viral neutralization. For example, non-neutralizing influenza-specific antibodies can mediate complement fixation, phagocytosis, and antibody-dependent cellular cytotoxicity (ADCC). IVIG produced before the 2009 H1N1 pandemic had moderate titers of cross-reactive ADCC antibodies that eliminated H1N1-infected respiratory cells *in vitro*.[3] IVIG can also have anti-inflammatory effects that target immune-mediated pathology frequently seen during and after infection. Thus, evidence supports therapeutic antiviral and anti-inflammatory activity of IVIG beyond neutralization.

Data on the clinical utility of IVIG in COVID-19 are limited. IVIG from 1 manufacturer contained antibodies with reactivity to components of various coronaviruses but neutralization studies were not performed.[4] Over time, of course, all commercial immunoglobulin will contain SARS-CoV-2 antibodies. A case report described prompt recovery in a patient with severe COVID-19 after receiving plasma exchange and IVIG, suggesting that plasma exchange may clear pathogenic or inflammatory mediators while IVIG provides immunomodulatory and antiviral effects.[5] Although limited by study size and confounding variables, other case series reported that IVIG improved clinical outcomes in severe COVID-19, supporting its potential as adjuvant therapy.[6,7]

In summary, even prepandemic IVIG contains cross-reactive SARS-COV-2 RBD, but does not neutralize viral spread. Nonetheless, activities beyond neutralization such as ADCC, complement activation, and anti-inflammation may warrant its use in COVID-19.

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REFERENCES

1. Mustafa S, Balkhy H, Gabere MN. Current treatment options and the role of peptides as potential therapeutic components for Middle East respiratory syndrome (MERS): a review. J Infect Public Health 2018;11:9-17.
2. Jegaskanda S, Vandenberg K, Laurie KL, Loh L, Kramski M, Winnall WR, et al. Cross-reactive influenza-specific antibody-dependent cellular cytotoxicity in intravenous immunoglobulin as a potential therapeutic against emerging influenza viruses. J Infect Dis 2014;210:1811-22.
3. Díez JM, Romero C, Gajardo R. Currently available intravenous immunoglobulin contains antibodies reacting against severe acute respiratory syndrome coronavirus 2 antigens. Immunotherapy 2020;12:571-6.
4. Shi H, Zhou C, He P, Huang S, Duan Y, Wang X, et al. Successful treatment with plasma exchange followed by intravenous immunogloblin in a critically ill patient with 2019 novel coronavirus infection. Int J Antimicrob Agents 2020;56:105974.
5. Cao W, Liu X, Bai T, Fan H, Hong K, Song H, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis 2020;7:ofaa102.
6. Xie Y, Cao S, Li Q, Chen E, Dong H, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect 2020;81:318-56.
7. Yuan M, Wu NC, Zhu X, Lee CC, So RT, Lv H, et al. A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and SARS-CoV. Science 2020;368:630-3.

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mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis

To the Editor:

Mastocytosis encompasses a heterogeneous group of diseases characterized by the presence of clonal mast cells (MCs) in tissues and symptoms of MC activation, including anaphylaxis.[1] Vaccination has been shown to cause exacerbation of MC mediator-related symptoms.[2] Vaccines against coronavirus disease 2019 (COVID-19) are the solution to the current pandemic, but reports of anaphylaxis following vaccination with the BNT162b2 Pfizer-BioNTech mRNA vaccine have emerged.[3] As such, it is important to provide evidence of the safety of mRNA vaccines in populations at risk for anaphylaxis, including patients with mastocytosis and MC activation symptoms.

We report here 2 cases of health care workers with direct contact with patients with COVID-19 and who had a diagnosis of cutaneous and systemic mastocytosis who had successful anti–COVID-19 vaccination. A 37-year-old female nurse with adult-onset monomorphic maculopapular cutaneous mastocytosis lesions, serum basal tryptase level of 12.4 ng/mL with indolent systemic mastocytosis, based on bone marrow MC aggregates with spindle-shape morphology, and negative KIT D816V mutation (World Health Organization major and minor criterion) presented with severe MC mediator-related symptoms including abdominal colicky pain, bloating and diarrhea, generalized pruritus and flare up of lesions, and osteopenia. She received the first dose of the Pfizer-BioNTech mRNA vaccine, BNT162b2, with premedication with H1 and H2 antihistamines, 1 hour before, and montelukast 10 mg, 1 and 24 hours, without side effects. A 47-year-old female nurse with adult-onset monomorphic maculopapular cutaneous mastocytosis, with serum basal tryptase level of 16.2 ng/mL and indolent systemic mastocytosis based on spindle-shaped bone marrow MCs, positive KIT D816V mutation, and MCs expressing CD25 and CD2 (World Health Organization 3 minor criteria) had a history of anaphylaxis with multiple drugs, and MC mediator-related symptoms including migraines, skin pruritus, gastroesophageal reflux, and osteopenia. She received the first dose of the same vaccine, with above premedication, and only had myalgias on the following day.

These 2 cases provide an initial evidence that mRNA COVID-19 vaccines are safe in patients with mastocytosis and MC activation symptoms, including anaphylaxis.

In patients with mastocytosis, the release of MC mediators following vaccination may be related to the activation of Toll-like receptors, noncanonical activation of FcεRI by superantigens bound to IgE, or complement activation.[2,3] Because the BNT162b2 vaccine contains polyethylene glycol (PEG),

a rare cause of IgE-mediated and complement-mediated anaphylaxis, it has been speculated that PEG could be involved in the initial anaphylactic events.[3-5] Although patients with MC activation disorders including mastocytosis are at risk for MC activation and anaphylaxis when exposed to certain drugs and procedures, there is no evidence of increased sensitization or reactivity to PEG. Patients with MC activation disorders may be good candidates for mRNA severe acute respiratory syndrome coronavirus 2 vaccines whenever indicated, with premedication, in an appropriate setting (hospital with available intensive care unit) and under medical surveillance.

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REFERENCES

1. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. Allergy 2008;63:226-32.
2. Parente R, Pucino V, Magliacane D, Petraroli A, Loffredo S, Marone G, et al. Evaluation of vaccination safety in children with mastocytosis. Pediatr Allergy Immunol 2017;28:93-5.
3. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines [published online ahead of print December 30, 2020]. N Engl J Med. https://doi.org/10.1056/NEJMra2035343.
4. Stone CA Jr, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. J Allergy Clin Immunol Pract 2019;7:1533-40.e8.
5. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. Clin Exp Allergy 2016;46:907-22.

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