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Brief Report: Rapid Clinical Recovery from Severe COVID-19 with High Dose Famotidine and High Dose Celecoxib Adjuvant Therapy

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Abstract

Celecoxib adjuvant therapy added to standard of care has been shown to provide clinical benefit in treating viral pneumonia. Prior clinical studies include one double blinded randomized clinical trial for hospitalized influenza pneumonia which demonstrated that celecoxib adjuvant treatment reduced overall mortality and circulating IL6 levels [1]. In a retrospective COVID-19 study, celecoxib was shown to reduce the high IL6 [2] levels associated with that disease, A prospective randomized COVID-19 trial demonstrated that celecoxib administration prevented clinical deterioration and rapidly improved characteristic COVID-19 thoracic computerized axial tomography (CT-chest) findings [3]. Multiple descriptive trials of high dose famotidine (both inpatient and outpatient) administered to patients with COVID-19 have demonstrated clinical responses [4-6]. In this case series, we describe the rapid clinical responses observed after increasing the celecoxib dosage from 200mg BID to 400mg BID when administered together with high dose famotidine (80mg PO QID) in three critical COVID-19 patients; one of whom on baseline required 55 liters per minute (l/min) (40 l/min nasal insufflation under a 15 l/min nonrebreather mask) at the time of hospital admission, another which required 40 l/min high velocity nasal insufflation on admission, and an outpatient who declined admission but had critical Covid-19 biomarkers.

Keywords: SARS-CoV-2; COVID-19; Acute respiratory distress syndrome; ARDS; Famotidine; Celecoxib

Background

A domain within the nucleocapsid protein (N) and spike glycoprotein (S) of SARS-CoV is transported to the nucleus of infected cells and can directly bind to the inducible COX-2 gene promoter, driving overexpression of COX-2 in a dose dependent manner [7,8]. SARS-CoV-2 infection is associated with high levels of prostaglandin E2 (PGE_2) production based on urinary levels of PGE^2 , which in one study of hospitalized cases were 9x higher on average than levels observed in normal uninfected individuals (170±40ng/ml vs 18.1±3.8ng/ml, $p<0.01$) and in some cases were observed to spike to 3,000 ng/ml or 150X normal [3]. A prospective randomized clinical trial of celecoxib as a treatment for COVID-19 showed that 100mg BID was insufficient to prevent clinical deterioration [3]. Even 200mg BID moderated disease severity, but urinary PGE-2 still spiked. Celecoxib 400mg BID has been given for six months for multiple familial polyposis with safety similar to 100 mg bid [9].

Recent evidence supports that famotidine acts via a well-documented mechanism of action involving histamine H2 receptor blockade as well as interference with mast cell autocrine amplification of activation and degranulation [10,11]. However, it is increasingly recognized that the innate immune system- particularly macrophage/ monocytes and neutrophils- play key roles in the COVID-19 host inflammatory cascade [11-13].

Famotidine's effect on macrophage/monocytes requires higher levels and greater dosage relative to levels required for treating gastro-esophageal reflux disease [10,14].

Most recently, a 25 patient consecutive case series of hospitalized COVID patients treated with high dose famotidine 80mg QID (HD famotidine) and celecoxib 400mg loading then 200mg bid reported no deaths, no dialysis, no apparent safety issues, consistent improvement in biomarkers, rapid radiological improvement and short hospital stays [5].

Clinical Report

Inpatient

An obese hypertensive patient required 55 liters/min to keep oxygen saturation above 90%. This patient improved rapidly to room air in 7 days with adjuvant therapy of famotidine 80mg PO qid and celecoxib 400mg PO BID with standard of care Figure 1 and Table 1. CT-chest shows marked clearing with almost normal black alveolar lung appearance compared to white opaque ground glass infiltrates. Adult respiratory distress syndrome (ARDS) severity from critical to normal PaO_2/FiO_2, C-reactive protein (CRP) almost normal, serum ferritin to normal, peripheral blood Lactate Dehydrogenase (LDH) from lethal by Wuhan predictive mortality model to normal15, restoration of lymphopenia to normal, and neutrophil lymphocyte ratio (NLR) to normal.

Figure 1. Radiographic and Biomarkers at Baseline, 7 Days later at Discharge.

