroquine (CQ) and HCQ are synthetic antimalarial drugs that interfere with lysosomal activity and autophagy, interact with membrane stability, and alter signaling pathways and transcriptional activity, which can result in inhibition of cytokine production and modulation

of certain costimulatory molecules.[46] HCQ is a safe and successful anti-inflammatory agent that has been used extensively in autoimmune diseases and can significantly decrease the production of cytokines and, in particular, pro-inflammatory factors.[46]

CQ, with respect to HCQ, has an additional antiviral activity as it increases endosomal pH, thus hindering several viruses—including influenza A and B, SARS-CoV-2, hepatitis A virus, and the Borna disease virus—which require a low endosomal pH to enter the host cell.[46,47] This suggests that CQ could also inhibit filoviruses' (eg, Ebolavirus) entry into the cytoplasm of susceptible cells and thereby abrogate their infection, since this is dependent on endosomal acidification and the activities of several host endosomal proteases.[46] CQ might also inhibit the assembly and budding of filoviruses—which partly require the late endosome for their assembly[46] (Table 1).

The experimental data in vitro, assessing the anti-SARS-CoV properties of HCQ and reported superiority of chloroquine vs control to inhibit pneumonia exacerbation,[47-51] support the possible use of these drugs in the treatment of COVID-19. Gautret et al conducted a non-randomized open-label trial showing a significant decrease in viral load and carriage duration in COVID-19 patients treated with HCQ (600 mg/day for 10 days).[51] In this regard, HCQ beneficial effects were enhanced when used in combination with azithromycin.[51]

Finally, HCQ in COVID-19 patients may also contribute to attenuate the maladaptive inflammatory response by decreasing the levels of proinflammatory cytokines.[46] On the other hand, Kutlu et al reported a case of psoriasis exacerbation in a COVID-19 patient treated with HCQ and oseltamivir.[52] Indeed, it is known that HCQ induces IL-17 production through p38-dependent IL-23 release, and that patients infected by SARS-CoV-2 have increased plasma concentration of several inflammatory cytokines; these two factors may together increase the risk of psoriasis exacerbation.[52]

2.4 | Colchicine

Colchicine is an alkaloid originally extracted from plants of the genus *Colchicum* (in particular *Colchicum autumnale*) and genus *Gloriosa*. Colchicine is an antimitotic agent: its binding to tubulin inhibits the mitotic spindle formation during metaphase. Colchicine is also an anti-inflammatory drug used for treating inflammatory and auto-inflammatory diseases (ie, gouty arthritis and familiar Mediterranean fever).[53] Indeed, colchicine may inhibit neutrophil and lymphocyte function, inducing an immunosuppressive effect with a reported increased risk of developing pneumonia.[53,54] However, at the same time, it is known that colchicine inhibits the assembly of the NLRP3 inflammasome, and, therefore, reduces the release of IL-1b and other ILs, including IL-6, therefore justifying the start of a clinical trial in Italy on the use of colchicine for treatment of the hyper-inflammatory phase of COVID-19.[55] Therefore, patients under treatment with colchicine should use standard practices including basic hygiene precautions and wear the recommended personal protective equipment as for the general population. In COVID-19 patients with pneumonia, colchicine may contribute to attenuate the inflammatory response (Table 1).

2.5 | Dapsone

Dapsone acts both as an antibiotic, by inhibiting the synthesis of bacterial dihydrofolic acid, and as antiinflammatory, by blocking myeloperoxidase. In dermatology, it is mostly used for inflammatory diseases (such as Hailey-Hailey disease, herpetiform dermatitis, cicatricial pemphigoid). The combination of both anti-inflammatory and antimicrobial effects proves dapsone's safety during COVID-19 pandemic emergency (Table 1).

2.6 | Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is an immunomodulating agent that has multiple effects: modulation of complement activation; suppression of idiotypic antibodies; saturation of Fc receptors on macrophages; and suppression of various inflammatory mediators (cytokines, chemokines, and metalloproteinases).[56]IVIG are sterile, purified IgG products that typically contain >95% unmodified IgG, with intact Fc-dependent effector functions, and only minor amounts of IgA or IgM.[57]No specific recommendations are needed for patients under treatment with IVIG, since there is no increased risk of infection, neither of immune hyper-activation (Table 1).

2.7 | Leflunomide

Leflunomide is an isoxazole immunomodulatory drug, part of the DMARD (Disease Modifying AntiRheumatic Drugs), that inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH) necessary for the DNA and RNA synthesis.[58]

Leflunomide is not frequently used in the dermatological practice, although it can be a valid therapeutic option in psoriatic arthritis. Regarding the risk of secondary infection associated with the treatment with leflunomide, no significant increase in the risk of infections was found.[58,59] To date, no specific recommendations are needed for patients under treatment with leflunomide (Table 1).

