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Short Communication

Interdisciplinary Approach on Treatment of Patients with Immune-Mediated Inflammatory Diseases in Times of COVID-19

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Since the first cases of acute atypical respiratory disease caused by the novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), occurred in Wuhan in December 2019, Coronavirus Disease 2019 (COVID-19) has spread around the globe with a wide range of severity [1]. With dysregulation of the immune system being a hallmark of COVID-19, it is of special interest whether the disease poses an added risk to patients with immune-mediated inflammatory diseases (IMIDs) and requires adaptation of their treatment.

1. Pathogenesis and Symptoms of COVID-19

SARS-CoV-2 presumably targets lung type-II pneumocytes, ileal absorptive enterocytes and nasal goblet secretory cells that co-express angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2. Upon SARS-CoV-2 infection of airway epithelial cells, interferon-mediated inflammation seems to stimulate upregulation of ACE2 [2]. Symptoms of

COVID-19 vary from mild to severe, including fever, dysgeusia, diarrhea, cough, sore throat, arthralgia, dyspnea, pneumonia, acute respiratory distress syndrome and death [1, 3, 4]. Disease deterioration has been associated with IL-6-driven immune dysregulation, mainly characterized by lymphopenia, and IL-1β-driven macrophage activation syndrome, causing an overproduction of pro-inflammatory cytokines [5].

Interestingly, there is evidence that approximately one in four COVID-19 patients presents with dermatological symptoms, some of which may emerge before more common clinical features. Respective cutaneous manifestations are diverse, including erythematous, urticarial, and vesicular lesions, with the trunk being the most commonly affected site [6]. Also chilblain-like lesions on toes and feet have been reported by suspected and confirmed COVID-19 patients [7].

2. Do Patients with IMIDs face an Increased Risk from COVID-19?

Major risk factors for severe progression of COVID-19 include older age and comorbidities, especially hypertension and diabetes [8]. Since serious outcomes of COVID-19 are associated with hallmark immunological features like hyperinflammation and lymphopenia, the question arises if patients with IMIDs, such as psoriasis, atopic dermatitis (AD), hidradenitis suppurativa (HS), inflammatory bowel diseases (IBD) and rheumatic diseases, also face an increased risk. There is no statistical evidence to date, meaning that we must rely on rational thinking and drawing analogies. From our current state of knowledge, patients with IMIDs do not per se face an increased risk for severe progression of COVID-19. This assumption is supported by a case series from New York including suspected and confirmed COVID-19 patients with IMIDs, who received anti-cytokine biologics, other immunomodulatory therapies, or both. The hospitalization rate among those patients was consistent with that among COVID-19 cases in the general population [4].

3. Recommendations for Clinical Practice

Here, we outline our recommendations for clinical practice based on our clinical observations and expert discussions (Table 1). Generally, initation of biological or systemic therapies should be evaluated after an individual benefit/risk assessment and immunomodulatory therapies should not be stopped prophylactically in times of COVID-19. Instead, flare-ups of inflammation should be prevented because they could increase the risk of COVID-19-related complications, as seen in patients with active IBD [3]. In COVID-19-positive patients, pausing biological or systemic treatment, especially immunosuppressive therapies, should be considered until recovery from COVID-19. Furthermore, telemedicine is increasingly coming into focus, enabling optimal remote consultations. Cases, treatments and outcomes should be registered and communicated to the community to rapidly define the impact of COVID-19 on patients with IMIDs.

3.1 Dermatological implications

For psoriasis, therapies based on IL-12/23, IL-23 and IL-17 inhibitors, as well as methotrexate, apremilast and fumaric acid esters are not associated with an obviously increased risk of viral infections or of complications during such infections. However, methotrexate very rarely causes pulmonary fibrosis or pleuritis. Even though transplant patients exposed to cyclosporine showed no increased risk of complications, we recommend paying special attention to these patients if they are at high risk or predisposed to infections.

TNF-α inhibitors, especially infliximab in psoriasis, are associated with a slightly increased risk of and during viral infections. The same holds true for adalimumab in

HS. Despite the dosage of adalimumab being higher for HS than for psoriasis, we recommend continuing the treatment. For AD and chronic spontaneous urticaria, no safety data linking dupilumab or omalizumab to COVID-19 are available. Since IL-4 does not seem to play a major role in its pathophysiology, both medications appear to be safe.

