COVID-19 and implications for dermatological and allergological diseases

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Introduction

COVID-19, caused by the coronavirus SARS-CoV-2, has become pandemic. The impact of SARS-CoV-2 infection on the immune system and its modulation or suppression by pharmacological intervention has been dissected in detail with regards to clinical implications of the various cytokines and cellular functions affected [1]. A further level of complexity opens up as soon as we look at diseases whose pathogenesis and therapy involve different immunological signaling pathways, which are potentially affected by COVID-19. Medical treatments must often be reassessed and questioned in connection with this infection.

This article summarizes the current knowledge of COVID-19 in the light of major dermatological and allergological diseases. It identifies medical areas lacking sufficient data and draws conclusions for the management of our patients during the pandemic. We focus on common chronic inflammatory skin diseases with complex immunological pathogenesis: psoriasis, eczema including atopic dermatitis, type I allergies, autoimmune blistering and inflammatory connective tissue diseases, vasculitis, and skin cancers. Since several other inflammatory skin diseases display related or comparable immunological reactions, clustering of the various inflammatory dermatoses into different disease patterns may help with therapeutic decisions. Thus, following these patterns of skin inflammation, our review may supply treatment recommendations and thoughtful considerations for disease management even beyond the most frequent diseases discussed here.

SARS-CoV-2 and psoriasis

Like other respiratory viral infections, SARS-CoV-2 infection may aggravate psoriasis [7]. Of practical relevance is the question whether antipsoriatic treatments increase the risk of infection with SARS-CoV-2 or aggravate the course of COVID-19 disease. Several aspects need to be considered in this discussion:

- Patients with untreated psoriasis and/or psoriatic arthritis (PsA) have a 1.5 fold increased risk of severe infections compared to control individuals [8–10] and therapeutic normalization of an intrinsically aberrant immune response may improve the host defense against infection.

- The immune response to SARS-CoV-2 is complex; elimination of the virus is associated with an innate and adaptive immune response involving T cells, NK cells, probably B cells and mediators such as IL-12, IL-15, interferon-α/β and -γ. In a small subgroup of patients with severe COVID-19 and persistent virus replication, a hyperinflammatory response may develop with overexpression of IL-6, TNFα, IL-17A and other cytokines that are also targets of psoriasis therapies [11]. In this situation, cytokine inhibition may be beneficial and/or have a preventive effect [12]. The JAK1/2 inhibitor baricitinib and cyclosporine may increase the risk of viral infections, but may also inhibit viral entry and replication, respectively [13, 14].

- Some risk factors for a more severe course of COVID-19 including arterial hypertension, type II diabetes, smoking
Table 1 Overview of dermatological and allergological diseases and the established or suspected effects of SARS-CoV-2 infection/COVID-19 on disease severity. Approved therapeutic compounds are listed as well as recommendations for continued use and novel introduction of systemic treatment.

| Disease                                      | Impact of COVID-19 or infection with SARS-CoV-2 on disease | Approved therapeutic compounds affecting immune responses | Recommendations for continued systemic therapy | Recommendations for novel introduction of systemic treatment |
|----------------------------------------------|------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------|----------------------------------------------------------|
| Psoriasis                                    | Possible aggravation of disease                            | – infliximab, adalimumab, certolizumab, etanercept, ustekinumab, guselkumab, risankizumab, tildrakizumab, secukinumab, ixekizumab, brodalumab, cyclosporine, methotrexate, retinoids, fumaric acid esters | Maintain immunomodulatory therapy without changes | No distinction is being made between labeled treatment options. Targeted therapy probably preferable over conventional systemic immune modulation |
| Eczema                                       | Possible aggravation of disease                            | – dupilumab, cyclosporine, retinoids, GCS               | Maintain immunomodulatory therapy without changes | Retinoids and targeted therapy with dupilumab probably preferable over conventional systemic immune modulation |
| Allergic bronchial asthma, allergic rhinitis, anaphylaxis | Possible aggravation of disease                            | – dupilumab, mepolizumab, benralizumab, reslizumab, omalizumab, antihistamines, GCS | Maintain immunomodulatory therapy without changes | New therapies may be started, since no specific risk has been identified |
| Autoimmune blistering dermatoses            | Possible aggravation of disease                            | – rituximab, azathioprine, dapsone, GCS                | Maintain immunomodulatory therapy when needed to avoid uncontrolled flares | Postpone rituximab to delay B cell depletion during peak COVID-19 when possible and consider use of IVIG instead |
| Connective tissue disease                   | Possible aggravation of disease                            | – belimumab, hydroxychloroquine, chloroquine, azathioprine, GCS | Maintain immunomodulatory therapy without changes | Introduce novel treatment regimen as needed |
| Vasculitis                                   | Aggravation of disease, and new onset of disease           | – rituximab, cyclophosphamide, intravenous immunoglobulins, azathioprine, GCS | Use of immunosuppressants for vasculitis treatment should be even more restricted | Use of immunosuppressants for vasculitis treatment should be even more restricted. Postpone rituximab and cyclophosphamide to delay immunosuppression during peak COVID-19 when possible and consider use of IVIG instead |
| Skin cancer                                  | Currently unclear                                          | – ipilimumab, nivolumab, pembrolizumab, avelumab, cemiplimab | Maintain immunomodulatory therapy without changes | Introduce novel treatment regimen as needed |

