Histamine Blockade for Inflammatory Illnesses

This novel therapy is a synergistic combination of cetirizine (antihistamine-1) and famotidine (antihistamine-2) initially studied to treat diarrhea illnesses at GI Associates (Flowood, MS). Murine (rat) experiments at the U of Oklahoma demonstrated a synergistic effect of dual histamine blockade by showing that both histamine pathways are required and that a therapeutic window exists in which the synergistic effect is maximized (1). Phase 2a study designs have been approved by the FDA and are pending. The use of dual histamine blockade for the treatment of diarrhea is a novel concept developed by The Clinical Research Team at GI associates of Flowood MS under the direction of Dr. Reed Hogan II, who began investigating this therapy in 2008. Previously, neither of these drug categories were used in the treatment of diarrhea. Both drugs have a pristine safety profile and have been approved by the FDA for OTC use. This team has extensively studied the histamine pathways with both animal studies and clinical studies over the past decade. These studies have shown incredible efficacy (2) which continues to be seen routinely in clinical practice. This experience and research has led to the consideration that dual-histamine blockade may play a therapeutic role in fighting multiple inflammatory illnesses that are driven by the Cytokine Storm.

The Cytokine Storm

The Cytokine Storm drives the inflammatory response in essentially any infectious or traumatic injury. This includes every insult from a scratch or bee sting to lethal infections such as Covid. Inflammatory issues and Infections such as COVID-19 have a reactive immune response that results in a cytokine release which is similar to other well defined viral infections including SARS, MERS, and influenza. Studies from Wuhan China have defined the COVID-19 cytokine profile (3) and identified risk factors that increase mortality (4). These retrospective studies suggests morbidity and mortality may be linked to inflammatory processes caused by viral infection and the "cytokine storm" which was very common in patients with severe COVID-19 infection (5).

COVID-19 Pulmonary Disease

Pulmonary pathology in early-phase COVID-19 pneumonia has shown exudative and proliferative phases of acute lung injury (edema, inflammatory infiltrates, pneumocyte hyperplasia) even prior to the development of any respiratory symptoms (6). In the later stage of disease, patients can develop Acute Respiratory Distress Syndrome (ARDS) and multi-organ failure. The main causes of death are thought to be massive alveolar damage and progressive respiratory failure (7). The initial autopsy report from novel coronavirus pneumonia patient in China showed an inflammatory response with deep airway and alveolar damage and a large amount of viscous secretions (8). The reason for the wide range in severity of disease for COVID-19 patients remains unclear. Some patients are completely asymptomatic, while others progress rapidly to respiratory failure and death. While the triggers remain unclear, ARDS has taken center stage with the "cytokine storm" emerging as a key mechanism leading to patient deterioration and death. Because of this, efforts are being made to find immunotherapies that resist or blunt the cytokine storm (9, 10, 11).

Histamines Role in Cytokine Storm, Lung Disease, T-Cells

The histamine-cytokine network has been studied extensively and is well defined in literature. Histamine modulates the release of cytokines, has well established pro-inflammatory effects, and influences local immune responses in the lung that can lead to pulmonary tissue damage (12). Coronavirus infected mice have shown that T-cell responses are required for protection from clinical

disease and for virus clearance in severe acute respiratory syndrome (13). The immunomodulation of histamine depends mostly on its influence of T-cells (14).

Histamine Blockade for ARDS and Pneumonia Treatment

Multiple remote studies have shown successful treatment of ARDS with therapies that include dual histamine blockade. When a combination of histamine-1 blocker + histamine-2 blocker + cyclooxygenase inhibitor + IV steroids + anti-hypertensives were studied in ARDS models, it was the dual-histamine blockade that proved to be the most beneficial. This study concluded that dual-histamine blockade + ibuprofen was essential in the treatment of hypoxemia, pulmonary hypertension, and pulmonary microvascular injury in this fulminant ARDS model (15). A more recent study evaluating H1N1 influenza models also showed that histamine blockade decreased inflammatory cytokines and decreased severe pneumonia (16).

Histamine Blockade with Famotidine alone to decrease Viral Replication

Famotidine alone has been tried in combination trials with Hydroxycloroquine to decrease viral replication. There is a papainlike protease which helps the pathogen replicate. Gene sequences of the COVID 19 virus were studied and famotidine was one of three compounds potentially able to interact with the new protease. Trials are underway (17).

Hypothesis / Considerations

Histamines play a key role in modulating the immune response, inflammation, and cytokine release. Blocking Histamine-1 and Histamine-2 (Dual-histamine blockade) is a very safe therapy that has shown significant efficacy in several clinical applications and peer-reviewed studies. These studies have shown positive results of dual-histamine blockade in both ARDS models and H1N1 influenza models. COVID-19 is known to cause pulmonary disease with a wide range of severity. Patients have shown significant pulmonary disease on radiographic imaging and pathology specimens even before exhibiting any pulmonary symptoms. The “cytokine storm” is thought to be a key mechanism of action that results in patient deterioration.

Our research team strongly believes it is very reasonable to consider the use of dual-histamine blockade to retard the histamine-cytokine network and blunt the cytokine storm. This cytokine storm is responsible for a plethora of inflammatory conditions including essentially all organ systems. Inflammation in our bodies is essentially triggered by the Cytokine storm, inhibiting this process can benefit many issues or a variety of illnesses. The incredible safety profile of dual-histamine blockade makes this an appealing consideration for many patients who have inflammatory issues. If dual-histamine blockade is able to blunt the cytokine system, the risk of progressing to severe disease would lessen. Successful studies of dual-histamine blockade on ARDS models and H1N1 influenza models support this possibility. If true, this could save many lives, dramatically reduce suffering, and have a tremendous positive impact on our healthcare system.

