

Editorial

Impact of Rupatidine on the Immunological Status of COVID-19 Patients

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WHO declared COVID-19 as a global pandemic on 11 March 2020, following the emergence of the virus in December 2019 in Wuhan, China.¹ Since it was a new virus causing an unknown infection, doctors at different levels of care tested empiric treatments in an attempt to reduce the severity of the disease. Despite these efforts, treatment options remained limited and outcomes varied widely.

The National Institute of Health (NIH) recommended the use of over-the-counter antipyretics, analgesics, or antitussives for the management of symptoms for outpatients COVID-19 patients. Antihistamines fall under the umbrella of antitussives. Several second generation antihistamines have a good safety profile when dosed up to four times the standard dose.² Commonly prescribed antihistamines include cetirizine, loratadine, ebastine, dexchlorpheniramine, bilastine, levocetirizine, fexofenadine, desloratadine, mizolastine and rupatidine.

Immunopathology of COVID-19 and rationale for rupatidine use

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or human coronavirus 2019 (HCoV-19) is the causative agent of corona virus disease 2019 (COVID-19).³ SARS-CoV-2 causes mild to severe infections in the respiratory tract and may lead to mortality in some patients, especially senescent individuals or those with underlying diseases such as diabetes. The current global pandemic caused by SARS-CoV-2 shows that the virus is more contagious which may be due to the capacity of SARS-CoV-2 to pass from one host to the next by easily crossing the respiratory mucosa.^{4,5}

In severe Covid-19 cases, damage to the lungs has been observed⁶⁻⁸ which can be the outcome of intense inflammatory responses associated with

immune dysregulation, direct infection of immune cells, or autoimmune reactions.⁹ Although the exact immune mechanism that brings about mortality among COVID-19 patients is still unknown, but yet immune responses in COVID-19 infection are induced in both mild and severe phases.¹⁰ Upon SARS-CoV-2 infection, the respiratory epithelial cells and alveolar macrophages initiate an innate immune response through secretion of inflammatory factors¹¹, leading to the recruitment of neutrophils and inflammatory monocyte-macrophages (IMMs) to the infection site.^{12,13}

Platelet Activating Factor (PAF) is an endogenous phospholipid mediator of inflammation made up of inflammatory cells such as alveolar macrophages, eosinophils, mast cells, basophils, platelets and neutrophils, which are released in response to allergic/inflammatory reactions. These reactions are associated with increased vascular permeability, eosinophil chemoattraction, bronchoconstriction and airway hyperresponsiveness.^{14,15} Researchers have hypothesized that PAF-mediated physiological actions could become pathogenic in the presence of excessive activity or dysregulation. The presence of inflammation and leukocytes stimulates the PAF production cycle. Infection or allergic stimuli are potent catalysts of PAF mediated increases in vascular permeability that induces localized swelling, edema, hypotension, and cytokine release.¹⁶ Patients with COVID-19 have a high incidence of both arterial and venous thrombotic complications.¹⁷ It was recently reported that platelets, via release of PAF, trigger perivascular mast cell activation, leading to inflammation.¹⁸ Moreover, mast cell degranulation associated with interstitial edema and immunothrombosis was recently reported in alveolar septa of deceased patients with COVID-19.¹⁹

The activation of pulmonary macrophages to viral infection also induces the release of histamine. If

this reaction is excessive, it will cause the release of proinflammatory cytokines, leading to the dreaded cytokine storm and ARDS aggravation.

Targeting cytokines during the management of COVID-19 patients could improve survival rates and reduce mortality.²⁰ Several antihistamines have shown inhibitory properties on the production and expression of interleukins, chemokines, and other cytokines.²¹ This suggests that antihistamines may help in the treatment of a COVID-19 cytokine storm through their immunomodulatory properties.^{22,23}

Rupatadine is an FDA-approved histamine receptor 1 (H1) and PAF receptor blocker. It also inhibits activation of human mast cells in response to PAF. Rupatadine could be repurposed for COVID-19 prophylaxis alone or together with other PAF-inhibitors of natural origin such as the flavonoids, quercetin and luteolin which have antiviral, anti-inflammatory, and anti-PAF actions.²⁴