2.8 | Corticosteroids

Topical and systemic corticosteroids are widely used in dermatology to treat immune-mediated and oncologic diseases. The main anti-inflammatory effect of glucocorticoids is to inhibit a large number of pro-inflammatory genes (encoding for cytokines, chemokines, cell adhesion molecules, inflammatory enzymes, and receptors) thus addressing the inflammatory process and restoring homeostasis. For this reason, they may increase the risk of viral and opportunistic infections (eg, herpes zoster, tuberculosis, and *Pneumocystis jirovecci* pneumonia). [60] High doses of prednisolone are considered immunosuppressive, but sudden stopping or significant reduction of dose, especially in patients on long-term systemic corticosteroids, is not suggested. The BAD defines high-risk patients as those taking a corticosteroid dose of ≥5 mg plus at one(or more) other

immunosuppressive medication or a corticosteroid dose of ≥20 mg.[9] The Vasculitis Task Force of the EADV highlights that during the COVID-19 pandemic, the use of steroids should be even more restricted when there is not sufficient evidence for their efficacy (such as in most cases of IgA vasculitis or polyarteritis nodosa), while they must not be stopped abruptly and prophylactically in ANCA associated- and other severe systemic vasculitides.[8] Other dermatology societies, and societies of other specialties, recommend patients to discontinue or postpone systemic corticosteroids in the event of COVID-19 diagnosis until the patient recovers from the infection.[61-63] However, the decision to discontinue or maintain treatment must take into account the risk-benefit ratio case-by-case in relation to the risk of SARS-CoV-2 infection.

Despite, in the past, numerous clinical studies have reported the efficacy of glucocorticoids in the treatment of coronavirus pneumonia (ie, SARS and MERS) and influenza pneumonia, there is no evidence from randomized clinical trials to support glucocorticoids treatment for COVID-19 and the benefit from glucocorticoids is likely outweighed by the adverse effects.[64] Therefore, the interim WHO guideline does not support the use of systemic corticosteroids for the treatment of COVID-19-associated pneumonia and ARDS.

In conclusion, there are no specific counter-indications to starting or suspending systemic steroid therapy during the COVID-19 pandemic emergency. The dosage should be always decreased as symptoms of the underlying dermatologic diseases improve, together with appropriate monitoring and prevention of adverse events, especially infections.[65]The risk of infection increases with higher dosages and long-term therapy (Table 1).

2.9 | Retinoids

Although retinoids are not immunomodulatory drugs, they are reported for their wide use in the daily clinical practice for several inflammatory dermatologic conditions. Retinoids are a class of compounds derived from vitamin A or having structural and/or functional similarities with vitamin A. Beside reducing epidermal proliferation and stimulating its differentiation,[66] this class of drugs also decreases inflammation in the epidermis and dermis by interfering with various cytokines. However, in contrast to other systemic antipsoriatic drugs, retinoids are neither cytotoxic nor immunosuppressive.[66] There is no evidence of a worse prognosis for viral infection in patients under systemic retinoids (acitretin, isotretinoin, and alitretinoin). In the general population, the increased frequency of hand washing during this pandemic may cause hand xerosis. Xerosis is a common side effect of systemic therapy with retinoids, which can worsen during this period and therefore requires a correct and continuous use of moisturizers. (Table 1).

3 | ONCO-DERMATOLOGY

In the field of oncodermatology, with the advent of new target drugs, important changes have occurred in the management of skin cancer. The "Precision Medicine Era" helped to better manage patients with melanoma and non-melanoma skin cancer (NMSC), consequently improving their quality of life. Regarding the management of patients with cutaneous malignancies and positivity to SARS-CoV-2, currently, limited clinical cancer-specific data are available and information is evolving.[67] In this regard, on 12th March 2020, the American Society of Clinical Oncology (ASCO) developed a statement with frequently asked questions (FAQs) about the issues and challenges they see emerging while caring for patients with cancer in the context of the coronavirus pandemic.[1] Also in Italy (one of the most involved country with infected SARS-CoV-2 patients and deaths related to COVID-19), the Italian Ministry of Health has published guidance (in Italian) specific to cancer.[68] According to these guidelines and to the present literature, there is no specific evidence of COVID-19 infection complications associated with any systemic cancer therapy regimen.[67] In a prospective cohort of 1571 patients with COVID-19, 18 of which had a prior history of cancer, Liang et al found that patients with a history of cancer had a higher incidence of severe events.[69] However, the same author specified that these 18 patients represent a heterogeneous group and are not an ideal representation of the entire population of patients with cancer.[68,70]

In oncodermatology, two main categories of therapy are currently used: target therapy and immune checkpoint inhibitors.