*Abbr.: GCS, glucocorticosteroids, IVIG, intravenous immunoglobulins.*
and overweight are more common among psoriasis patients [15]. On the other hand, there is increasing evidence that successful treatment of psoriasis improves cardiovascular comorbidity [16].

- Most studies and registries have not demonstrated a significantly elevated risk of viral or respiratory tract infections in systemically treated patients with psoriasis [15].

In light of this complex discussion, national and international recommendations suggest not to delay the onset of appropriate systemic therapy and not to stop such therapy in patients without symptoms [17]. No significant differentiation is being made between labeled treatment options. As a precautionary measure in patients with typical symptoms of COVID-19, systemic therapy should not be started and an existing therapy paused until a possible SARS-CoV-2 infection has been excluded or resolved. Clinical evidence based on larger cohorts is only beginning to emerge. In one retrospective Italian study comparing patients with psoriasis on systemic therapy (n = 1,193) with the background population of Lombardy since March 2020, the authors reported a higher rate of symptomatic SARS-CoV-2 infection, self-quarantine (n = 17) and hospitalization (n = 5) for patients on biologics, but no increased risk of ICU admission or death [18]. In another Italian multicenter study, patients with psoriasis on biologics (n = 5,206) were followed between February 20th and April 1st 2020 [19]. There were no COVID-19-related deaths and the hospitalization rate was similar to that observed in the general population. Together with an earlier case series from New York City (n = 86) [20], these findings support the above recommendations and should reassure patients with psoriasis and their treating physicians.

**SARS-CoV-2, atopic dermatitis and other types of eczema**

Although respiratory and cutaneous viral infections may worsen or complicate atopic dermatitis and other types of eczema [21], data on effects of SARS-CoV-2 infection on eczema patients have not been published. Since T cells are centrally involved in the complex immuno-pathophysiology of eczema and associated diseases, SARS-CoV-2 infections may be of special concern in eczema patients with comorbid diseases such as asthma/chronic obstructive lung disease, eosinophilic esophagitis, or severe allergies [22]. SARS-CoV-2-induced lymphopenia may hamper antiviral immunity and currently serves as a biomarker and a possible target for intervention by stimulation of lymphocyte proliferation or prevention of apoptosis to reduce the risk of severe disease [22]. Preliminary data points towards a direct infection of T lymphocytes with SARS-CoV-2, which may also cause cytopathic effects on infected T cells [23].

Following the sanitary recommendations for more frequent hand washing and disinfection procedures during the pandemic, the prevalence of hand eczema is rising significantly, even among persons not previously affected [24, 25]. Basic topical treatment with emollients, as well as specific treatment with topical corticosteroids and calcineurin inhibitors should be initiated or continued according to current guidelines without any specific requirements, including UV-light therapies. Since exacerbations of the skin disease may negatively affect the patients’ immunity, systemic treatment in eczema patients should be continued for all immune-modulating drugs including immuno-suppressive therapy, as consented and advised by the European Task Force on Atopic Dermatitis (ETFAD) [26].