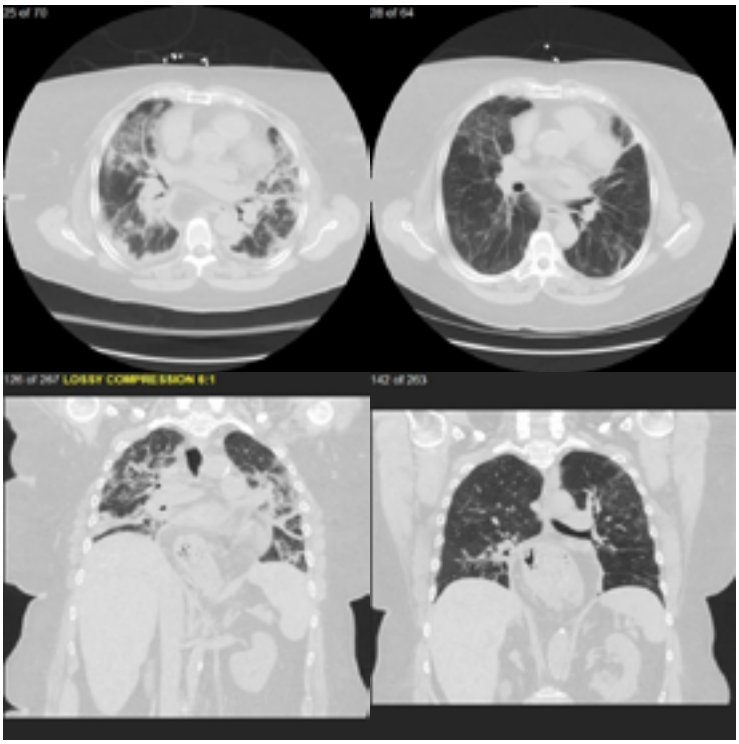

Table:1

	Day 0 celecoxib 400mg bid/ Famotidine 80mg bid	Day 7 discharge
PaO_2/FiO_2	59.2	310
CRP	16.5	1.4
D-dimer	0.38	0.49
Ferritin	219	149
LDH	406	247
% lymphocytes	6	36
Neutrophil/Lymphocyte Ratio (NLR)	6.9	3.2
eGFR ml/min	85	85

Inpatient

Hypertensive male presented after a week of cough with oxygen saturation levels (SATS) of 72% requiring 40 liters/minute high flow nasal insufflation with 100% oxygen. He improved to only 3 liters/minute when administered HD famotidine + celecoxib (400mg loading, 200mg BID subsequent) but following a second unit of convalescent plasma deteriorated to requiring 8 liters/min of supplemental oxygen with rise in the biomarkers of both neutrophil lymphocyte ratio (NLR) and ferritin. Celecoxib dosage was increased to 400mg bid (Day 0) with immediate improvement in supplemental oxygen requirement by next morning to only 3 liters/minute. Further improvement to room air at rest and in the discharge CT chest radiographic findings as summarized in Figure 2 and Table 2. CT-chest at baseline showing almost no normal lung with massive bilateral ground glass infiltrates. CT-chest at day 0 showing more normal black alveolar lung but consolidation with ground glass. CT-chest at discharge showing still prominent ground glass but improvement in consolidation. Spike in % lymphocyte, NLR, ferritin and oxygen at Day 0 with improvement in all biomarkers with estimated Glomerular filtration rate (eGFR), C-reactive protein (CRP), and D-dimer back to normal.

Figure 2. Radiographic and Biomarkers at baseline, 7 days later when celecoxib increased to 400mg bid, and 9 days later at discharge.

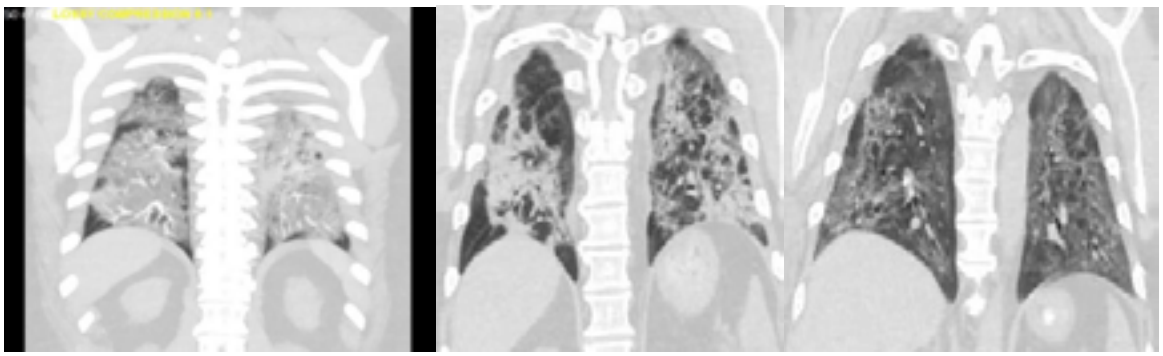

TABLE: 2

	Baseline 200mg Celecoxib + famotidine 80mg qid	Day 0 400mg celecoxib bid +famotidine 80mg qid	At discharge
Ferritin	609	464	320
CRP	4.7	2.2	0.5
LDH	416	312	310
% lymph	5.9	5.5	13
NLR	15	18	6.1
d-dimer	3.4	1.4	0.4
eGFR	55	91	91
Oxygen	40 l/min	8 l/min	Room air

Outpatient

A non-obese hypertensive male presented with 8 days of symptoms; cough, myalgia, fatigue, shortness of breath. His room air saturation was 90%, did not drop with activity, and he declined admission. His emergency room labs are shown and he was started on famotidine 80 mg QID and celecoxib 200 mg BID. The next morning (as shown in the Table 3 as Day 0) the celecoxib was increased to 400mg bid with rapid improvement in biomarkers, oxygen saturations, global assessment and chest x-ray (Figure 3). Chest x-ray showing infiltrates and retrosternal lucent areas on lateral films both significantly improved 2 days later. Significant improvement in all biomarkers within 2 days with normalization of D-dimer and NLR values.