3.1 | Anti-BRAF target therapy

In melanoma target therapy (ie, anti-BRAF combined with MEK inhibitors), Xu et al reported that these treatments can alter the immunosuppressive cytokine milieu of tumor cells and enhance infiltration of immune effector cells; indeed BRAF inhibition may decrease the levels of immunomodulatory cytokines IL-10, VEGF, and IL-6, showing increased expression of T-cell exhaustion markers like TIM3 and PD-1, allowing tumor cells to escape immune detection.[70] This, on the one hand, translates into a greater infectious risk and a greater viral load in the hosts, on the other, the dampened immune response (especially decreased IL-6 levels) could protect from COVID-19-associated complications (ie, cytokine storm, ARDS).[71,72] However, there are currently no certain data to confirm this assertion. Therefore, the relevant parameters regarding optimizing dose, sequence, and timing of target therapy should be considered in order to maximize the overall antitumor efficacy and minimize the toxicity profiles.[70] (Table 2).

An increased risk of secondary viral infections in patients undergoing target therapy is not currently reported.

3.2 | Immune checkpoint inhibitors

In the time of the COVID-19 pandemic, therapy with immune checkpoint inhibitors (ICI) (ie, ipilimumab, nivolumab, pembrolizumab, and cemiplimab) should be strictly controlled. According to a recent meta-analysis of 125 clinical trials involving 20 128 patients, ICI adverse effects, such as severe myocarditis and pneumonitis, are challenging to diagnose and might not be treated promptly, finally affecting

TABLE 2 Onco-dermatologic drugs during SARS-CoV-2 pandemic era

Drugs	Target	Rationale	Risk of infection	Immune hyperactivation	Recommendation[a]
Vemurafenib Dabrafenib Encorafenib	BRAF BRAF BRAF	↓ IL-10, VEGF IL-6 ↑ TIM3, PD-1	+/.	–	Up to date no evidence for specific recommendations PTT can be discussed in specific cases. No evidence for a preventive suspension[c]
Ipilimumab Nivolumab Pembrolizumab Cemiplimab	CTLA4 PD1 PD1 PD1	↑ IL-6, IFN-γ	–	+	Attention for those patients presenting flu-like symptoms Evaluate pneumotoxicity PTT should be performed No evidence for a preventive suspension[c]
Vismodegib Sonidegib	HHI HHI	↓ IL-6, STAT3	–	–	Up to date no evidence for specific recommendations
Cetuximab	EGFR	↓ TLR	+	–	Increased risk of infection and relative complications PTT should be always performed
Rituximab[b]	CD20	↓ B cells ↓Neutrophils ↓ gamma globulins	+	–	Start in necessary and selected cases. PTT should be always performed Increased risk of infection and relative complications. No evidence for a preventive suspension[c]
Bexarotene	RXRs	↓ IL-4, CCR4 ↓ lymphocytes	+	–	Increased risk of infection and relative complications. A PTT should be always performed No evidence for a preventive suspension[c]
PUVA	DNA	Binds DNA and apoptosis	NR	NR	No specific recommendations No evidence for a preventive suspension[c]
Cyclophosphamide[b]	DNA	Apoptosis	+	–	Start in necessary and selected cases. PTT should be always performed. Increased risk of infection and complications. No evidence for a preventive suspension[c]
ECT Bleomycin Cisplatin	DNA DNA	↑ IL-6, IFN-γ, IL-5, TGF-β, ILD Fibrosis, leukopenia	+ +	+ Undetermined	Avoid, at least during the acute pandemic period. PTT should be always performed. Start in necessary and selected cases (risk-benefit context). PTT should be always performed.

