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COVID-19 and immunological regulations – from basic and translational aspects to clinical implications

Michael P. Schön[1,2], Carola Berking[3], Tilo Biedermann[4], Timo Buhl[1,2], Luise Erpenbeck[1], Kilian Eyerich[4,5], Stefanie Eyerich[6], Kamran Ghoreschi[7], Matthias Goebeler[8], Ralf J. Ludwig[9], Knut Schäkel[10], Bastian Schilling[8], Christoph Schlapbach[11], Georg Stary[12], Esther von Stebut[13], Kerstin Steinbrink[14]

(1) Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Germany
(2) Lower Saxony Institute of Occupational Dermatology, University Medical Center Göttingen, Germany
(3) Department of Dermatology, University Medical Center Erlangen, Deutsches Zentrum Immuntherapie, Friedrich Alexander University Erlangen-Nürnberg, Germany
(4) Department of Dermatology and Allergy Biederstein, Technical University Munich, Germany
(5) Department of Medicine Solna, Unit of Dermatology and Venereology, Karolinska Institutet, Stockholm, Sweden
(6) ZAUM – Center of Allergy and Environment, Technical University and Helmholtz Center Munich, Germany
(7) Department of Dermatology, Venereology and Allergology, Charité – University Medical Center Berlin, Germany
(8) Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, Germany
(9) Lübeck Institute of Experimental Dermatology, University of Lübeck, Germany
(10) Department of Dermatology, University Medical Center Heidelberg, Germany
(11) Department of Dermatology, Inselspital University Medical Center, Bern, Switzerland
(12) Department of Dermatology, Medical University of Vienna, Austria
(13) Department of Dermatology, University Hospital Cologne, Germany
(14) Department of Dermatology, Westfälische Wilhelms University Münster, Germany

Summary

The COVID-19 pandemic caused by SARS-CoV-2 has far-reaching direct and indirect medical consequences. These include both the course and treatment of diseases. It is becoming increasingly clear that infections with SARS-CoV-2 can cause considerable

immunological alterations, which particularly also affect pathogenetically and/or therapeutically relevant factors.

Against this background we summarize here the current state of knowledge on the interaction of SARS-CoV-2/COVID-19 with mediators of the acute phase of inflammation (TNF, IL-1, IL-6), type 1 and type 17 immune responses (IL-12, IL-23, IL-17, IL-36), type 2 immune reactions (IL-4, IL-13, IL-5, IL-31, IgE), B-cell immunity, checkpoint regulators (PD-1, PD-L1, CTLA4), and orally druggable signaling pathways (JAK, PDE4, calcineurin). In addition, we discuss in this context non-specific immune modulation by glucocorticosteroids, methotrexate, antimalarial drugs, azathioprine, dapsone, mycophenolate mofetil and fumaric acid esters, as well as neutrophil granulocyte-mediated innate immune mechanisms.

From these recent findings we derive possible implications for the therapeutic modulation of said immunological mechanisms in connection with SARS-CoV-2/COVID-19. Although, of course, the greatest care should be taken with patients with immunologically mediated diseases or immunomodulating therapies, it appears that many treatments can also be carried out during the COVID-19 pandemic; some even appear to alleviate COVID-19.

SARS-CoV-2/COVID-19 and immunity: Our present view in a nutshell

The coronavirus SARS-CoV-2 can cause COVID-19 disease in infected patients [1, 2]. This new disease holds the world in thrall in many ways and it confronts our society with unprecedented challenges [3]. As impressively demonstrated by the more than 35,000 scientific publications on COVID-19 in only seven months (MedLine access 29. July 2020), the amount of data available is increasing rapidly.

The virus preferentially enters macrophages, type II pneumocytes, pericytes and muscle cells, thus causing direct organ damage, especially in patients with pre-existing comorbid conditions. The first symptoms of COVID-19 usually manifest five to six days after infection [4, 5]. Shedding of virus particles begins two to three days before the onset of symptoms, and although the virus can be detected for up to 37 days, infectivity decreases significantly about ten days after the first symptoms [4, 6, 7]. IgM against SARS-CoV-2 develops about eight to twelve days after infection and disappears after about twelve weeks. The IgG seroconversion occurs after approximately 14 days, and IgG lasts longer than IgM [8–10]. Antibodies against SARS-CoV-2 are likely protective, since passive transfer of convalescent plasma can attenuate the course of disease in severely affected patients with COVID-19 [11–15]. However, serious pulmonary complications in some patients may be related to adaptive immunity [16–18].