Figure 3. Chest x-ray and biomarkers at baseline, Day 0 when celecoxib increased to 400mg bid, and Day 2.

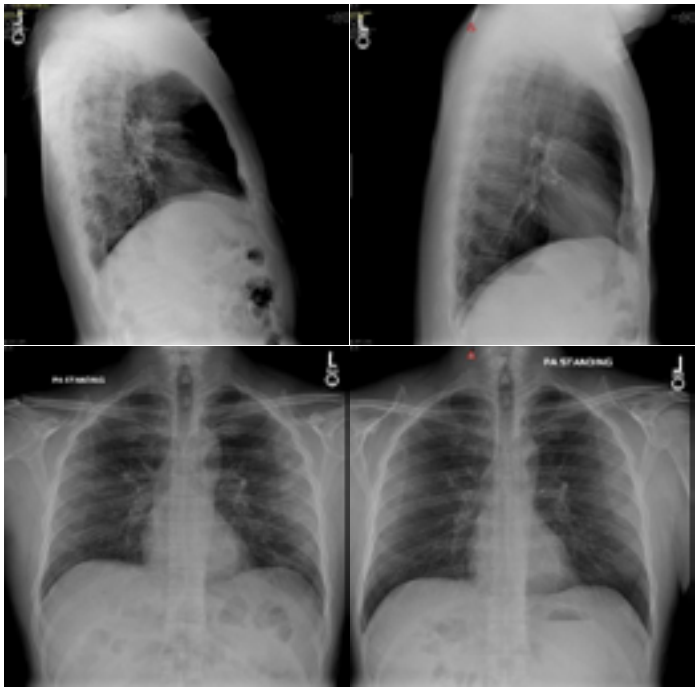

Table: 3

	Baseline	Day 0	Day 1	Day 2
Ferritin	985	1200	1220	671
CRP	16	21	20	3.7
LDH	353	399	362	330
% lymph	7.6	6.0	10.8	21
NLR	12	16	7.8	3.3
d-dimer	0.4	0.4	0.5	0.4
eGFR	64	79	79	79
O2 sats rm air	90%	94%	97%	98%
Global assessment	Short of breath Very tired severe cough	Very tired cough slightly better	Cough better	Went for a walk Cough almost gone

Discussion

The rapid response to increased Celecoxib in both oxygen requirements and biomarkers supports the hypothesis that SARS-CoV-2 COX-2 overexpression and subsequent production of prostaglandin E2 (and related metabolites) involves dose dependent inhibition of COX-2 enzymatic activity. Although there may be safety concerns regarding this dose, studies with celecoxib 400mg BID for six months for familial adenomatous polyposis have demonstrated no difference in the incidence of any adverse event between celecoxib 400mg bid, celecoxib 100mg bid and placebo [9].

Famotidine acts via a well-documented mechanism of action involving histamine H2 receptor blockade, interference with mast cell autocrine amplification of activation and degranulation, and inhibition of neutrophil and monocyte/macrophage upregulation [10,11,14]. An anecdotal report from Wuhan, China is purported to have indicated that famotidine may be partially protective for COVID-19, but that cimetidine was not protective [16]. Famotidine reaches functionally relevant systemic concentration while cimetidine does not [10]. Unbound cimetidine levels at standard doses of 200 or 300 mg daily (q.d.), achieve a Css that is a fraction of the reported IC50 range of 400-780 mg/L. While pharmacokinetic calculations do not account for local tissue levels of histamine (which will compete with famotidine for H2 receptor occupancy), 60mg PO TID of famotidine is calculated to achieve 10-fold the half maximum inhibitory concentration (MIC50) for H2 blockade in the absence of histamine as a competitor [17,18]. Higher levels are required for the inhibition of neutrophils and monocyte/macrophage upregulation [10,14,17,18].

Recent evidence has supported the use of dexamethasone in COVID-19. Dexamethasone is a very broad-spectrum glucocorticoid inhibitor of inflammatory and immune processes, and components of dexamethasone activity may overlap with the pharmacologic activity of celecoxib (COX-

2 inhibition and 5-lipoxygenase activity) [18,19]. The leukotriene receptor antagonist montelukast has also been advocated for treatment of COVID-19, and since celecoxib-mediated 5-lipoxygenase inhibition will reduce production of leukotrienes, concurrent use of these two agents may or may not provide additional benefits over celecoxib alone.

Conclusion

In these three initial cases (two inpatient, one outpatient), the rapid clinical improvement observed after increasing the dosage of celecoxib to 400mg bid is consistent with the theory that SARS-CoV-2 driven COX-2 overexpression in infected cells with subsequent production prostaglandin E2 (and other arachidonic acid metabolites) is responsive to dose dependent inhibition by celecoxib. The clinical, biomarker, and radiographic results observed after treatment with the combination of these two paracrine inhibitors; high dose famotidine and high dose celecoxib, provide further evidence supporting randomized clinical trials with this adjuvant therapy for treatment of COVID-19 disease.

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