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.

Famotidine Against SARS-CoV2: A Hope or Hype?

To the Editor: Coronavirus disease 2019 (COVID-19) is globe-trotting, and thousands of researchers and stakeholders are spending reposeless days and sleepless nights in search of effective therapies. Currently, the entire research sphere is dealing with a pandemic triad: hypes, hypotheses, and hopes. In the absence of a specific antiviral agent or vaccine against novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), "repurposing" of old time-tested medications is being tried. Famotidine is the most recent addition to this trend, creating a lot of hustle among the public and stirring criticism in the scientific arena.[1] A phase 3 trial "Multi-site Adaptive Trials Using Hydroxychloroquine for COVID-19" (MATCH; ClinicalTrials.gov identifier: NCT04370262) has already been launched inconspicuously.[1,2] This randomized double-blind clinical trial (N=1170) has been designed to compare clinical outcomes between 2 arms: one receiving hydroxychloroquine 200 mg plus famotidine (360 mg/d intravenously) and the other receiving hydroxychloroquine plus placebo. Famotidine will be administered for a maximum of 14 days or up to hospital discharge, whichever will come earlier.[2] In this briefing, we will try to enlighten some facts regarding whether it is truly possible for famotidine to have a beneficial effect in COVID-19 or is it just hitting the castle in a Don Quixote way.

Antithetical to the initial belief, SARS-CoV-2 is a multisystemic illness with an array of manifestations protean in disease progression, severity, and outcome. The key pathogenesis revolves around the "cytokine storm" occurring because of the disruption of a delicate balance between proinflammatory and anti-inflammatory mediators and a depressed immune system.[3] The climacteric role for the resolution of viral infection will be imparted upon the complex interplay between innate and adaptive immune systems in the host. Although an irrefutable pathogenesis and an efficacious vaccine is still a dream, attenuation of perpetual hyperinflammation is the bull's-eye at this moment.

It is not the maiden time that the scientists have decided to "repurpose" the drug famotidine, an age-old antacid, to combat a viral disease. The effects of histamine on different substrates of immune system and immunomodulatory effects of H_2 receptor antagonists (H_2RAs) are well recognized.[4] Through binding with histamine receptor 2 and modulating the effector pathways mediated by protein kinase A, famotidine potentially regulates innate and adaptive immune responses (Figures 1 and 2). It modulates antibody generation by B cells, cytokine release by T helper cell 1 (Th1), T-cell differentiation and proliferation, mast cell degranulation, and dendritic cell response.[5] Innate immune system function is potentially boosted by stimulatory effects of H_2RAs on its effectors, that is, macrophages, neutrophils, monocytes, dendritic cells, natural killer cells, and natural killer—T cells, and the adaptive system is filliped by activation of helper T cells (Th1, Th2, and Th17), regulatory T cells, and cytotoxic $CD8^+$ T cells.[6]

