Expert recommendations for the management of autoimmune bullous diseases during the COVID-19 pandemic

Editor

Autoimmune bullous diseases (AIBDs) are potentially life-threatening disorders comprising intra-epidermal/epithelial (pemphigus) and sub-epidermal/epithelial blistering diseases (pemphigoid and dermatitis herpetiformis). Corticosteroids and non-steroid immunomodulatory agents are the mainstays of treatment. Treatment can be challenging particularly in pemphigus, mucous membrane pemphigoid and epidermolysis bullosa acquisita which may require more intense immunosuppressive approaches.[1,2]

A novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for the recent worldwide coronavirus disease 2019 (COVID-19) pandemic. Since immunosuppressive therapy can generally inhibit antiviral immunity, patients with AIBDs undergoing immunomodulatory treatment, especially elderly patients with comorbidities, may be at higher risk of worse outcomes should they develop COVID-19. On the other hand, it has been postulated that immune system over-activation is responsible for the lung injury caused by SARS-CoV-2 and that a subgroup of patients might actually benefit from immunosuppressive drugs.[3]

Similar to a recent publication concerning atopic dermatitis,[4] a panel of AIBD experts from different academic centres addressed questions regarding COVID-19 and the use of common immunomodulators (corticosteroids, azathioprine, mycophenolate mofetil/sodium, cyclophosphamide, methotrexate, cyclosporine, dapsone/sulphapyridine, doxycycline/tetracycline, colchicine, rituximab, high-dose intravenous immunoglobulins [IVIG] and immunoadsorption/plasmapheresis) in patients with AIBDs.

What do we recommend for AIBD patients treated with immunomodulating therapy during the SARS-CoV-2 pandemic?

- Maintain immunomodulatory therapy when needed since unjustified withdrawal could lead to uncontrolled AIBD activity associated with high morbidity and mortality.[1,2]
- Adhere to the advice from local health authorities in each country.
- Follow standard precautions including social distancing and hygienic procedures.

What considerations should be made regarding immunomodulating therapy in SARS-CoV-2-infected patients with AIBDs?

- Patients with confirmed COVID-19 should initially undergo risk evaluation.
- Azathioprine, mycophenolate mofetil/sodium, cyclophosphamide, methotrexate and cyclosporine may be stopped for the duration of COVID-19 symptoms, whereas topical corticosteroids, prednis(ol)one ≤10 mg/day, dapsone/sulphapyridine, doxycycline/tetracycline, colchicine and IVIG can be continued.
- Prednis(ol)one >10 mg/day may be reduced depending on the activity/severity of the AIBD, age, comorbidities and severity of COVID-19 in collaboration between the dermatologist and physician in charge of COVID-19.
- Abrupt termination or considerable dose reduction of systemic corticosteroids should be avoided, particularly in patients with severe forms of AIBDs. Of note, there is some evidence that prednis(ol)one may potentially have beneficial impacts on COVID-19.[3]

Can we predict interactions of AIBDs, its complications and immunomodulating therapies with COVID-19?

- Patients with AIBDs on immunosuppressive therapies are generally prone to develop opportunistic infections including viral infections, and microbial pathogens may potentially in turn trigger the bullous disease. Of note, both pemphigus and pemphigoid are associated with increased risk of death due to pneumonia and, in the case of paraneoplastic pemphigus, bronchiolitis obliterans.[1,2] However, there is currently little information specifically pertaining to SARS-CoV-2 and AIBDs.
- Dapsone/sulphapyridine, doxycycline/tetracycline or IVIG are usually not considered to increase the risk for infections and may even decrease the risk of some infections, thus may be preferred in the COVID-19 pandemic where applicable.
- AIBD patients treated with rituximab were reported to have no additional risks for infections over high-dose corticosteroids without rituximab in general.[5] However, since long-lived SARS-CoV-2-specific plasma cells are not expected to be present in most individuals, AIBD patients treated with rituximab within the last 1 year may have a more severe/prolonged COVID-19 infection compared to healthy persons.
- Initiation of rituximab or immunoadsorption/plasmapheresis in patients with AIBDs must be weighed against the risks of conventional immunomodulatory regimens.

Finally, it is advised to remain updated through the WHO/CDC homepage (www.who.int, www.cdc.gov). Recommendations directed to AIBD patients and their families during the COVID-19 pandemic have been recently released by the European Academy of Dermatology and Venereology (www.eadv.org/covid-19/task-force).