If a patient on systemic treatment is diagnosed with COVID-19, interdisciplinary risk assessments are necessary on whether to continue or pause systemic treatment, preferably in tertiary care centers [27]. In atopic dermatitis, immune-modulating medication may also control the severity of asthma/chronic obstructive lung disease and other comorbid conditions. Hence, termination of a stable treatment regimen with immune-modulating drugs may not be beneficial [28]. However, in patients with exclusive skin disease such as hand eczema, pausing of immune-modulating therapies seems to be less problematic in case of COVID-19, since flare-ups of the skin disease may be acceptable during the critical time of the viral infection. Whenever immune-modulating therapy is stopped, patients need to be supplied with ample topical treatment and detailed instructions to control the skin disease for the following weeks. Close monitoring of comorbid diseases is important in these individuals. Targeting specific cytokines may even benefit patients with COVID-19, since therapeutic cytokine blockade without affecting viral clearance may inhibit hyper-inflammatory host responses [11].

If patients need to be started on systemic treatment for different types of eczema during the pandemic, exclusively anecdotal clinical data may support the following theoretical considerations. In general, conventional systemic immune-modulating drugs such as glucocorticoids, cyclosporine, azathioprine, or methotrexate affect the cellular immune response, mainly via inhibition of lymphocyte function and activation. Retinoids or type II immune response-directed therapies such as dupilumab affect the immune defense against viral infection to a lesser degree and may therefore be preferred [29]. Patients treated with dupilumab showed no increase in systemic infections, and occurrence of eczema herpeticum was significantly reduced in comparison to placebo treatment.
SARS-CoV-2 and type I allergies

IgE-mediated type I allergic diseases affect up to 25% of the population and dealing with these common diseases during the pandemic is necessary. The following comments refer to allergic bronchial asthma, allergic rhinitis and anaphylaxis.

Diagnosis of a type I allergy should currently focus primarily on in vitro tests, if possible. Exceptions are drug and food intolerance reactions, as only few reliable in vitro tests are available. Skin prick tests and provocation tests with aerosols (e.g. rhinomanometry) should only be performed after a strict indication and with sufficient protection of the personnel. Gloves, protective goggles, gowns and FFP2/FFP3 respiratory masks should be worn to prevent the transmission of droplets and direct contact [30–32]. If this is not possible, the test should not be performed. To optimize the use of personal protective equipment in the event of inadequate supply, personnel should be assigned to specific tasks and procedures should be performed in specially designated areas.

Considerations for therapy of patients with type I allergic diseases

- Symptomatic topical antiallergic treatment, including topical corticosteroids, should be initiated or continued without restriction according to patient needs.
- Systemic antihistamines and leukotriene antagonists may be initiated or continued without restriction as needed. There is no evidence that this could adversely affect the susceptibility to infection or the course of SARS-CoV-2 infection.
- Systemic corticosteroid therapy, especially at a dose of more than 10 mg/d, should be avoided or used only after a very strict indication and if possible only for a short period.
- The treatment of allergic bronchial asthma, nasal polyps or rarely anaphylactic reactions with biologicals should be continued. New therapies may be started, since no specific risk has been identified in SARS-CoV-2 infected patients [33].
- Anaphylactic shock should be treated acutely with epinephrines according to the current guidelines.
- The indication for administration of high-dose corticosteroids should be strictly defined, especially since the efficacy of corticosteroids in anaphylaxis is not clear.
- Specific subcutaneous or sublingual immunotherapy can be continued in symptom-free and healthy patients, and the treatment regimen should not be interrupted. In case of symptoms such as fever, unclear cough or reduced general condition, immunotherapy should be suspended and continued at a later (symptom-free) time [34].

- In the case of interruption of subcutaneous immunotherapy (SCIT), the dose of SCIT should be adjusted according to the manufacturer’s recommendations. Recom mencement of sublingual immunotherapy should be performed under medical supervision.

