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None.

Systemic immunosuppression in times of COVID-19: Do we need to rethink our standards?

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Summary

The current SARS-CoV-2 pandemic particularly endangers older people with pre-existing cardiopulmonary and metabolic conditions. However, it is also currently under discussion whether patients under immunosuppressive therapy also have a higher risk of suffering a severe course of the COVID-19 disease. In principle though, there is currently no data available for a general reduction or pause of immunosuppression in patients with autoimmune diseases because of the SARS-CoV-2 pandemic. However, since there is currently neither an effective therapy nor corresponding vaccination protection, the indication for a prolonged immunosuppressive therapy should be made with special care. In particular, immunotherapeutic agents that produce long-term effects (e.g., rituximab) should be used with special caution. In contrast, immunomodulating substances that do not suppress antiviral immunity (e.g. systemic immunoglobulins, doxycycline), or that have intrinsic effects on SARS-CoV-2 (calcineurin inhibitors, chloroquine, hydroxychloroquine) may be useful alternatives.

Effects of SARS-CoV-2 on the immune system

Viruses activate the innate immune system (especially macrophages, dendritic cells and other myeloid cell types) by binding to so-called "pattern recognition" receptors, which include Toll-like receptors (TLR) on the cell membrane and in endosomes as well as cytoplasmic inflammasome activators [1]. These lead to the production of type 1 interferon and a multitude of inflammatory cytokines. In this way, the adaptive immune system (especially T and B cells) is activated, the expansion of virus-recognizing T cells and the formation of neutralizing antibodies is stimulated and the virus, in most cases, eliminated. Although this is the normal case also in COVID-19 patients, in individual patients the virus can cause hyperactivation of the immune system, which then triggers the clinical picture of acute respiratory distress syndrome (ARDS). Typical findings in this situation are, in addition to increasing respiratory distress, maximally elevated inflammatory parameters and inflammatory cytokines (especially IL-6, IL-1β, IL-17) in serum. Neutrophilia, lymphopenia as well as the ratio of these leukocyte populations to each other, the extent of the increase in ferritin, CRP, IL-6, D-dimers and fibrinogen and the oxygen saturation parameters (SaO2/FiO2) are suitable prognostic parameters for the course of the disease [2–6]. The laboratory parameters for severe COVID-19 disease are very similar to those for hemophagocytic lymphohistiocytosis (HLH), which can occur in the course of hematological neoplasia or as a side effect of immune checkpoint inhibitor or CAR-T cell therapy [7]. The severe inflammatory response (hyperinflammation) is the rationale for clinical testing of cytokine antagonists (anti-IL-6: tocilizumab, IL-1RA: anakinra, anti-IL-1β: canakinumab) or for administration of corticosteroids in severe SARS-CoV-2 infections.

In addition to hyperinflammation, however, most patients suffer from an exhaustion of the adaptive immune system (immune exhaustion) later in the course of the disease, accompanied by increasing lymphopenia and reduced activation of T cells, which can be recognized, for example, by T cell expression of the surface markers PD-1 and TIM-3 [8, 9]. This state of exhaustion of the immune system after

hyperactivation, comparable to muscular exhaustion after extensive physical activity, can ultimately lead to a collapse of the antiviral immune response and the death of the patient. For this reason, the early therapeutic administration of corticosteroids in this disease is very controversial, especially as it is also mostly counterproductive in other severe viral infections [10, 11]. However, high-dose corticosteroids can be beneficial to hospitalized patients in the later course of the disease [12].

Immunosuppression – a risk for severe forms of COVID-19 disease?

Due to the complex immune regulation in SARS-CoV-2 infections, in which too much immune activation ultimately causes the failure of immune control of the pathogen and inflammatory regulation, the question arises as to how patients who have a therapeutically altered immune system react to this infection. In this regard, initial, still very preliminary findings are already available; several publications unanimously report that the course of the disease is significantly more severe in immunocompromised patients who have undergone a heart or kidney transplant and is fatal in about 20–30 % of these patients [13–17]. In contrast, the mortality rate was not significantly increased in patients with chronic inflammatory bowel disease, though it should be noted that only a minority of these patients had taken immunosuppressive drugs in higher doses [18]. There was also no increased risk of severe disease progression in patients with systemic psoriasis [19, 20]. However, an individual case report describes a severe course in a vasculitis patient taking rituximab [21]. Due to their profound and long-term effect on antibody production, the administration of B-cell-depleting anti-CD20 antibodies may be particularly problematic in this context, though conclusive studies are still lacking. Overall, the data to date suggest that high-dose and long-term immunosuppression can worsen the course of COVID-19 and is associated with a higher risk of death.