Evidence from preclinical and clinical studies

Mullol et al²⁵ in their studies have confirmed that rupatadine exhibits inhibitory effects on mast cell degranulation and eosinophil chemotaxis.²⁵ Rupatadine induces an excellent anti-inflammatory and antioxidant effect on the respiratory system through its dual actions and by modulating mast cell degranulation.²⁶⁻²⁹ Vasiadi et al³⁰ in their studies found that rupatadine can inhibit histamine and cytokine secretion from human mast cells in response to allergic, immune and neuropeptide triggers. A recent study suggested using rupatadine for COVID-19 prophylaxis either alone or with other PAF inhibitors to dampen the release of proinflammatory mediators from mast cells in the lungs.²⁴

Safety profile and feasibility

Rupatadine is well-tolerated with minimal sedative effects, making it a safe adjunct therapy. Its oral administration and availability enhance its potential for widespread use, especially in resource-limited settings.²⁸

Limitations and the need for further research

Despite promising preliminary findings, robust randomized controlled trials are lacking.³¹ Randomized, placebo-controlled trials are recommended as a next step to evaluate the efficacy of rupatadine in the treatment protocol for the early management of SARS-CoV-2 infection.

Rupatadine offers a promising adjunct in the immunomodulation arsenal against COVID-19, primarily due to its anti-inflammatory and immune-enhancing properties. Future research, especially well-designed clinical trials, is essential to delineate its definitive role and establish evidence-based protocols to incorporate rupatadine into COVID-19 management strategies.

Zaida Rahman

Professor, Department of Pharmacology
Enam Medical college, Savar, Dhaka
Email: Zaida.rahman53@gmail.com

References

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta bio medica: Atenei parmensis* 2020; 91(1): 157–160.
2. Cataldi M, Maurer M, Taglialatela M, Church MK. Cardiac safety of second-generation H1-antihistamines when up dosed in chronic spontaneous urticaria. *Clinical & Experimental Allergy* 2019; 49(12): 1615–1623.
3. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z et al. Potent binding of 2019 novel corona virus spike protein by a SARS corona virus-specific human monoclonal antibody. *Emerging microbes & infections* 2020; 9(1): 382–385.
4. Keshavarz M, Tavakoli A, Zanganeh S, Mousavi MJ, Vahdat K, Mahmudpour M et al. Clinical characteristics of outpatients and inpatients with COVID-19 in Bushehr: a report from the south of Iran. *Future Virology* 2021; 16(2): 99–106.
5. Omrani M, Keshavarz M, Nejad Ebrahimi S, Mehrabi M, McGaw LJ, Ali Abdalla M et al. Potential natural products against respiratory viruses: a perspective to develop anti-COVID-19 medicines. *Frontiers in Pharmacology* 2021; 11: 586993.