On the one hand, elements of innate immunity play a decisive role in whether and how COVID-19 develops after infection with SARS-CoV-2 [8, 17, 19, 20]. Cellular components (such as natural killer cells, γδ-T cells and cells of myeloid origin) work together with humoral factors (complement and coagulation system, natural antibodies, cytokines, chemokines and pathogen-binding glycans) to mount an innate antiviral immune response [21–23]. On the other hand, profound changes in innate and acquired immune responses, even up to an uncontrolled cytokine storm, may occur during the disease and in case of complications [24]. As patients with immune-mediated disorders or immunomodulatory therapies have altered immune functions, it is conceivable that this impacts the course of the infection and *vice versa* (Figure 1).

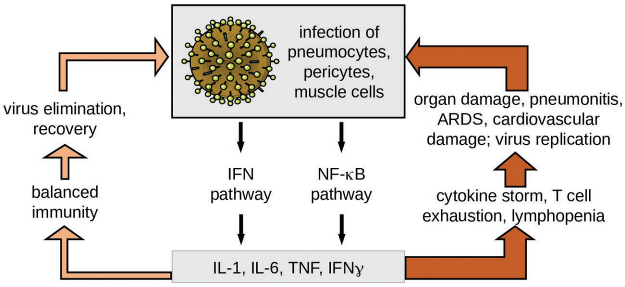

Figure 1 Schematic representation of immune activation in COVID-19. SARS-CoV-2 preferentially attacks pneumocytes, pericytes and muscle cells. Numerous mediators, for example IL-1, IL-6 and TNF, are induced mainly via the interferon and NF-κB signaling pathways. A balanced immune response leads to elimination of the viruses and healing (left side). In predisposed patients, however, a so-called cytokine storm with an uncontrolled increase in proinflammatory mediators can also occur. This may lead to severe organ damage (right side).

Research on immunological regulatory pathways has led to many selectively acting biologicals and small molecule drugs which have revolutionized the treatment of chronic inflammatory diseases and tumor therapy. In addition, numerous conventional drugs also interfere with immunological processes, albeit usually in a less specific way. In this situation it is quite conceivable that infections with SARS-CoV-2 influence relevant immunoregulatory pathways and therapies. Neutrophilia and lymphopenia as well as elevated serum concentrations of numerous cytokines and chemokines including therapeutically or pathogenetically relevant mediators have been described [19, 25, 26]. We currently assume that many immunological mediators altered by COVID-19 are not primarily involved in virus elimination [27].

A pattern of immunological consequences of an infection with SARS-CoV-2 is now emerging that makes it appropriate to rethink some diseases and their treatments (Figure 2). It is, however, not easily predictable from the outset whether and how an infection with SARS-CoV-2 would interfere with a given therapy or signaling pathway. Some anti-inflammatory therapies might even have positive effects in severe COVID-19 cases. Insight into how immunological mechanisms are influenced by SARS-CoV-2 would therefore be relevant for disease management (Table 1). It seems important to us to outline specifics of the new knowledge that touch on pathogenesis or therapy.

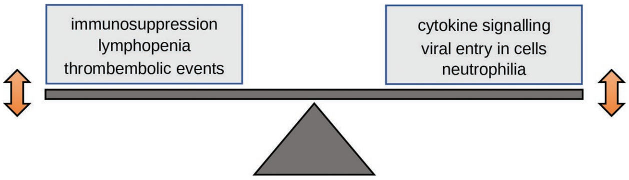

Figure 2 Potential influence of immunomodulatory therapies on COVID-19. In COVID-19 patients treated with immunomodulatory drugs, different effects can occur, which must be weighed against each other, as there is a fine-tuned balance of possible beneficial and detrimental effects. Some of these are schematically depicted here. For example, immunomodulators could influence cytokine formation and action, virus entry into cells, thromboembolic events or lymphocyte functions. On the other hand, the course of immune-mediated diseases could also be altered by infection with SARS-CoV-2. Many aspects of how drug therapies influence the immunological balance are not yet known. Nevertheless, it is becoming apparent that some specific therapies, such as blocking IL-6, can positively influence the excessive immune response triggered by COVID-19. On the other hand, checkpoint inhibitors could act synergistically with the immune activation in COVID-19. Further details are explained in the text.