There is thus some evidence that therapeutic immunosuppression might increase the risk of a severe course of SARS-CoV-2 infection, at least in multimorbid patients with pre-damaged organs or cardiovascular damage. Although Di Altobrando et al. [22] did not find indications for a particularly severe course of disease in immunosuppressed patients with bullous autoimmune dermatoses, one should considered whether the indication for a potent immunosuppression in dermatological diseases in times of the corona pandemic needs to be more strictly defined, particularly since bullous autoimmune diseases, collagenoses, drug allergies or vasculitis typically occur in elderly patients with comorbidities which are anyway associated with the risk of a severe course of disease. However, this does not apply equally to all immunosuppressants and immunotherapeutic agents, as the substances have different mechanisms of action and some have little or no suppressive effect on the immune system as a whole. It is known from approval studies and registry data that therapy with most biologicals is not associated with a significantly increased risk of viral diseases. Similarly, in a recent meta-analysis, there was no evidence of a severe course of SARS-CoV-2 infection under therapy with TNF blockers, IL-1 blockers or IL-6 blockers [23, 24], and the latter two are even used therapeutically to combat SARS-CoV-2 induced hyperinflammation. So far, there are also no indications for a disease-worsening effect for other immunosuppressive drugs (methotrexate [MTX], azathioprine, JAK-inhibitors, tacrolimus). A report on Covid-19 disease in 86 patients with a range of autoimmune diseases of the skin, joints and intestines treated with various immunosuppressive drugs showed a hospitalization rate comparable to that of COVID-19 patients in the general population [24]. There is also little data on the effects of long-term glucocorticoid therapy on the course of COVID-19 disease. However, a first study in this area also found no evidence of more severe disease progression in cortisone-pretreated patients, although the dose and duration of steroid therapy were not recorded [25].

In summary, there is currently no evidence for a generally aggravated course of infection of COVID-19 disease in patients that are under chronic immunosuppression.

Considerations for the treatment of dermatological autoimmune diseases

Despite a paucity of data, a general discomfort remains when interfering with the immune system in a situation where antiviral defense is of particular relevance. However, some immunotherapeutic agents appear to be particularly unproblematic for pharmacological reasons alone in the context of a SARS-CoV-2 infection. These include in particular chloroquine and hydroxychloroquine. There has already been speculation in the lay press about a possible therapeutic efficacy of chloroquine or hydroxychloroquine in COVID-19 disease, so that these substances are often regarded as uncritical for the long-term treatment of patients with autoimmune diseases. However, Borba et al. [26] report on a randomized clinical trial for the therapy of advanced, severe COVID-19 disease with high-dose chloroquine (1,200 mg/die), which showed an increased mortality in the chloroquine-treated group. Thus, chloroquine (or hydroxychloroquine) therapy is probably not effective or even counterproductive in advanced COVID-19 disease. In contrast, there is at least some pharmacological rationale for a possible prophylactic effectiveness of this substance in protection against SARS-CoV-2

infection, since chloroquine inhibits endosomal NADPH oxidase and virus uptake into cells [27–29]. However, in clinical practice, long-term therapeutic use of hydroxychloroquine in patients with systemic lupus erythematosus does not appear to protect against covid-19 disease or a severe course of the disease [30, 31]. Thus, there is currently no evidence that therapy with chloroquine or hydroxychloroquine has any negative or protective effects on SARS-CoV-2 infection or that it changes the course of infection.

Cyclosporine also seems to be less problematic, since on the one hand humoral immunity is only slightly affected by this substance and no increased rates of viral infections have been described even with long-term therapy [32], and on the other hand because cyclosporine has an intrinsic antiviral activity, which also acts against *Coronaviridae* [33].

For the treatment of bullous pemphigoid there is, besides the systemic corticosteroids, also the option of a therapy with tetracycline, nicotinamide and topical clobetasol, which in a recently published long-term study showed a survival advantage over systemic steroid treatment for the mostly elderly and multimorbid patients independent of a risk of SARS-CoV-2 infection [34]. In the opinion of the authors, this therapeutic alternative, which is currently not widely used in Germany, therefore merits greater consideration at the present time.

The administration of intravenous immunoglobulins is a further, particularly interesting alternative to conventional immunosuppressants. This is especially true for all bullous autoimmune skin diseases, but also for most collagenoses, neurological autoimmune diseases, scleromyxedema, severe drug allergies (e.g., toxic epidermal necrolysis) and vasculitis, for which this therapy is a therapeutic alternative according to the European S1 guideline [35]. Interestingly, there is even evidence that common commercially available immunoglobulin preparations contain antibodies reactive to SARS-CoV-2 [36], probably due to cross-reactivity with conventional corona viruses with which the donors have had contact. In addition, the successful therapeutic use of immunoglobulins in severe COVID-19 disease has already been reported [37]. In this respect, therapy with intravenous immunoglobulins may not only improve the underlying disease without having to accept immunosuppression, but may even offer some protection against SARS-CoV-2 infections. Therefore, the authors recommend that this therapy option should be considered especially in patients with other risk factors for a severe course of SARS-CoV-2 infection.

Conclusion and recommendations

The current SARS-CoV-2 pandemic presents us with new challenges, not least in the selection of immunotherapeutic agents for the treatment of autoimmune diseases. A differentiated consideration of the various substances appears to be just as necessary as a careful scientific analysis of the course of disease in immunocompromised patients with COVID-19 disease.

Essentially, there is currently no data available for a general reduction or pause of immunosuppression in patients with autoimmune diseases, since the risk of an insufficient therapy of these mostly severe diseases is clearly higher than that of an aggravated course of COVID-19 disease. Nevertheless, due to their pharmacological effects, the indication for a long-term and high-dose systemic steroid therapy as well as for a therapy with anti-CD20 antibodies should currently be defined with particular care.

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