6. AbdulmirAS, Hafidh RR. The Possible Immunological Pathways for the Variable Immunopathogenesis of COVID-19 Infections among Healthy Adults, Elderly and Children. *Electronic Journal of General Medicine* 2020; 17(4): em 202.
7. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet* 2020; 395(10224): 565–574.
8. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 579(7798): 270–273.
9. Dandekar AA, Perlman S. Immunopathogenesis of coronavirus infections: implications for SARS. *Nature reviews immunology* 2005; 5(12): 917–927.
10. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X et al. COVID-19 infection: the perspectives on immune responses. *Cell Death & Differentiation* 2020;27(5):1451–1454.
11. Alosaimi B, Hamed ME, Naeem A, Alsharef AA, AlQahtani SY, AlDosari KM et al. MERS-CoV infection is associated with downregulation of genes encoding Th1 and Th2 cytokines/chemokines and elevated inflammatory innate immune response in the lower respiratory tract. *Cytokine* 2020; 126: 154895.
12. Channappanavar R, Perlman S. Evaluation of activation and inflammatory activity of myeloid cells during pathogenic human coronavirus infection. In *MERS coronavirus: Methods and protocols* 2019 Dec 28 (pp. 195–204). New York, NY: Springer US.
13. Kindler E, Thiel V. SARS-CoV and IFN: too little, too late. *Cell host & microbe* 2016;19(2): 139–141.
14. Ring J, Brockow K, Ollert M, Engst R. Antihistamines in urticaria. *Clinical & Experimental Allergy* 1999;29: 31–37.
15. Brockow K, Kiehn M, Riethmüllerb C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. *Journal of allergy and clinical immunology* 1997; 100(4): 458–463.
16. Zimmerman GA, McIntyre TM, Prescott SM, Stafforini DM. The platelet-activating factor signaling system and its regulators in syndromes of inflammation and thrombosis. *Critical care medicine* 2002; 30(5): S294–301.
17. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York City health system. *Jama* 2020; 324(8): 799–801.
18. Karhausen J, Choi HW, Maddipati KR, Mathew JP, Ma Q, Boulaftali Y et al. Platelets trigger perivascular mast cell degranulation to cause inflammatory responses and tissue injury. *Science advances* 2020; 6(12): eaay6314.
19. Motta Junior JD, Miggiolaro AF, Nagashima S, De Paula CB, Baena CP, Scharfstein J. Mast cells in alveolar septa of COVID-19 patients: a pathogenic pathway that may link interstitial edema to immunothrombosis. *Frontiers in Immunology* 2020; 11: 574862.
20. Hogan II RB, Hogan III RB, Cannon T, Rappai M, Studdard J, Paul D et al. Dual-histamine receptor blockade with cetirizine-famotidine reduces pulmonary symptoms in COVID-19 patients. *Pulmonary pharmacology & therapeutics* 2020; 63: 101942.
21. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. *Frontiers in immunology* 2020; 11(1446): 1–4.
22. Aydin S, Aydin S. Could Antihistamines Help in the Treatment and Spread of COVID-19 Via Re-Modulating Cytokines and by Reducing Sneezing. *Acta Scientific Nutritional Health* 2020;4(4): 172–173.
23. Eldanasory OA, Eljaaly K, Memish ZA, Al-Tawfiq JA. Histamine release theory and roles of antihistamine in the treatment of cytokines storm of COVID-19. *Travel medicine and infectious disease* 2020; 37: 101874.
24. Demopoulos C, Antonopoulou S, Theoharides TC. COVID-19, micro thromboses, inflammation, and platelet activating factor. *Bifactors* 2020; 46(6): 927–933.

25. Mullol J, Muñoz-Cano R, Torres-Atencio I, Ainsua E, Martín Met al. Platelet activating factor-induced mast cell degranulation is inhibited by rupatadine, and to a lower extent by levocetirizine and desloratadine, in a mast cell line (LAD-2). *Clinical and Translational Allergy* 2013; 3: 6.
26. Kahveci OK, Kuzu S, Altıntaş M, Vurmaz A, Çelik S. The effect of nasal steroid and antihistamine use on total oxidative stress and antioxidant status in the treatment of allergic rhinitis. *American Journal of Rhinology & Allergy* 2021;35(1):52–58.
27. Merlos M, Giral M, Balsa D, Ferrando R, Queralt M, Puigdemont A et al. Rupatadine, a new potent, orally active dual antagonist of histamine and platelet-activating factor (PAF). *The Journal of pharmacology and experimental therapeutics* 1997; 280(1): 114–121.
28. Mullol J, Bousquet J, Bachert C, Canonica WG, Gimenez-Arnau A, Kowalski ML et al. Rupatadine in allergic rhinitis and chronic urticaria. *Allergy* 2008; 63: 5–28.
29. Shamizadeh S, Brockow K, Ring J. Rupatadine: efficacy and safety of a non-sedating antihistamine with PAF-antagonist effects. *Allergo journal international* 2014; 23(3): 87–95.
30. Vasiadi M, Kalogeromitros D, Kempuraj D, Clemons A, Zhang B, Chliva C et al. Rupatadine inhibits proinflammatory mediator secretion from human mast cells triggered by different stimuli. *International archives of allergy and immunology* 2009; 151(1): 38–45.
31. Blanco JJ, Bonilla JA, Fremont-Smith P, de Las Heras KV. Antihistamines as an early treatment for Covid-19. *Heliyon*. 2023; 9(5): e15772.