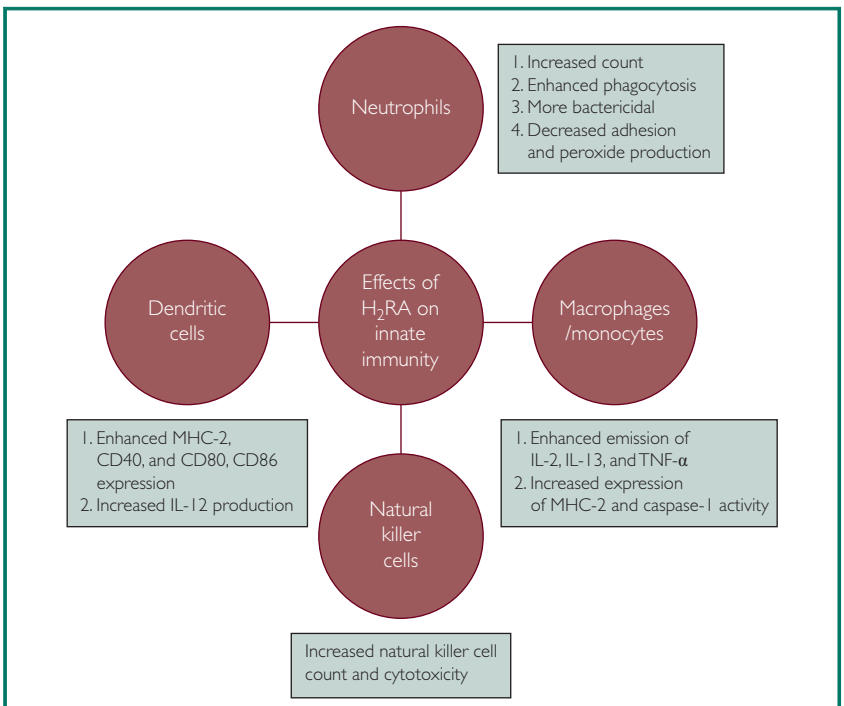

FIGURE 1. Effects of H_2 receptor antagonist (H_2RA) on the innate immune system. IL-# = interleukin #; MHC-2 = major histocompatibility complex-2; TNF-α = tumor necrosis factor α.

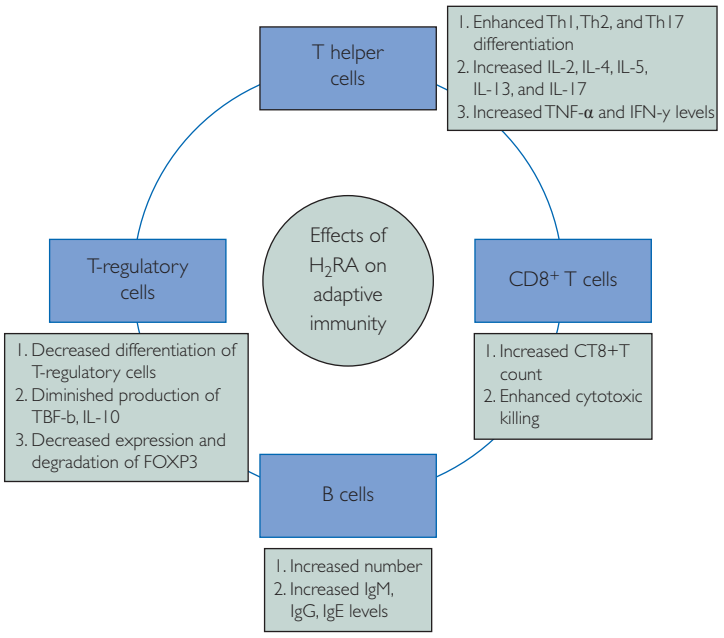

FIGURE 2. Effects of H_2 receptor antagonist (H_2RA) on the adaptive immune system. FOXP3 = forkhead box P3; IL-# = interleukin #, INF-γ = interferon-γ; TGF-β = transforming growth factor beta; Th# = T helper cell #; TNF-α = tumor necrosis factor.

It has been documented that famotidine completely demolishes histamine receptor 2—mediated negative effects on cytokine production, especially tumor necrosis factor-α (TNF-α) and interferon-γ[7]; lipopolysaccharide-induced TNF-α production; and B7-1 expression on monocytes,[8] and also curtails the inhibitory effects of histamine on the production of Th1-mediated cytokine release.[9] H_2RAs have been used in many other conditions, such as cancer, viral infection, bone remodeling, burn management, and vaccine potency enhancer, with mixed results.[6] Previously, H_2RA has been used with some success against HIV,[10,11] human papilloma virus,[12] herpes simplex virus,[13] Epstein-Barr virus,[14] and chronic hepatitis B infection.[15] Ranitidine bismuth citrate has been found to inhibit the nucleoside triphosphate hydrolase and DNA unwinding activities of the SARS-CoV helicase and hinders its replication.[16]

Although the above mechanistic explanations sound reasonable, the real outcomes in clinical trials might be completely futile as evidenced previously.[11] The unpublished Chinese data that received publicity in the press claiming that the mortality rate for patients with COVID-19 taking famotidine was 14% compared with 27% for those not taking the drug reported not to be statistically significant.[1] However, before concluding anything from this, one needs to analyze actual complete data along with the confounders. Moreover, scientists' claims of famotidine having antiprotease—like effects[1] have not stemmed from any strong published evidence, but rather from the evidence of the negative pharmacokinetic effects of famotidine on protease inhibitors.[17] The dosage of famotidine being used in the MATCH trial is nearly 10 times greater than the usual dosage used for severe forms of peptic ulcer diseases. Although famotidine is a time-tested and safe drug, excessive inhibition of gastric acid secretion might precipitate pneumonia.[18] Cardiac failure and arrhythmias have also been reported with high doses of intravenous famotidine administration.[19]