SARS-CoV-2/COVID-19 and primary acute phase mediators (TNF, IL-1, IL-6)

The infection primarily activates two signaling cascades of innate immunity, the interferon and the NF-κB pathways [28]. Consequently, serum and tissue levels of IL-1, TNF and IL-6 are elevated in COVID-19 patients [19, 29]. Indeed, the balance of proinflammatory cytokines seems to impact the outcome. IL-1, IL-6 and TNF might be protective as they facilitate killing of virus-infected host cells by $CD8^+$ T cells and phagocytes. They also promote the production of virus-specific antibodies. However, excessive levels of these cytokines can induce the potentially fatal “cytokine storm” [30].

Th1 cells can stimulate $CD14^+CD16^+$ monocytes to produce IL-6 and differentiate into tissue macrophages. This causes T cell exhaustion and tissue cell death [20, 31]. Excessively high levels of IL-6 thus facilitate acute respiratory distress as well as cardiovascular damage [32]. Clinically, increased levels of IL-6 predict severe courses and complications of COVID-19 [33, 34]. Moreover, tocilizumab (a humanized IL-6 receptor-directed antibody) impressively alleviated COVID-19 in 20 critically ill patients [35]. Within five days, oxygen could be reduced, and after 15 days, patients were discharged with improved lymphocyte counts and CRP. Adverse events were not observed. However, the results of this small non-controlled study need to be confirmed in larger controlled trials. In any case, as far as we know, IL-6 seems to be important for the course of a SARS-CoV-2 infection.

IL-1α/β is another target relevant for macrophage-associated inflammation. When nine patients with acute COVID-19 pneumonia were treated with anakinra, a human IL-1 receptor antagonist, all except one improved, were non-feverish from day 3 and showed decreased CRP levels together with good clinical outcomes [36]. This is in line with earlier results in septic patients [37]. Trials targeting IL-1 in patients with COVID-19 are underway [38].

Reports about anti-TNF treatment are not available yet, clinical trials are ongoing. However, COVID-19 patients with pre-existing inflammatory bowel disease (IBD) had better outcomes if they were on anti-TNF treatment compared to corticosteroids [39].

Thus, it appears that specific targeting of the proinflammatory cytokines IL-1, IL-6 and TNF as part of the cytokine storm is beneficial for COVID-19 patients with pneumonia.

SARS-CoV-2/COVID-19 and type 1/type 17 immunity (IL-12/IL-23, IL-17, IL-36)

In terms of T cell mediated immunity, IL-12 predominantly induces Th1 immune responses, whereas IL-23 contributes to

Table 1 Synopsis of immunological pathways and mechanisms that can potentially interfere with SARS-CoV-2 infection. The table lists primarily those immunological pathways for which approved therapeutic compounds are available.

Immunological factors that can be regulated	Impact of COVID-19 or infection with SARS-CoV-2 on indicated pathway	Selected approved therapeutic compound(s)	Potential interference of SARS-CoV-2 infection with targeting of indicated pathway
TNF	Upregulated in COVID-19	– Infliximab – Adalimumab – Golimumab – Etanercept – Certolizumab pegol	No specific trials yet; better outcome of COVID-19 in IBD patients on TNF blockers compared to glucocorticoids
IL-1	Induced in COVID-19	– Anakinra (IL-1RA) – Canakinumab (anti-IL-1β) – Rilonacept	Inhibition alleviated severe COVID-19 symptoms
IL-6	Induced in COVID-19, potential prognostic marker	– Tocilizumab (anti IL-6R)	Inhibition alleviated severe COVID-19 symptoms
IL-12	Upregulated in one study but not in another; no dependence on the severity of COVID-19 disease, no change during infection	– Ustekinumab (anti IL-12/IL-23p40)	No clinical data yet
IL-23	Possibly upregulated, transcription downregulated in PBMC	– Ustekinumab (anti IL-12/IL-23p40) – Guselkumab (anti-IL-23p19) – Risankizumab (anti-IL-23p19) – tildrakizumab (anti-IL-23p19)	No clinical data yet
IL-17	Increased serum concentration in COVID-19; no association with disease severity	– Secukinumab (anti-IL-17A) – Ixekizumab (anti-IL-17A) – Brodalumab (anti-IL-17R)	No clinical data yet
IL-4/IL-13	No significant change	– Dupilumab (anti IL4/IL-13) – Tralokinumab (anti IL-13) – Lebrikizumab (anti-IL-13)	No data indicating increased risk of patients with atopic dermatitis for/with SARS-CoV-2 infection; blocking type 2 cytokines without negative outcome in single COVID-19 infections.
IL-5	No significant change	– Mepolizumab (anti-IL-5) – Benralizumab (anti-IL-5) – Reslizumab (anti-IL-5)	Treating asthma with IL-5 inhibition and sparing steroids potentially of benefit in COVID-19 infections
IL-31	No significant change	– Nemolizumab (anti-IL-31RA)	No clinical data
IgE	No significant change	– Omalizumab (anti-IgE) – Ligelizumab (anti-IgE)	No clinical data
B-cells/CD20	No data reported	– Rituximab (anti-CD20)	No negative effect of CD20 blockade on the resolution of COVID-19
checkpoint regulators	PD-1 expression possibly elevated in COVID-19	– Ipilimumab (anti-CTLA-4) – Nivolumab (anti-PD-1) – Pembrolizumab (anti-PD-1) – Avelumab (anti-PD-L1) – Cemiplimab (anti-PD-L1)	Potential synergism between SARS-CoV-2 infection and immune checkpoint inhibitors, no actual data

