Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Treatment considerations for patients with pemphigus during the COVID-19 pandemic

To the Editor: COVID-19, a serious pulmonary illness caused by the highly contagious novel coronavirus, severe acute respiratory syndrome (SARS) coronavirus 2, is a global pandemic. COVID-19–related mortality risk factors include advanced age, male sex, and certain comorbidities, including immunosuppression.[1] Besides direct viral-induced injury, the host cytokine-mediated antiviral response potentiates tissue damage.[1]

Pemphigus, a mucocutaneous autoimmune blistering disease, increases infection risk via multiple mechanisms, including epithelial barrier breakdown and therapy-related immunosuppression. Given the need to balance appropriate pemphigus treatment with reduction of COVID-19–associated mortality risk, we have outlined treatment considerations for this particularly vulnerable patient population below.

Rituximab, a chimeric CD20 monoclonal antibody and the only United States Food and Drug Administration (FDA)-approved medication for moderate to severe pemphigus, is considered first-line therapy based on its well-documented efficacy and safety profile.[2] However, its effect on B-cells is irreversible. Reconstitution of B-cell immunity can take months, which could be problematic for patients who contract COVID-19. In addition, logistics of intravenous infusions may not be feasible when limits on nonemergent medical care are mandated. We have taken the approach of postponing rituximab infusions temporarily, with the aim of delaying peak patient immunosuppression during peak COVID-19 incidence to reduce the risk of adverse outcomes.

Besides rituximab, the mainstay of pemphigus treatment is glucocorticoids, due to their rapid onset, efficacy, and low cost. However, their nonspecific immunosuppressive effects increase infection risk, among other complications, in a dose-dependent manner. A basic therapeutic principle with particular importance during the pandemic is that glucocorticoids and steroid-sparing immunosuppressive agents, such as azathioprine and mycophenolate mofetil, should be tapered to the lowest effective dose. In active COVID-19 infection, immunosuppressive steroid-sparing medications should be discontinued when possible, although glucocorticoid cessation often cannot be considered due to risk for adrenal insufficiency.

Effective as adjuvant treatment in both pemphigus[3] and COVID-19,[4] intravenous immunoglobulin supports immunity and therefore may be useful in this setting. In addition, hydroxychloroquine can be used to treat pemphigus in the elderly[5] and in pregnancy and has been proposed in the treatment of COVID-19. Although proof of plasmapheresis efficacy is mainly anecdotal in pemphigus and COVID-19, it could also be considered. The effect of convalescent plasma, a FDA-approved COVID-19 treatment under active investigation, on pemphigus is unknown.

Emerging selective agents for pemphigus may offer certain pharmacologic advantages. For example, a new oral Bruton tyrosine kinase inhibitor (PRN1008; currently in phase 3 clinical trials; NCT02704429) works via reversible covalent binding and therefore has a self-limited immunomodulatory effect. Compassionate access to this agent under these extraordinary circumstances would be very useful.

In addition, ofatumumab, a fully human monoclonal CD20 antibody, is shorter acting than rituximab. Despite early promise of this agent in pemphigus, a phase 3 clinical trial (NCT01920477) was prematurely terminated due to changing sponsor priorities. Tocilizumab, a humanized monoclonal antibody against interleukin 6, has been proposed to treat the inflammatory phase of COVID-19 and has been reported anecdotally to help pemphigus.

Until sufficient experience with pemphigus and COVID-19 is available to guide therapeutic decision making, we advocate for thoughtful pharmacologic selection as well as adherence to basic infection-prevention principles, such as social distancing, hand washing, and reduction of iatrogenic immunosuppression as feasible.

Hadir Shakshouk, MBBS,[a,b] Maryam Daneshpazhooh, MD,[c] Dedee F. Murrell, MD,[d] and Julia S. Lehman, MD[a]

From the Department of Dermatology, Mayo Clinic, Rochester, Minnesota[a]; the Department of Dermatology, Andrology and Venereology, Alexandria University, Alexandria, Egypt[b]; the Department of Dermatology, Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran[c]; and the Department of Dermatology, University of New South Wales, Sydney, Australia.[d]

Funding sources: None.

Conflicts of interest: Dr Murrell is an investigator and speaker for Roche, is an investigator for and on an advisory board for Principia Biopharma and Sanofi, and is also on an advisory board for Immune Pharmaceuticals and Lilly. Dr Lehman

is an investigator for Principia Biopharma. Principia is the maker of PRN1008 which is mentioned in the article. Drs. Shakshouk and Daneshpazhooh have no conflicts of interest to declare.

IRB approval status: Not applicable.

Reprints not available from the authors.

Correspondence to: Julia S. Lehman, MD, 200 First St SW, Rochester, MN 55905

E-mail: lehman.julia@mayo.edu

REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
2. Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. *Lancet*. 2017;389:2031-2040.
3. Amagai M, Ikeda S, Shimizu H, et al. A randomized double-blind trial of intravenous immunoglobulin for pemphigus. *J Am Acad Dermatol*. 2009;60:595-603.
4. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infect Dis*. 2020;7(3):ofaa102.
5. Ingen-Housz-Oro S, Alexandre M, Le Roux-Villet C, et al. Pemphigus in elderly adults: clinical presentation, treatment, and prognosis. *J Am Geriatr Soc*. 2012;60:1185-1187.

https://doi.org/10.1016/j.jaad.2020.04.005