SARS-CoV-2 and autoimmune blistering dermatoses

Autoimmune blistering dermatoses (AIBD) are a heterogeneous group of potentially life-threatening disorders that characteristically present with blisters and erosions on the skin and/or mucous membranes near the outer skin surface [35–38]. Patients with AIBD likely belong to the COVID-19 risk group [39]. An increased risk is arguably due to the long-term use of corticosteroids, immunosuppressive adjuvants and rituximab [40]. In addition, the advanced age of patients with pemphigoid diseases, which accounts for two thirds of AIBDs in Europe and Northern America, is another major risk factor [36, 41]. Whether SARS-CoV-2 can enter through uncovered erosive skin lesions or oropharyngeal erosions can be debated.

The AIBD task force of the European Academy of Dermatology and Venereology (EADV) has provided patient information, in addition to general advice on SARS-CoV-2, on how to take immunosuppressive drugs and on general precautions [42]. Patient recommendations in German can be accessed via the websites of the Deutsche Dermatologische Gesellschaft [32] and the Pemphigus und Pemphigoid Selbsthilfegruppe e.V. [43]. These are in line with international expert recommendations and the International Pemphigus and Pemphigoid Foundation [44–46]. Some authors suggest to postpone rituximab to delay immunosuppression during peak COVID-19 and to use intravenous immunoglobulins (IVIG) instead [46]. The latter have shown promise in severe COVID-19 [35, 47]. Others propose to maintain immunomodulatory therapy when needed to avoid uncontrolled flares with high morbidity and mortality. In COVID-19 patients with AIBD, immunosuppressants may be interrupted, and prednisone equivalent > 10 mg/d reduced, while topical corticosteroids, prednisone (≤ 10 mg/d), dapsone (with normal hemoglobin levels), doxycycline/tetracycline, colchicine, and IVIG can be continued [45].

Several clinical studies for the treatment of COVID-19 are currently ongoing including the use of inhibitors of pro-inflammatory IL-6, IL-1α, and JAK1/2. These mediators are, however, probably not centrally involved in the pathophysiology of AIBD [35, 36, 48]. In contrast, C5 activation has been identified as crucial for lesion formation in experimental bullous pemphigoid and mucous membrane pemphigoid [49–51]. Since inhibition of C5 may result in...
immediate clinical improvement of severe COVID-19 [52], its blockade may alleviate both, COVID-19 and pemphigoid diseases. Overall, beneficial anti-inflammatory effects should be weighed up against the potentially detrimental effects of inhibiting antiviral immunity [53].

So far, seven Italian AIBD patients with COVID-19 have been published [54–56]. Of the four patients with bullous pemphigoid who had to be hospitalized due to severe COVID-19, three died, while one recovered [55]. In a survey by the AIBD task force of the EADV, 36 AIBD patients including 13 (23 %) fatal cases with COVID-19 were identified in 51 centers from 22 countries worldwide until April 30, 2020. While no centers from China or the USA were included, most cases were reported from Iran and France. To gather more information on potential risk factors, a registry for AIBD patients with COVID-19 has been launched by the AIBD task force of the EADV [57].

SARS-CoV-2 and inflammatory connective tissue disease (collagenoses)

Systemic autoimmune diseases such as lupus erythematosus (SLE) or systemic sclerosis (SSc) are associated with increased IL-6, TNFα, IL-17 and IL-23 that induce autoreactive T-cells and autoantibodies. Only few data are available on SLE and SSc, so far none on cutaneous LE, morphea or dermatomyositis [58].

Recently, the clinical course of COVID-19 in 17 SLE patients was reported [59]. All patients received long-term hydroxychloroquine (HCQ), 71 % prednisone below 10 mg/d and 41 % immunosuppressants. During COVID-19, a higher rate of dyspnea, headache and diarrhea was detected in SLE patients compared to a previously reported Chinese general population from the Wuhan area [33, 60]. The majority of patients (76 %) developed viral pneumonia, 65 % with respiratory failure and 29 % with acute respiratory distress syndrome. All patients were hospitalized, and two patients died during the 4-weeks observation period. None of the SLE patients showed clinical signs or deterioration of LE during COVID-19. In another study on 165 Italian SLE patients, clinical data on COVID-19 contact and infection were collected [61]. 77 % of patients were treated with HCQ, 25 % with mycophenolic acid and 7 % with other immunosuppressants. Twelve patients (7.2 %) developed COVID-19. Only one patient with confirmed infection and severe SLE had to be admitted to hospital with ICU treatment and non-invasive ventilation. Seven other SLE patients did not develop any symptoms of infection despite contact with COVID-19 patients. These early findings document the course of SARS-CoV-2 infection in SLE and suggest that long-term intake of HCQ does not prevent severe COVID-19, nor does standard treatment affect the disease course. The relevance of HCQ is still much-debated [62–64] and respective trials have been stopped. Yet, the current shortage of the drug poses a serious hazard to SLE patients as a stable and effective treatment of the disease is recommended to minimize consequences of COVID-19.

