



PERSPECTIVE

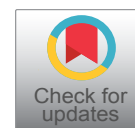
COVID-19 Histamine Theory: Why Anti-Histamines Should Be Incorporated as the Basic Component in COVID-19 Management?

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Introduction

Since the emergency of COVID-19 in December 2019 in Wuhan, China, WHO declared COVID-19 to be a global pandemic crisis on March 11, 2020 [1]. The key in facing this outbreak lies greatly on proper understanding of its pathophysiology. A number of mechanisms have been proposed up to date with some supported clinical findings from the cases which has been successful treated [2]. Some of these have determined the medical management of the disease in clinical settings despite some little progressive management plan fluctuations depending on the pathophysiology updates from recent studies. One among the suggested mechanisms was COVID-19 Histamine theory [3]. It explains the severity of the disease as the clinical consequences depends on the number of histamine mediated pathways activated in particular patient.

Covid-19 Histamine theory explain clinical presentations of the disease as a result of Histamine activated pathways to a greater extent [3]. It is basically activation of histamine pathways which lead to cytokine storm in Covid-19 pathogenesis [4] and other related complications. There are four classes of Histamine Receptors: H1, H2, H3 and H4 [5]. All of these plays a role in Histamine pathways. Pathologically, Histamine pathways has been found to significantly be able to modulate immune response and inflammation [6] hence cytokine storm, tissue response to inflammation [7], coagulation process including deep vein thrombosis

through Histamine H1 receptor [8,9] and can trigger acute symptoms due to its very rapid activity on vascular endothelium, bronchial and smooth muscles [10] etc. All of these makes it one of the important cytokine for therapeutic target.

Of the most Histamine Receptors, H2 and H1 have gained the most clinical attention among researcher [11-13] when comes to Covid-19 pathogenesis. Although some experts argue that the use of anti-histamines might interfere with the body first line defense mechanism against respiratory tract infections like corona virus [14], a number of Randomized Clinical trials and *in vitro* studies have shown several antihistamines to be of interest in management of Covid-19 with good prognosis including reducing pulmonary symptoms. Some showed Famotidine, Cimetidine and cetirizine [11,12,15,16] while others has shown significantly antiviral effects from Hydroxyzine and possibly Azelastine which binds to ACE-2 and Sigma-1 receptor as off-targets for viral attachment and replication [17] even though the clear mechanism is not well known.

Taking into consideration COVID-19 clinical presentation and its severity spectrum to death plus the clinical trials done already, histamine mediated pathways might be contributing to a great extent the prognosis of the Covid-19 disease. Immunologically, it becomes so hard to point out quantitatively the role of every cytokine in the pathogenesis of the disease so as to know which cytokine specifically plays a major

role. But at least from clinical presentation of a disease together with researched evidences, it shows histamines might hold a great deal hence anti-histamines. Several studies have shown that a number of Covid-19 patients improved significantly when on anti-histamines due to their antiviral and anti-inflammatory properties [18-20]. Moreover, anti-histamines have shown to be effective in the management of long term symptoms post covid-19 infection [21].

Among all anti-histamines, second generation seems to be of less side effects due to its specificity. Regarding whether Histamine H1 Receptor Antagonists can be used to in the management of Covid-19 or not, some studies showed significant promise of the drugs as anti-SARS-Cov-2 and immune-modulating agent suitable for covid-19 treatment [22]. H1 anti-histamines have been used mostly to treat symptoms which are secondarily to histamine release. Some second generation anti-histamines shows anti-allergic and ant-inflammatory effects which outlined in one study [23] as through decrease in 1) Production of cytokines by pro-inflammatory drugs and in the release of other mediators by mastocytes and basophils, 2) Recruitment of eosinophils in the late phase of allergic reactions, 3) Expression of membrane receptors in nasal epithelia cells and the vascular endothelium, particularly the leukocyte Intercellular Adhesion Molecule 1 (ICAM-1), which favors leukocyte migration from the blood to the respiratory mucosa and constitutes the main receptor for respiratory viruses to which the untreated atopic subject appear to be more susceptible.

Since anti-histamines seems to hold a crucial prognostic role in the management of Covid-19, there is a need to identify and repurpose some potential anti-histamine drugs. One study suggested diphenhydramine, hydroxyzine and azelastine to be considered in repositioning, then further research in them [17]. Due to its potent, less side effects, rapid onset of action, specificity, anti-allergic and anti-inflammatory properties [24], Cetirizine might be an important drug of consideration in managing Covid-19 patients at the moment compared to other anti-histamines or histamine receptors (H2, H3 and H4).

Histamines pathways have been shown to mediate a number of clinical presentations including cytokine storm, runny nose, blood clotting issues, bronchoconstriction, lung-hypersecretion etc, all of which have been presented with Covid-19 patient. Its great role in modulating the immune response, viral viability and influencing a number of systemic pathologies makes it an important target for the management of diseases like Covid-19 which seems to trigger its pathway and bring a number of clinical complications.

From the above discussed findings on Anti-

Histamines and Covid-19, specific antihistamines should be identified and included as a basic therapeutic approach towards Covid-19 management plan along with other approaches. They seem to be promising in the management of Covid-19 with short time of taking away the symptoms while giving the body enough time to reset its defense mechanism hence fast recovery. They work both by modulating the histamine pathways and suppressing viral growth. Despite the fact that still further clinical trials and studies should be done on the matter in identification and repositioning of potential anti-histamines in the management of Covid-19, there is no enough time for that while fighting this global health crisis. Selected anti-histamines especially among Histamine H1 Receptor Antagonists should be approved for emergency use towards Covid-19 management at the moment.

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Conflicts of Interest

The author declares no conflict of interest.

Ethical Approval

Not applicable.

Declaration of Competing Interest

None.

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