3.2 Rheumatological implications

We do not recommend stopping rheumatoid arthritis therapy prophylactically, but its intensity could be reconsidered. Even though TNF-α inhibitors carry a slightly increased risk of viral infections, we did not observe any signals indicating serious progression due to viral infections associated with TNF-α inhibitors. Furthermore, in contrast to methotrexate and cell-targeting therapies, TNF-α inhibition did not reduce the immune response to influenza vaccines [9]. Tocilizumab, a registered rheumatoid arthritis medication, is approved for treating cytokine release syndrome and could potentially be protective in severe cases of COVID-19 [10]. If the hypothesis of overwhelming cytokine activation underlying the serious progression of COVID-19 holds true, continuation of therapy based on TNF-α, IL-1 or IL-6 inhibition should be seriously considered in COVID-19 patients.

On the contrary, therapies based on T-cell inhibition or steroids should be paused during infection. Furthermore, to reduce the antiproliferative effect of methotrexate, patients should take folinic acid instead of folic acid 24 hours after methotrexate injections. Generally, we endorse switching from intravenous to subcutaneous drug administration, especially for elderly patients, to enable staying at home.

3.3 Gastroenterological implications

Optimal treatment of patients with IBD should be ensured to prevent flare-ups. Importantly, patients with IBD depend on invasive and radiological examinations as well as elective surgery, which makes excretion of SARS-CoV-2 particles via the stool a particular concern. We also have evidence that around 30% of COVID-19 patients show gastroenterological manifestations, which needs to be considered when IBD patients present with diarrhea. Since prednisolone can increase the risk of a SARS-CoV-2 infection and the severity of COVID-19, cortisone-based therapies should be avoided in times of COVID-19. Furthermore, steroid treatment of COVID-19 patients has been associated with increased mortality. First signals indicate that combination therapies of TNF-α inhibitors and immunosuppressants, such as azathioprine, 6-mercaptopurine and methotrexate, may correlate with the severity of COVID-19, although we have not observed such signals on TNF-α inhibitor monotherapies.

Medication	**Indication**	**Recommendation***
Oral corticosteroids	Psoriatic arthritis Rheumatoid arthritis Ankylosing spondylitis Juvenile idiopathic arthritis Inflammatory bowel diseases	Could be started and should be continued with precaution and careful risk/benefit assessment
Immunosuppressants - Methotrexate - Azathioprine	Plaque psoriasis Psoriatic arthritis Rheumatoid arthritis	Could be started and should be continued

- Mycophenolate mofetil - Sulfasalazine - Budesonide - Mercaptopurine - Cyclosporine - Leflunomide - Hydroxychloroquine - Chloroquine	Ankylosing spondylitis Juvenile idiopathic arthritis Inflammatory bowel diseases	
Fumaric acid ester	Plaque psoriasis	Could be started and should be continued
Phosphodiesterase-4 inhibitor apremilast	Plaque psoriasis Psoriatic arthritis	Could be started and should be continued
Janus kinase (JAK) inhibitors	Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	Could be started and should be continued
TNF- blockers	Plaque psoriasis Psoriatic arthritis Rheumatoid arthritis Ankylosing spondylitis Juvenile idiopathic arthritis Inflammatory bowel diseases Hidradenitis suppurativa	Could be started and should be continued
IL-12/23 blocker ustekinumab	Plaque psoriasis Psoriatic arthritis Inflammatory bowel diseases	Could be started and should be continued
IL-23 blockers	Plaque psoriasis	Could be started and should be continued
IL-17 blockers	Plaque psoriasis Psoriatic arthritis Ankylosing spondylitis	Could be started and should be continued
Anti-IgE antibody omalizumab	Chronic spontaneous urticaria	Could be started and should be continued
IL-4/IL-13 blocker dupilumab	Atopic dermatitis	Could be started and should be continued
T-cell blocker abatacept	Rheumatoid arthritis Juvenile idiopathic arthritis	Start or re-administration must be postponed
Anti-CD20 antibody rituximab	Rheumatoid arthritis	Start or re-administration must be postponed
IL-6 receptor blockers	Rheumatoid arthritis Juvenile idiopathic arthritis	Could be started and should be continued
IL-6 receptor blockers tocilizumab	Giant cell arteritis Cytokine release syndrome	Could be started and should be continued

* These recommendations are based on expert opinions. For the time being, there is not enough scientific data to support them with a high degree of certainty. Decisions should be made individually, taking important factors such as comorbidities into consideration and paying special attention to cardiovascular diseases and diabetes. Irrespective of the medication, we do not recommend starting or continuing treatment in patients with confirmed or suspected COVID-19, no matter what the COVID-19 severity.

Table 1: Treatment recommendations for patients with immune-mediated inflammatory diseases in times of COVID-19.

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