Safety

The incredible safety profile of dual-histamine blockade makes this an appealing consideration for all patients with inflammatory conditions. If able to blunt the Cytokine Storm, it is hypothesized that the severity of many disease states would lessen, decrease admissions, and suffering would decrease. Reducing severity of disease and the need for more toxic treatments, often ineffective treatments, would have a tremendous impact on our healthcare and quality of life.

Previous clinical studies on COVID19 hospitalized patients to evaluate the effect of aggressive dual-histamine blockade revealed dramatic improvement in very sick patients. Subsequent anecdotal trials in a variety of illnesses including chronic diarrhea, chemotherapy induced diarrhea, interstitial cystitis, allergic reactions drive the investigators to offer a pathway to symptomatic relief with this unique therapy. (18, 19)

Ready to proceed

We have an action ready plan to proceed with a quick trial. With expected approval of a novel COVID-19 AASA which would be a protocol addendum or new IRB we can proceed to screen 2000-5000 patients with suspected disease. The tip of the COVID spear is in Jackson, MS, expected to peak shortly. We can implement, in an outpatient setting, rapidly expand to other locals, but need to start fast.

In our prior work in the GI inflammatory cascade, our combination's efficacy is 65% compared to the best analog in market less than 20%. Consultants from around the country encouraged expanding this approach with high hopes that we can help find a solutions for many disease states involving inflammatory issues. Preliminary data in a variety of patient populations suggest a definite synergistic benefit of the H1R H2R combination of antagonists.

The H1R H2R blockade is an amazingly complex pathway, a remarkably safe therapy, low cost, and easy to implement. Just need more data, and more satisfied outcomes. For suffering patients we have the potential to be a game changer for those who suffer..

References:

(1) Mohammadi E, Fix J, Hogan RB, Greenwood-Van Meerveld B. Exploring an anti-histamine combination therapy for diarrhea predominant irritable bowel syndrome. Abstract and research presentation, DDW 2018.

(2) Hogan R, Hogan III R. Double-blinded, randomized, placebo controlled trial of histamine-1 and histamine-2 blockade for chronic diarrhea. 2013. Unpublished.

(3) Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–50

(4) Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020; published online March 3. DOI:10.1007/s00134-020-05991-x.

(5) Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet March 16, 2020; 395(10229):1033-4

(6) Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. J Thorac Oncol. 2020 Feb 28. pii: S1556-0864(20)30132-5. [Epub ahead of print].

(7) Cao Y, Liu X, Xiong L, Cai K. Imaging and Clinical Features of Patients With 2019 Novel Coronavirus SARS-CoV-2: A systemic review and meta-analysis. J Med Virol. 2020 Apr 3. doi: 10.1002/jmv.25822. [Epub ahead of print].

(8) Liu Q, Wang RS, Qu GQ, Wang YY, Liu P, Zhu YZ, Fei G, Ren L, Zhou YW, Liu L. Gross examination report of a COVID-19 death autopsy. Journal of Forensic Medicine 2020;36(1):21-23.

(9) Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J. 2014;20(2):119-122.

(10) Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J. Biol. Regul. Homeost. Agents. 2020;34

(11) Zhang W, Zhao Y, Zhang F, Want Q, LiT, Liu Z, Want J, Qin Y, Zhang X, Yan X, Zeng X, Zhang S. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol. 2020 Mar 25;214:108393.

(12) Branco AC, Yoshikawa FY, Pietrobon AJ, Sato MN. Role of Histamine in Modulating the Immune Response and Inflammation. Mediators Inflamm. 2018 Aug 27;2018:9524075.

(13) Zhao J, Zhao J, Perlman S. T cell responses are required for protection from clinical disease and for virus clearance in severe acute respiratory syndrome coronavirus-infected mice. J Virol. 2010;84(18):9318-9325. doi:10.1128/JVI.01049-10
(14) Kmiecik T, Otocka-Kmiecik A, Górska-Ciebiada M, Ciebiada M. T lymphocytes as a target of histamine action. Arch Med Sci. 2012;8(1):154–161.
(15) Sielaff TD, Sugerman HJ, Tatum JL, Blocher CR. Successful treatment of adult respiratory distress syndrome by histamine and prostaglandin blockade in a porcine Pseudomonas model. Surgery. 1987;102(2):350-357
(16) Jang Y, Jin M, Seo SH. Histamine contributes to severe pneumonia in pigs infected with 2009 pandemic H1N1 influenza virus. Arch Virol. 2018 Nov;163(11):3015-3022.
(17) Borrell B, New York clinical trial quietly tests heartburn remedy against coronavirus. https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus
(18) Hogan II RB, Hogan III RB, Cannon T, Rappai M, Studdard J, Paul D, Dooley TP. Dual-histamine receptor blockade with cetirizine-famotidine reduces pulmonary symptoms in COVID-19 patients. Pulmonary Pharmacology & Therapeutics. 2020 (63).
(19) Hogan II RB, Moore III PH, Paul D, Dooley TP. Treatment and maintenance of Interstitial Cystitis/Bladder Pain Syndrome in Female Patients with Cetirizine-Famotidine: A Case Series. Case Reports in Clinical Medicine, 2023, 12, 61-71.