Abbreviations: CCR4, C-C chemokine receptor type 4; HHI, hedgehog inhibitors; ILD, interstitial lung disease; NR, not reported; PTT, pre-therapy screening with SARS-CoV-2 test and evaluate risk-benefit of the treatment; PUVA, psoralene + UVA therapy; RXRs, retinoid X receptors; TLR, Toll-like receptors.
[a]Always in association with the basic recommendations to the general population according to the WHO.
[b]High-risk patients according to BAD guidlines.
[c]Except in the case of COVID-19 patients with complications (such as pneumonia, respiratory failure), treatment can be suspended, always taking into account the general condition of the patient and the risk-benefit ratio and also the pathophysiology of the worsening of the COVID-19 infection.

patients' survival.[73] Indeed, while in this class of patients, the general risk of bacteria and viral infections is low and not widely investigated in literature,[74] an ICI-correlated pulmonary toxicity has been previously reported.[75] The overall incidence rate of ICI-related pneumonitis ranges from 2.5% to 5% with anti-PD-1/PD-L1 monotherapy from 7% to 10% with anti-CTLA-4 + anti-PD-1 combination therapy.[76] Accordingly, it could be reasonable taking into account the risk of treating patients while they are developing an initial form of COVID-19.[76] Besides, a cytokine-release syndrome characterized by elevated levels of IL-6, IFN- γ, and other cytokines, provoking consequences and symptoms related to immune activation is a phenomenon widely present in ICI patients, increasing the risk of leading to acute respiratory distress syndrome or even multiple organ failure.[76] Recently Bersanelli concluded that the hypothesis of a synergy between ICI mechanisms and COVID-19 pathogenesis, both contributing to a noxious immune hyperactivation, cannot be excluded and careful attention should be dedicated in delaying treatment with ICI for those patients presenting flu-like symptoms.[76] (Table 2).

3.3 | Hedgehog pathway inhibitors

Regarding hedgehog pathway inhibitors (eg, vismodegib, sonidegib), the interaction of hedgehog (HH)/glioma (GLI) and pro-inflammatory IL-6/STAT3 signaling synergistically regulates common GLI-STAT3 target genes, thereby supporting cancer growth and survival.[77,78] Therefore,

the persistent production of pro-inflammatory cytokines such as IL-6, TNF, and IL-1 within the tumor and its microenvironment plays a key role in mediating the tumor-promoting effect of inflammation.[78] To this regard, hedgehog pathway inhibitors, by inhibiting HH/GLI pathway, are supposed to reduce inflammatory process, including IL-6 overexpression, usually reported in severe SARS-CoV-2 pneumonia. Therefore, to date, there is no evidence for a greater risk of fatality in patients receiving hedgehog pathway inhibitors. The possible increased risk of viral infections in patients taking hedgehog pathway inhibitors has not been investigated (Table 2).

3.4 | Anti-epidermal growth factor receptor antibodies

Anti-epidermal growth factor receptor (EGFR) monoclonal antibodies offer the potential to improve outcomes in invasive NMSC. In a meta-analysis, Qi et al revealed an increase in the risk of infection following therapy with HER family-directed antibodies.[79] This is determined by the suppression of Toll-like receptors: an important class of immune sensors, expressed on macrophages and dendritic cells, allowing the synthesis of protective antimicrobial molecules such as interferon. These receptors require tyrosine phosphorylation to recruit adaptor proteins, and this process depends on EGFR activation.[79] Dysregulated EGFR function, as during anti-EGFR therapy, of the normal respiratory epithelium and dendritic cells could thus result in an increased risk of severe infection (including viral infections).[79] Therefore, in the light of the coronavirus pandemic, special attention should be paid to this class of patients, as they are considered to be at greater risk of contagion. There are no data, however, on a possible drug-related exacerbated immune response.

At the same time, patients scheduled for anti EGFR therapy and at risk of exposure per local public health guidance should be screened, when possible, for COVID-19 prior to the start of therapy in order to guide decision-making.[67]

3.5 | Rituximab

Regarding the use of rituximab (an anti-CD20 monoclonal antibody), it is known that patients under treatment show an increased risk of bacterial and viral infections due to a variety of mechanisms: prolonged B-cell depletion, B-cell/T-cell crosstalk, pan-hypogammaglobulinemia and late-onset neutropenia.[80] However, it is undeniable that the risk of infections cannot be entirely attributed to rituximab; disease and patient factors are relevant as well, as shown in lymphoma and rheumatic patients.[80] Therefore, patients with cutaneous lymphoma and candidate to rituximab therapy should be screened for SARS-CoV-2 prior to the initiation of therapy in order to guide decision-making (Table 2).

In the field of cutaneous lymphoma and leukemia, we refer to what reported in the ASCO FAQs, highlighting how currently no specific recommendation can be made (except for stem cell transplantation) for delay in therapy or choosing alternate therapy in the context of SARS-CoV-2 infection (Table 2).