Immunological factors that can be regulated	Impact of COVID-19 or infection with SARS-CoV-2 on indicated pathway	Selected approved therapeutic compound(s)	Potential interference of SARS-CoV-2 infection with targeting of indicated pathway
JAK	COVID-19-induced cytokine production mediated by JAK-STAT pathway	– Tofacitinib (anti-JAK1/3) – Baricitinib (anti-JAK1/2) – Upadacitinib (anti-JAK1/2)	Beneficial effect of JAK inhibitors on COVID-19-associated immune hyperactivation is likely
PDE4	No data reported	– Apremilast	No clinical data yet
Calcineurin, cyclophilins		– Cyclosporin A – Tacrolimus – Sirolimus	Limited data, possibly beneficial in COVID-19
Pleiotropic (broad or nonspecific) immunomodulation or -suppression		– Glucocorticosteroids (GC) – Methotrexate – Azathioprine – Mycophenolate mofetil/ Mycophenolic acid – Fumaric acid esters – Dapsone – Colchicine – Antimalarials (4-Aminoquinolines) – Immunoglobulins	No general contraindication; continue necessary therapies, no evidence-based data in COVID-19
Innate immune responses, neutrophil functions	Neutrophilia and (probably) NETosis in COVID-19	– DNase I (cleaves free DNA)	No data, possibly beneficial

Th17 immunity [40]. Various viruses including SARS-CoV-1 from the 2003 outbreak can induce IL-12 [41, 42]. Comparing 50 COVID-19 patients with eight healthy controls revealed an increase of a multitude of pro-inflammatory cytokines and chemokines including IL-12p70 and IL-12p40. The upregulation was independent of the disease severity and did not change up to day 15 [26]. Another study did not detect increased serum levels of IL-12p70 in 60 COVID-19 patients compared to four healthy controls [19]. Potential confounding factors in both studies were the heterogeneity of the COVID-19 patients and the low number of controls.

In a transcriptomic study, IL-23 tended to be downregulated in peripheral blood mononuclear cells (PBMC) of COVID-19 patients [43]. Collectively, an infection with SARS-CoV-2 likely leads to enhanced IL-12 and IL-23 serum concentrations.

Th17 cells, Tc17 cells, subsets of innate lymphocytes including ILC3 and natural killer T cells, and cells of myeloid origin are sources of IL-17 [44–46]. IL-17 contributes to anti-infectious responses and to cytokine and chemokine production particularly at epithelial sites including the lung [47]. The incorporation of IL-17 in some large viruses, such as HSV, suggests a role in anti-viral immunity, and virus-specific IL-17 producing T cells have been detected [48]. However, IL-17 enhances the respiratory-syncytial-virus-induced production of neutrophil-attracting chemokines, thereby increasing neutrophil recruitment into the lung [49]. A study of 41 COVID-19 patients demonstrated a significant increase of IL-17 serum concentration of intensive care unit (ICU) patients compared to healthy subjects but not to non-ICU patients [19]. Comparison of 123 COVID-19 patients with mild versus severe symptoms did not show significant differences [50]. Like IL-12 and IL-23, the serum concentration of IL-17 seems to increase in COVID-19 patients, but this needs to be validated in larger trials.