A number of reports encompassing 201 COVID-19 patients described acro-ischemic lesions resembling chilblain LE [65]. In a larger retrospective case series with 132 patients from Spain (mean age 19.9 years), 41 % had close contact to a confirmed COVID-19 patient, 14.4 % were clinically diagnosed, but only two tested positive by PCR [66]. A chilblain-like pattern was found in 72 %, an erythema multiforme-like pattern in 28 % of the patients. All published patients had mild infectious disease and mostly developed cutaneous lesions up to three weeks after clinical symptoms suggestive of COVID-19. Cutaneous lesions may be induced by a SARS-CoV-2 infection-associated vasculopathy [67]. Only recently, relations to Kawasaki syndrome were described which is discussed in the next section on vascular changes.

A potentially high-risk group for developing severe COVID-19 are patients with systemic sclerosis and interstitial lung disease (SSc-ILD). A case report described a 57-year old female with SSc-ILD and SARS-CoV-2 infection [68]. Tocilizumab (anti-IL-6 receptor antibody) was initiated four weeks prior to SARS-CoV-2 infection, which presented with mild symptoms. Larger trials are underway to evaluate the risks and benefits of tocilizumab in COVID-19 [69].

SARS-CoV-2 and vascular changes and diseases

Many case reports and case series observed “vascular skin symptoms” in COVID-19 patients. A study from France considering 14 confirmed SARS-CoV-2 patients reported acral chilblain- and livedo-like lesions as well as purpura [70]. Case reports on at least clinically confirmed vasculitis of small vessels or immune-complex vasculitis are rare [71]. More (including histological) evidence exists on occlusive vasculopathies, especially on acral chilblain-like dermatoses, which appear to accumulate in patients with COVID-19 [72]. Histologically, they show occlusive vasculopathy rather than actual vasculitis. Livedo-like lesions and necrosis occurred in 6 % of the cases in one study and mostly affected elderly patients with severe disease [65, 72]. Another report from France described acral lesions in 142 of 277 patients; 75 % of these presented with chilblain-like lesions [73]. In children, acral lesions mimicking perriones have attracted attention during the pandemic as well [74, 75]. Thus, chilblain-like lesions could be a sign of pauci-symptomatic SARS-CoV-2 infection [70, 73].
Of particular note are the recent cases of SARS-CoV-2-associated Kawasaki disease. Previously, this disease has been suspected to be associated with yet unidentified infectious triggers that provoke an intense proinflammatory response in genetically predisposed patients [76, 77]. In a study from Bergamo, Italy, Kawasaki-like disease was found 30-fold more often in children after start of the COVID-19 pandemic than before. Affected children were relatively older, presented with a higher rate of cardiac involvement and macrophage activation syndrome resulting in arterial hypotension and peripheral hypoperfusion than children diagnosed with Kawasaki disease before the COVID-19 pandemic [78–80]. Interestingly, the majority of the Kawasaki patients were negative for SARS-CoV-2 nucleic acid testing but all except two were positive for IgG/IgM antibodies to SARS-CoV-2 [78, 79]. It was hypothesized that the mounting of an immune response against the virus rather than the initial infection itself had been responsible for Kawasaki disease, suggesting that it is a post-infectious, possibly immune complex-mediated inflammatory syndrome [78, 80]. Treatment with intravenous immunoglobulins and glucocorticoids led to disease control in most patients [78, 80].