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M. Kasperkiewicz,[1,*] E. Schmidt,[2,3] J.A. Fairley,[4] P. Joly,[5] A.S. Payne,[6] M.L. Yale,[7] D. Zillikens,[2] D.T. Woodley[1]

[1]Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA, [2]Department of Dermatology, University of Lübeck, Lübeck, Germany, [3]Lübeck Institute of Experimental Dermatology (LIED), University of Lübeck, Lübeck, Germany, [4]Department of Dermatology, University of Iowa, Iowa City, IA, USA, [5]Department of Dermatology, Rouen University Hospital, Rouen, France, [6]Department of Dermatology, University of Pennsylvania, Philadelphia, PA, USA, [7]International Pemphigus and Pemphigoid Foundation, Sacramento, CA, USA

*Correspondence: M. Kasperkiewicz. E-mail: michael.kasperkiewicz@med.usc.edu

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Safety of dupilumab in severe atopic dermatitis and infection of Covid-19: two case reports

Editor

Dupilumab is a fully human monoclonal antibody against the alpha subunit of interleukin (IL)-4 receptor that blocks signalling from both IL-4 and IL-13, which are key type 2 cytokines in the pathophysiology of atopic dermatitis (AD).[1] It shows good efficacy with a rapid response and good safety with few side-effects.[2–8] In a paper of Deleuran et al.,[9] the authors showed long-term safety and efficacy of dupilumab; they reported viral upper respiratory tract infection, cough and influenza in about 2% of patients. The European Task Force on Atopic Dermatitis in a recent paper[10] stated that dupilumab didn't increase the risk for viral infections and might thus be preferred compared to conventional systemic immunosuppressive treatments in a situation such as the COVID-19 pandemic. However, this theoretical advantage is not supported by robust clinical data and they recommended all doctors treating AD patients to remain vigilant and updated. We reported two patients with AD and COVID-19 infection in therapy with dupilumab for severe AD. The first patient is a 40-year-old man affected by AD since his early childhood. Due to his severe AD in November 2019, he started subcutaneous injections treated with dupilumab 300 mg every two weeks after a loading dose of 600 mg. Serum examination prior to the beginning of the treatment revealed high levels of immunoglobulin E (IgE) (2152 international unit (IU)/millilitre) and lactate dehydrogenase (LDH 516 unit/L). The Eczema Area and Severity Index (EASI) was 24, while the Dermatology Life Quality Index (DLQI) was 18. After 1 month, the EASI and DLQI were slightly decreased (5 and 8, respectively) and the same trend was reached by IgE (1776 IU/mL) and LDH (400 unit/L). During the third month of therapy, the patient and his father showed symptoms of COVID-19 infection. The patient developed a mild form, while his father died of interstitial pneumonia during hospitalization. The infectivologist decided to continue with dupilumab for our patient and administered acetaminophen obtaining a regular course without complications. The second patient is a 56-year-old woman affected by AD since early childhood. The patient underwent treatment with cyclosporine for 5 months in 2015 without improvement; so, in the last five years, she took prednisone continuously. In October 2019, she was admitted to our outpatient clinic for the persistence of AD despite therapy with prednisone. The patient began treatment with dupilumab in November 2019. At the baseline, serum examination revealed high levels of IgE (560 IU/mL) and normal LDH. The EASI was 28, while the DLQI was 18. After 1 month, EASI and DLQI were slightly decreased (5 and 8, respectively) and IgE was 400 IU/mL. During the fourth month of therapy, the patient and her husband showed symptoms of COVID-19 infection. They were both hospitalized, and her husband died of interstitial pneumonia. Despite the finding of interstitial pneumonia also in our patient, the infectivologist decided to continue therapy with dupilumab and to start therapy with darunavir/cobicistat and hydroxychloroquine. In addition, antibiotic coverage (ceftriaxone) was associated. The patient did not need oxygen therapy due to good respiratory exchange over the time. After 10 days, they obtained a progressive improvement of the clinical picture and the inflammatory indexes without complications or AD flares. We here reported only two cases of patients affected by COVID-19 infection in treatment with dupilumab for severe AD. In our Dermatology Department in Milan, geographic area with a high incidence of COVID-19 infection, we collected 245 patients in therapy with dupilumab and only 2 (0.82%) developed COVID-19 infection. Of these 2 patients, none had complications or abnormal course of the infectious disease. So, based on our experience, we can confirm that dupilumab is an effective and safe therapy for patients with severe AD also in cases of severe infections.