Transcriptomics of bronchoalveolar lavage fluid (BAL) and PMBC of small numbers of COVID-19 patients and healthy controls identified complement activation and humoral immune responses among the top-differentially regulated pathways [43]. While several cytokines were differentially expressed, molecules of the IL-36 pathway were not among them. Although these data have not been validated, IL-36 seems to be unaffected by COVID-19.

SARS-CoV-2/COVID-19 and type 2 immunity (IL-4, IL-13, IL-5, IL-31, IgE)

Type 2 cytokines such as IL-4, IL-13, IL-5 and IL-31 as well as IgE have scarcely been studied in SARS-CoV-2 infections.

Theoretically, they may even oppose COVID-19-associated inflammation depending on the phase of the infection. They could weaken the early immune defense as observed in atopic dermatitis (AD) and herpes viruses or modulate later phases. Type 2 cytokines are not part of the hyperinflammation in the lungs of COVID-19 patients [30] but may modulate the cytokine storm as we know that these mediators can inhibit type 1 and type 17 immune responses [51]. Among hospitalized patients with COVID-19, those with allergic diathesis are only a minority [52]. Until reliable registry entries are available, data on targeted therapies with reported side-effects and safety issues in other viral infections could help us to approach a possible risk in SARS-CoV-2 infected patients.

Likewise, no data on SARS-CoV-2 infections in AD patients, a prototypic IL-4/IL-13-mediated type 2 disease, is available yet. AD patients often suffer from comorbid viral infections as a consequence of type 2 immunity dominance [53]. Clinical studies indicated that dupilumab did not reduce control of airway infection, but rather improved control of herpes virus infection [54]. Accordingly, two Italian studies indicate no increased risk of AD patients under dupilumab therapy to succumb to SARS-CoV-2 infection [55, 56]. Regarding IL-13 blockade (tralokinumab, lebrikizumab), the few data available similarly suggest no effect on viral disease [57, 58].

Eosinophils are a hallmark of type 2 diseases; their reduction by inhibiting IL-5 function (mepolizumab, benralizumab, reslizumab) in eosinophilic asthma leads to disease control and helps to reduce steroids. A positive effect of IL-5 inhibition was postulated on the course of COVID-19 in patients with asthma [59]. Like IL-4 and IL-13, IL-5 has not been attributed an essential role in COVID-19.

Another type 2 cytokine that can be targeted in patients with intense pruritus is IL-31. Within the limited patient cohort treated with nemolizumab, no increased risk for upper airway infections, but gastrointestinal and musculoskeletal side effects occurred [60]. The development of peripheral edema under therapy is not well understood [61].

Targeting IgE with omalizumab in asthma or chronic spontaneous urticaria patients did not increase upper airway infections [62]. IgE is low or not detectable under normal conditions, and it is not secreted in response to SARS-CoV-2 infection.

There is currently no scientific evidence to suggest that inhibition of type 2 mediators in patients with the respective diseases should be avoided due to the SARS-CoV-2 pandemic.

SARS-CoV-2/COVID-19 and B-cell immunity

The anti-CD20 antibody rituximab, approved for the treatment of pemphigus vulgaris and B cell lymphoma, depletes B lymphocytes for months resulting in abrogation of humoral responses. It may therefore be problematic for patients infected with SARS-CoV-2. On the other hand, production of high levels of SARS-CoV anti-spike IgG may contribute to a more severe course of COVID-19 [63], which might be avoided when B cells are depleted. Two patients suffering from granulomatosis with polyangiitis who had been treated with rituximab before observed quite rapid resolution of COVID-19 [64, 65]. While systematic studies on COVID-19 and B cell depletion are not available, the application of rituximab during the pandemic needs to be considered very carefully in each individual case.

SARS-CoV-2/COVID-19 and immune checkpoint regulators

While immune checkpoint molecules can be expressed constitutively, induction by TCR binding or cytokines is more common [66, 67]. They control important balances within the immune system, the modulation of which has revolutionized anti-tumor therapies [68, 69]. Although HIV or HBV infections lead to increased and persistent PD-1 expression on T cells [70], immune checkpoint inhibitors (ICI) appear to be safe and effective in patients with chronic viral hepatitis or HIV infection [71–73]. There are no actual data on the influence of COVID-19 on expression or function of CTLA-4, PD-1 or PD-L1. In a cohort of patients with lung cancer, no association of prior exposure to PD-1 blockade and severity of a SARS-CoV-2 infection was found [74]. In a melanoma patient treated with PD-1 inhibitors no particularly severe course of COVID-19 occurred [75].