During the COVID-19 pandemic, the use of immunosuppressants for vasculitis treatment should be even more restricted when there is no sufficient evidence for their efficacy as in most cases of IgA vasculitis or polyarteritis nodosa cutanea. However, they must not be stopped abruptly or prophylactically in ANCA-associated and other severe systemic vasculitides. During the peak of the pandemic, 162 Italian patients with previously diagnosed large vessel vasculitis (67 with Takayasu arteritis, 95 with giant cell arteritis) on treatment were surveyed [81]. Four patients had a microbiological diagnosis of SARS-CoV-2 infection, and two of them required hospitalization from which both fully recovered. Importantly, their vasculitis treatment was initiated before the SARS-CoV-2 outbreak (including tocilizumab [n = 53], methotrexate [n = 51], infliximab [n = 25]), and it was not stopped or reduced indicating that immunosuppression did not necessarily result in negative outcomes [81].

**SARS-CoV-2 and skin cancer**

The current COVID-19 pandemic also presents several challenges for the daily care of patients with skin cancer. The first challenge is to protect individuals with advanced disease (e.g. metastatic melanoma or carcinoma as well as late stage cutaneous lymphoma). These patients could be at above-average risk of SARS-CoV-2 infections due to systemic immunosuppression. This view is supported by publications, according to which cancer patients have a higher risk of SARS-CoV-2 infections as well as of more severe courses of COVID-19 [82–84]. However, these reports were hampered by small cohort sizes and limited clinical information. A more recent multi-center study revealed that patients with hematological malignancies, lung cancer or metastatic disease had the highest rates of severe events during COVID-19 and the highest death rate [85]. Detailed data assessing the risk of COVID-19 for patients with advanced skin cancer are not available yet. Therefore, individual decisions should be made adapted to the patient’s current health situation. A second challenge is to maintain regular services for skin cancer patients because many fear to acquire a SARS-CoV-2 infection in the hospital and therefore cancel their appointments. At the same time, government regulations and supply shortages have transiently limited the access of patients to regular health services [86].

This has led to concerns of some patients that their urgently needed treatments are postponed during the pandemic. It is therefore important to balance the necessity of skin cancer treatment with the potential morbidity and mortality due to an infection with SARS-CoV-2 on an individual basis [87].

The European Society for Medical Oncology (ESMO) as well as several other oncology societies have published guidelines for cancer patient management during the COVID-19 pandemic [88, 89]. According to the ESMO guidelines, all cancer patients undergoing surgery, radiotherapy, chemotherapy, or immunotherapy should be regularly tested for SARS-CoV-2 infections before each treatment cycle. In the case of melanoma, patients with a new diagnosis of invasive primary cancer or with complications during targeted therapies or immunotherapies for inoperably advanced stage III or IV disease should be prioritized for regular visits and continuous treatment [88]. Especially patients treated with checkpoint inhibitors need to be carefully controlled for COVID-19 symptoms since some side effects such as autoimmune pneumonitis cannot easily be differentiated from progressive COVID-19 disease.

In Germany, a task force consisting of the *Deutsche Krebsforschungszentrum* (DKFZ), the *Deutsche Krebshilfe* and the *Deutsche Krebgesellschaft* is continuously documenting the effects of the COVID-19 pandemic on the care of cancer patients. So far, there is no measurable shortage in the care of these patients. However, the large number of canceled appointments could reduce the diagnosis of early cancer stages, which could perhaps later translate into an increased number of more advanced stages. It is therefore important to explain to patients that the fear of SARS-CoV-2 infection should not prevent them from potentially life-saving visits to the doctor.

**Conclusions**

Generally, patients who feel ill with typical respiratory symptoms should be advised to have an initial telephone or video
consultation, and for the time being no careless visits to the practice or hospital should be arranged. The medical knowledge as well as diagnostic and therapeutic recommendations on COVID-19 and its impact on dermatological and allergic diseases may change rapidly and need to be updated regularly. Since tremendous efforts are undertaken to improve our understanding and to consolidate optimal treatment regimens of COVID-19 patients, we encourage physicians to check regularly the homepages and recommendations of the different national and European societies for updates on patient management during the pandemic.

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