3.6 | Bexarotene

Bexarotene is a retinoid that selectively activates retinoid X receptors (RXRs) and is used for the treatment of cutaneous T-cell lymphomas, as it causes malignant cell apoptosis. It is usually associated with a reduction of TH2 cytokines (eg, IL-4) and appears to inhibit expression on the malignant T-cells of certain chemokine receptors, particularly CCR4, which are critical for the cell to gain access to the skin.[81] Leukopenia is associated with an increased risk of bacteria and viral infections, including SARS-CoV-2, and it is one of the most common side effects of Bexarotene. Therefore, patients candidate to bexarotene treatment should be screened for COVID-19, prior to the initiation of therapy in order to guide decision-making (Table 2).

3.7 | Psoralen and UltraViolet A (PUVA) therapy

Phototherapy and photochemotherapy (PUVA) are a valuable option in psoriasis and all stages of mycosis fungoides. According to Hannani et al, the expression of costimulatory and adhesion molecules and the secretion of cytokines are not modified by PUVA therapy.[82] Therefore, no special attention is required for patients under treatment with PUVA therapy (compared with the general population) (Table 2).

3.8 | Cyclophosphamide

Cyclophosphamide is a chemiotherapic agent with application in the treatment of autoimmune diseases. Although used for immunosuppression, since it was born as an antineoplastic, it has been treated among the dermato-oncological agents. Indeed cyclophosphamide is a nitrogen mustard alkylating agent, causing apoptosis and a cytotoxic effect on rapidly replicating cells. As a result of this, it causes apoptosis of leukocytes leading to immunosuppression (ie, myelosuppression) and increased risk of infections, such as community-acquired pneumonia and reactivation of latent infections.[83]

Treatment with cyclophosphamide is contraindicated during an active infection. In case a treatment with cyclophosphamide is needed, a pre-therapy screening with SARS-CoV-2 test is recommended. Patients already under treatment with cyclophosphamide may continue their therapy, except in case of COVID-19 complicated infections (such as pneumonia, respiratory failure), where the treatment can be suspended, always taking into account the general condition of the patient and the risk-benefit ratio (Table 2).

3.9 | Electrochemotherapy

Electrochemotherapy (ECT) is a technique in which high-intensity electrical pulses are sent into the tumor via electrodes to increase drug absorption.[84] Bleomycin or cisplatin are usually administered via ECT for primary, locally advanced and metastatic NMSC.[84] A release of intact tumor antigens due to substance shedding by the damaged

cells has been observed in ECT.[85] Released tumor antigens are subsequently exposed to the patients' immune system, which activates a tumor antigen-directed immune response.[23] However, although ECT is primarily a local treatment, distant metastases can also be affected by a minimal "abscopal effect," driven by the systemic immune response system elicited by the released tumor antigens.[85]

One could superficially conclude that, as ECT is a local(skin) therapy, no specific recommendation for ECT is required during the SARS-CoV-2 pandemic. However, the drugs (bleomycin and cisplatin) injected during ECT in the context of the coronavirus pandemic should raise the physician' awareness. Indeed one of the possible side effects of bleomycin and an exclusion criteria for ECT is pulmonary fibrosis, which is induced above all by a massive release of IL-6.[86,87] Besides, bleomycin is known to induce diffuse alveolar damage and pulmonary fibrosis with accumulation of macrophages and a rich TH2 cytokine environment, enhancing viral replication in the lungs.[88] Bleomycin-induced pulmonary fibrosis and a TH2 cytokine milieu may worsen the prognosis of a future or ongoing COVID-19-related interstitial lung disease.

Regarding cisplatin, recent studies showed its implication in the development of pulmonary fibrosis and that the treatment of cancer patients with cisplatin may alter fibroblast viability;[89,90] while the interaction between cisplatin and the immune system (cytokines) is less clear compared with bleomycin.[91] The cisplatin-induced leukopenia is definitely a relevant risk factor for infections. Therefore, considering that ECT is not yet a standardized treatment and according to the abovementioned relationship between pulmonary fibrosis and bleomycin/cisplatin, ECT should be performed only in very rare selected cases and always preceded by a pre-therapy screening for SARS-CoV-2 (Table 2).

4 | COMMENTS

This quick review highlights that, except rare cases, systemic immunobiological, immunosuppressant, and oncologic agents for dermatologic treatments do not require suspension of treatment and do not require special measures, if not those commonly observed. Indeed, all patients should use standard practices including basic hygiene precautions and the use of recommended Personal Protective Equipment as prescribed for the daily life in general population. At the same time, although it is important to avoid treating patients who might be at risk of developing important COVID-19-related complications, physicians should avoid undertreatment of dermatological diseases. This quick review and related recommendations should be considered as a starting point for future reviews as new dermatological guidelines are updated. The COVID-19 emergency pandemic does not imply an undertreatment of skin conditions, as unnecessary re-exacerbations of dermatological disease may jeopardize the patient's quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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