Considering its relative cheapness, wide availability, and previous use as an antiviral agent, famotidine might usher some hope; however, we must wait for the trial results. Until then, hoarding and therapeutic misadventure with this drug must be condemned.

Ritwik Ghosh, MBBS, MD
Department of General Medicine
Burdwan Medical College and Hospital
Burdwan, West Bengal, India

Subhankar Chatterjee, MBBS, MD
Department of General Medicine
Rajendra Institute of Medical Sciences
Ranchi, Jharkhand, India

Souvik Dubey, MD, DM
Department of Neuromedicine
Bangur Institute of Neurosciences
Institute of Post Graduate Medical Education and Research and SSKM Hospital
Kolkata, West Bengal, India

Carl J. Lavie, MD
Department of Cardiovascular Diseases
John Ochsner Heart and Vascular Institute
Ochsner Clinical School
The University of Queensland School of Medicine
New Orleans, LA

Potential Competing Interests: The authors report no competing interests.

ORCID
Subhankar Chatterjee: https://orcid.org/0000-0002-3555-4412; Carl J. Lavie: https://orcid.org/0000-0003-3906-1911

1. Borrell B. New York clinical trial quietly tests heartburn remedy against coronavirus. *Science*. Published April 26, 2020, https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus. Accessed May 3, 2020.

2. Multi-site Adaptive Trials Using Hydroxychloroquine for COVID-19 (MATCH). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT04370262. Accessed May 3, 2020.
3. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034.
4. Hahm KB, Kim WH, Lee SI, Kang JK, Park IS. Comparison of immunomodulative effects of the histamine-2 receptor antagonists cimetidine, ranitidine, and famotidine on peripheral blood mononuclear cells in gastric cancer patients. *Scand J Gastroenterol*. 1995;30(3):265-271.
5. Frei R, Ferstl R, Konieczna P, et al. Histamine receptor 2 modifies dendritic cell responses to microbial ligands. *J Allergy Clin Immunol*. 2013;132(1):194-204.
6. Jafarzadeh A, Nemati M, Khorramdelazad H, Hassan ZM. Immunomodulatory properties of cimetidine: Its therapeutic potentials for treatment of immune-related diseases. *Int Immunopharmacol*. 2019;70:156-166.
7. Smolinska S, Groeger D, Perez NR, et al. Histamine receptor 2 is required to suppress innate immune responses to bacterial ligands in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2016;22(7):1575-1586.
8. Takagaki K, Osawa S, Horio Y, et al. Cytokine responses of intraepithelial lymphocytes are regulated by histamine H(2) receptor. *J Gastroenterol*. 2009;44(4):285-296.
9. Morichika T, Takahashi HK, Iwagaki H, et al. Histamine inhibits lipopolysaccharide-induced tumor necrosis factor-alpha production in an intercellular adhesion molecule-1- and B7.1-dependent manner. *J Pharmacol Exp Ther*. 2003;304(2):624-633.
10. Bourinbaiar AS, Fruhstorfer EC. The effect of histamine type 2 receptor antagonists on human immunodeficiency virus (HIV) replication: identification of a new class of antiviral agents. *Life Sci*. 1996;59(23):PL365-PL370.
11. Bartlett JA, Berry PS, Bockman KW, et al. A placebo-controlled trial of ranitidine in patients with early human immunodeficiency virus infection. *J Infect Dis*. 1998;177(1):231-234.
12. Gooptu C, Higgins CR, James MP. Treatment of viral warts with cimetidine: an open-label study. *Clin Exp Dermatol*. 2000;25(3):183-185.
13. Kürkçüoğlu N, Alli N. Cimetidine prevents recurrent erythema multiforme major resulting from herpes simplex virus infection. *J Am Acad Dermatol*. 1989;21(4, pt 1):814-815.
14. Goldstein JA. Cimetidine, ranitidine, and Epstein-Barr virus infection. *Ann Intern Med*. 1986;105(1):139.
15. Xie X, Geng S, Liu H, Li C, Yang Y, Wang B. Cimetidine synergizes with praziquantel to enhance the immune response of HBV DNA vaccine via activating cytotoxic CD8(+) T cell. *Hum Vaccin Immunother*. 2014;10(6):1688-1699.
16. Yang N, Tanner JA, Zheng BJ, et al. Bismuth complexes inhibit the SARS coronavirus. *Angew Chem Int Ed Engl*. 2007;46(34):6464-6468.
17. Wang X, Boffito M, Zhang J, et al. Effects of the H2-receptor antagonist famotidine on the pharmacokinetics of atazanavir-ritonavir with or without tenofovir in HIV-infected patients. *AIDS Patient Care STDS*. 2011;25(9):509-515.
18. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ*. 2011;183(3):310-319.
19. Schoenwald PK, Sprung J, Abdelmalak B, Mraović B, Tetzlaff JE, Gurm HS. Complete atrioventricular block and cardiac arrest following intravenous famotidine administration. *Anesthesiology*. 1999;90(2):623-626.