A not yet peer-reviewed retrospective analysis by Diao et al. in MedRxiV (pre-print server) found significant lymphopenia in 522 Chinese patients with COVID-19, which corroborates earlier findings in a single Chinese patient [76] and in a Greek cohort [77]. In the study by Diao et al., PD-1 expression by peripheral T cells of 14 SARS-CoV-2-infected patients was significantly higher compared to three healthy donors and seemed to correlate with disease severity. Increasing PD-1 and TIM-3 expression on T cells over time correlated with the severity of COVID-19 in three patients. Although preliminary, these data are in line with the increase of immune checkpoint molecules in viral infections.

Since viral infections increase the expression of checkpoint molecules, and ICI can trigger a cytokine storm (cytokine release syndrome) similar to COVID-19 [78], it is conceivable that ICI could worsen the course of COVID-19 or, conversely, COVID-19 could increase the (desired and undesired) effects of ICI [78, 79]. Interestingly, the cytokine storm induced by either COVID-19 or ICI can be successfully treated with tocilizumab (anti-IL-6R) [80, 81]. Thus, the ICI mode of action and COVID-19 share remarkable similarities with both leading to adverse immune hyperactivation.

SARS-CoV-2/COVID-19 and orally targeted molecules (JAK, PDE4, calcineurin)

Patients treated with small molecule inhibitors of immunological pathways might be vulnerable in the current pandemic. However, direct evidence is missing, whether they are at higher risk of acquiring SARS-CoV-2, of developing a more severe disease course, or of generating a non-protective anti-viral immune response. It is also conceivable that some small molecules can alleviate the cytokine storm in COVID-19 patients.

As JAK inhibitors (JAKi) prevent signaling of many cytokine receptors, common infections are frequent severe adverse events and serious herpes zoster is a drug class-specific risk [82]. Tofacitinib (JAK1/3 inhibitor), baricitinib and upadacitinib (both JAK1/2 inhibitors) are currently approved drugs [83]. JAK2 inhibition appears to block cellular entry of SARS-CoV-2 and may thus decrease the infectivity in lung cells [84]. Many cytokines released during a COVID-19-associated cytokine storm signal *via* the JAK-STAT pathway [84]. Moreover, Th17 cells likely contribute to this cytokine storm resulting in tissue damage and pulmonary edema. Although JAK inhibition can weaken host inflammatory responses and impair hematopoiesis, therapies using JAKi may decrease unwanted inflammatory reactions. Thus, as JAKi may alleviate acute respiratory distress syndrome (ARDS) in COVID-19 patients, several phase 2 trials are currently underway.

The immunosuppressants cyclosporin (CsA) and tacrolimus act rather selectively on T cells by inhibiting calcineurin phosphatase. No data is available on their effect in COVID-19 patients [85]. Interestingly, CsA demonstrated antiviral activity *in vitro*. It inhibits replication of some RNA viruses including *Betacoronaviridae*, which employ cyclophilins as chaperones and NFAT signaling. These data led to the speculation that CsA may ameliorate SARS. It is unclear whether the antiviral activity may impair the mounting of an immune response to coronaviruses and, consequently, increase vulnerability to future infections. These immunosuppressants might only be successful in SARS-CoV-2-infected patients, if no uncontrolled viral replication occurs. Tacrolimus is currently being tested in a phase 3 trial for COVID-19 lung injury.

Apremilast is a PDE4 inhibitor which increases cellular cyclic AMP levels, thereby controlling production of inflammatory cytokines in leukocytes and epithelial cells. It does not lead to apparent immunosuppression, and severe viral infections are not common adverse events. Although actual data are missing, apremilast, because of its overall low risk of severe immunological deterioration, may have a comparably favorable risk profile in patients with chronic inflammatory diseases during the current COVID19 pandemic.

SARS-CoV-2/COVID-19 and antimalarials

Hydroxychloroquine (HCQ) and chloroquine (CQ) accumulate in lysosomes where they inhibit endocytosis, autophagy and, consequently, MHC class II (auto)antigen presentation. They also inhibit TLR7 and TLR9 binding to the respective ligands (DNA, RNA), the type I interferon response, cytokine (IL-1, TNF, IL-6) and chemokine synthesis (CCL4), and down-regulate CD40L [86].