https://doi.org/10.1016/j.mayocp.2020.05.027

Guillain-Barré Syndrome in a Patient With Evidence of Recent SARS-CoV-2 Infection

To the Editor: A 58-year-old woman presented with rapidly progressive gait difficulty and dysgeusia after recovering from a febrile illness. Two weeks before presentation, she had returned from Florida but reported no contacts with persons who had confirmed or suspected coronavirus disease 2019 (COVID-19). She then developed an 11-day illness characterized by fever, myalgia, and asthenia but no respiratory symptoms (Figure).

Six days after recovery, she noted dysgeusia without anosmia, followed by rapidly progressive bilateral paraparesis, imbalance, and severe lower thoracic pain without radiation. One week later, she was admitted locally because of progression of symptoms and now required a gait aid for ambulation. Results of a computed tomography angiogram of the chest and abdomen were negative for dissection but revealed peripheral predominant opacities (Figure). Laboratory workup revealed a normal complete blood count and mild elevation in alanine aminotransferase at 73 U/L but otherwise normal liver function tests. She had an elevated D-dimer at 690 ng/mL, ferritin 575 µg/L, and sedimentation rate 26 mm/hour. Nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was negative by an emergency-use authorized real-time polymerase chain reaction (RT-PCR) test.[1]

Given concern for COVID-19 despite the negative RT-PCR result, the patient was started on a 5-day course of hydroxychloroquine, zinc, and methylprednisolone 40 mg twice daily for 5 days, based on local hospital COVID-19 guidelines at that time. Because of progressive paraparesis and evolving areflexia, the local neurologist suspected Guillain-Barré syndrome (GBS). Cerebrospinal fluid (CSF) analysis revealed a protein of 273 mg/dL and 2 total nucleated cells; results of the meningitis/encephalitis panel were negative. Magnetic resonance imaging of the lumbar spine demonstrated smooth enhancement of the cauda equine roots (Figure). Results of locally performed anti-SARS-CoV-2 IgA and IgG serology (Euroimmun Inc., Lubeck, Germany) were positive. The patient was initiated on plasma exchange and received 1 treatment before transfer to our institution for further care.

Upon admission, cranial nerve examination—including olfaction—was normal. The patient had mild neck flexion weakness (Medical Research Council grade 4/5), mild/moderate (4/5) distal upper, and proximal and distal lower-limb weakness. Modified Erasmus GBS Outcome Score (mEGOS) was 1. Deep-tendon reflexes were absent in the legs and decreased in the upper extremities. Plantar responses were flexor. She had moderately severe length-dependent sensory loss in the feet, predominantly affecting large fiber modalities, and associated ataxic gait requiring 1-person assistance. Results of repeated nasopharyngeal SARS-CoV-2 RT-PCR were negative. Results of a qualitative SARS-CoV-2 IgG ELISA (Euroimmun) were again positive, with a signal to cutoff ratio (index