Several studies demonstrated *in vitro* antiviral activity of antimalarials. During the SARS 2003 outbreak caused by SARS-CoV-1, CQ was proposed as potential agent [87]. It was demonstrated later that antimalarials also impair the glycosylation of ACE2, the cellular receptor of SARS-CoV-1 (and SARS-CoV-2) thus inhibiting virus entry into the cell [88]. Chloroquine is active against SARS-CoV-2 *in vitro* [89], and it was recommended by Chinese experts for the treatment of COVID-19-associated pneumonia despite lack of clinical data [90]. A small uncontrolled French study combined HCQ with azithromycin and reported a significant reduction of viral load [91]. A double-blinded randomized trial from Brazil was prematurely terminated after enrolling 81 of the intended 440 patients because of serious adverse events including many fatalities [92]. An observational study of 1,376 COVID-19 patients revealed no difference regarding the primary endpoint, freedom of intubation or death, between HCQ-treated and -untreated patients [93]. In view of these data the conducting center withdrew its institutional suggestion to treat COVID-19 patients with HCQ.

The US Food and Drug Administration has issued "Emergence Use Authorizations" to provide CQ and HCQ for treating adults and teenagers when participation in clinical trials is not possible [94] but later revoked those authorizations since on basis of newer data it is now considered unlikely that CQ and HCQ are effective in treating COVID-19 (https: //www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and; published on June 15, 2020; accessed on June 21, 2020). The European Medicines Agency recommended CQ and HCQ in the context of COVID-19 only in clinical trials or within national emergency use programs [95]. A recent editorial on the use of HCQ for COVID-19 concluded that the current data situation should prompt "some degree of skepticism toward the enthusiastic claims about chloroquine and perhaps serve(s) to curb the exuberant use" [96].

It appears reasonable to continue CQ or HCQ for approved or long established off-label conditions when indicated. While the doses prescribed in dermatology are usually lower than in COVID-19 studies, health care professionals should nevertheless carefully monitor their patients for adverse events and report side effects to regulatory authorities [86, 97].

SARS-CoV-2/COVID-19 and general immunosuppression

In patients with immune-mediated diseases the question arises whether immunosuppressive therapies should be maintained, reduced or discontinued in the context of SARS-CoV-2. Of course, there is no general answer but three basic considerations: First, immunosuppression could interfere with infection control and thus be detrimental. Second, immunosuppression could support treatment by suppressing the COVID-19-associated immunopathology [30]. Third, discontinuation could trigger exacerbation of the treated underlying disease, which would be harmful [98]. There is no evidence for an increased risk of immunosuppressed patients from COVID-19.

COVID-19 did not affect the hospitalization or death rates of psoriasis patients [99, 100]. However, there is also no evidence of protection of immunosuppressed patients from COVID-19-associated immunopathology, as reported for renal transplant recipients [101]. Therefore, current guidelines for classical immunosuppressants can be summarized as follows: *i)* In patients without SARS-CoV-2 infection, immunosuppressive therapy can be continued; *ii)* In mild or asymptomatic COVID-19 cases, continuation of therapy should be decided on a case-by-case basis; *iii)* In COVID-19 patients with severe symptoms, withdrawal of immunosuppressive medications is advisable; however, the final decision should be made by the treating physician and the ICU team.

Glucocorticosteroids

There is no general evidence that patients with SARS-CoV-2 infection benefit from glucocorticosteroids (GC) [31, 102]. For instance, the use of oral GC was higher among COVID-19 patients with immune-mediated inflammatory disease who were hospitalized [103]. A retrospective analysis of COVID-19 patients receiving methylprednisolone did not show a beneficial clinical outcome [101]. Overall, it appears that systemically administered GC rather have a negative effect on the course of COVID-19. Thus, GC treatment of severe SARS-CoV-2 infection is recommended only in the context of clinical trials [101, 104] or if indicated within a necessary therapy regimen [105].

Methotrexate

The relevance of methotrexate for the clinical course of COVID-19 is unknown. While a case study of patients with immune-mediated inflammatory disease found that those taking methotrexate required hospitalization more often [103], a systematic review – also including reports of SARS-CoV-1 and MERS – concludes that there is no definitive evidence for contraindication of methotrexate in auto-immune diseases [100, 106].

Mycophenolate mofetil (MPM)/mycophenolic acid (MPA)

In vitro, MPA showed anti-viral activity against MERS-CoV and SARS-CoV-1 [100, 107], [108] but was detrimental in animal studies [109]. A psoriasis patient on MPM treatment experienced a very mild form of COVID-19, suggesting that MPM can be continued [110].

Azathioprine

In renal transplant recipients infected with SARS-CoV-2, patients taking azathioprine did not have higher risk of severe disease [98].

Dapsone and colchicine

Both agents may inhibit the cytokine storm and neutrophil chemotaxis to the lungs [111, 112]. However, there are no clinical trials available to support this hypothesis.

Dimethyl fumarate

There are also speculations about a potential therapeutic benefit of dimethyl fumarate because of its ability to scavenge oxidative stress. Again, evidence to support this hypothesis is missing.

SARS-CoV-2/COVID-19 and neutrophil-mediated innate immunity

Neutrophils as part of the innate immune system can produce NETs (neutrophil extracellular traps) [113]. Excessive NETosis can be deleterious, as NET-components are cytotoxic, immunogenic and pro-thrombotic [114, 115] and can damage organs in several diseases [38, 116], [117], which are also affected in severe COVID-19. Neutrophils directly or indirectly contribute to cytokine release, such as IL-1β or IL-6 [118], thus facilitating the COVID-19 cytokine storm. Hence, activated neutrophils and NETs may contribute to COVID-19. Indeed, neutrophilia predicts poor outcome [25] and severe neutrophilic infiltrations were noted in patients who died from COVID-19 [38, 119].

NETs can also contribute to mucus thickening and bacterial superinfection in respiratory diseases such as cystic fibrosis [120]. Inhalative DNase I improves lung function through degradation of extracellular DNA [121] and could be a simple, effective and safe addition to the therapy of COVID-19 [122].

Furthermore, NETs link immunopathology and thrombosis. They degrade antithrombin III, activate platelets and the contact pathway of coagulation. Blood clots occur in 20–30 % of patients with COVID-19 [123]. These patients are not only prone to large thromboembolic events but also to microvascular thrombosis in many organs [38, 124]. In animal models, systemic DNase I treatment dissolved NETs and restored organ perfusion [125], which fuels corresponding speculations in COVID-19. Thus, targeting neutrophils and NETs could potentially ameliorate COVID-19. In addition to the abovementioned DNAse I, a number of other compounds are currently being developed and may disrupt detrimental neutrophil functions in the future.

Conclusions

According to our current state of knowledge, there is no evidence-based reason to discontinue or not start necessary immunomodulatory therapies in patients with inflammatory diseases or tumors during the SARS-CoV-2 pandemic. But of course – as is often the case in uncertain situations with insufficient and constantly evolving data – we must be careful and vigilant. As the example of 4-aminoquinolines shows, perspectives can change rapidly. In any case, there is no general recommendation regarding discontinuation of immunomodulatory therapies. Some cytokine inhibitors or other immune modulators could even have a positive effect on the course of COVID-19 disease. Depending on the specific therapy, the possible interaction with SARS-CoV-2-induced effects must be considered in a differentiated way and often individual case decisions must be made. Of course, our knowledge is in a state of flux, and our considerations delineated herein are based on the currently emerging pattern of immunological changes in COVID-19. Some of our statements should therefore be regarded as preliminary or a matter of opinion, respectively. We must remain vigilant and we would encourage our colleagues to critically evaluate their observations in patients infected with SARS-CoV-2.

Abbreviations

COVID-19	coronavirus disease 2019
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
HBV	hepatitis B virus
HIV	human immunodeficiency virus
ICI	immune checkpoint inhibitor
Ig	immunoglobulin
IL	interleukin
ILC	innate lymphoid cell
JAK	Janus kinase
JAKi	Janus kinase inhibitor
NET	neutrophil extracellular trap
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B-cells
NFAT	nuclear factor of activated T cells
PBMC	peripheral blood mononuclear cell
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand-1
PDE4	phosphodiesterase 4
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Tc	cytotoxic T cell
TCR	T cell receptor
Th	helper T cell
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
TLR	toll-like receptor
TNF	tumor necrosis factor

Correspondence to

Michael P. Schön, MD
Department of Dermatology, Venereology and Allergology
University Medical Center Göttingen

Robert-Koch-Strasse 40
37075 Göttingen, Germany

E-mail: michael.schoen@med.uni-goettingen.de

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