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

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Summary: Celecoxib as adjuvant therapy has been shown in a small randomized trial for Covid-19 to prevent clinical deterioration and rapidly improve thoracic computerized axial tomography (CT-chest)¹. Multiple descriptive trials of high dose famotidine (both inpatient and outpatient) have demonstrated clinical response²,³,⁴. We describe the rapid clinical responses after increasing the celecoxib dosage to 400mg bid with high dose famotidine 80mg qid in both a critical inpatient who on baseline required 40 liters per minute high flow nasal insufflation and an outpatient who declined admission but had critical Covid-19 biomarkers.
Background

The nucleocapsid protein (N) and spike glycoprotein (S) of SARS-CoV can directly bind to the inducible COX-2 gene promoter, driving overexpression of COX-2 in a dose dependent manner. SARS-CoV-2 infection is associated with high levels of PGE₂ production based on urinary levels of PGE₂, 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. The randomized clinical trial of celecoxib showed that 100mg bid was insufficient to prevent clinical deterioration. Even 200mg bid moderated but urinary PGE-2 still spiked. Levels of celecoxib 400mg bid have been given for six months for multiple familial polyposis with safety similar to 100 mg bid.

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. However, it is increasing recognized that the innate immune system particularly the macrophage/monocytes are part of the COVID cascade. Famotidine’s effect on macrophage/monocytes requires higher levels and greater dosage.

Recently a consecutive case series of hospitalized COVID patients treated with high dose famotidine 80mg qid 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.

Clinical Report

Inpatient.

A hypertensive male presented after a week of cough with oxygen saturation levels (SATS) of 72% required 40 liters/minute high flow nasal insufflation with 100% oxygen improved to only 3 liters/minute but following convalescent plasma deteriorated to requiring 8 liters/min of supplemental oxygen with rise in the biomarkers of both neutrophil lymphocyte ratio (NLR) and ferritin spike. Celecoxib 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 C- chest.

**Figure 1. Radiographic and Biomarkers at baseline, 7 days later when celecoxib increased to 400mg bid, and 9 days later at discharge.** 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.
Outpatient.

A hypertensive male presented with 8 days of symptoms: cough, myalgia, fatigue, shortness of breath. His room air saturation was 90% but 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 as Day 0 the celecoxib was increased to 400mg bid with rapid improvement in biomarkers, oxygen saturations global assessment and chest x-ray.
Figure 2. Chest x-ray and biomarkers at baseline, Day 0 when celecoxib increased to 400mg bid, and Day 2. 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.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
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<tr>
<td>Ferritin</td>
<td>985</td>
<td>1200</td>
<td>1220</td>
<td>671</td>
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<tr>
<td>CRP</td>
<td>16</td>
<td>21</td>
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<td>LDH</td>
<td>353</td>
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<td>% lymph</td>
<td>7.6</td>
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<tr>
<td>NLR</td>
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<td>16</td>
<td>7.8</td>
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<tr>
<td>d-dimer</td>
<td>0.4</td>
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<td>0.5</td>
<td>0.4</td>
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<tr>
<td>eGFR</td>
<td>64</td>
<td>79</td>
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<td>79</td>
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<td>O2 sats rm air</td>
<td>90%</td>
<td>94%</td>
<td>97%</td>
<td>98%</td>
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<td>Global assessment</td>
<td>Short of breath</td>
<td>Very tired</td>
<td>cough slightly</td>
<td>better</td>
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Discussion

The rapid response to increased Celecoxib in both oxygen requirements and biomarkers supports that SARS-CoV-2 cox2 overexpression and prostaglandin E2 is dose dependent inhibition. Furthermore, 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.

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 monocyte/macrophage upregulation. While pharmacokinetic calculations do not account for local tissue levels of histamine (which will compete with famotidine for H2 receptor occupancy), 60mg PO TID is calculated to achieve 10-fold the half maximum inhibitory concentration (MIC50) for H2 blockade in the absence of histamine as a competitor. Higher levels are required for the inhibition of monocyte/macrophage upregulation.

Conclusion

The rapid clinical improvement after increasing the dosage of celecoxib to 400mg bid is consistent with the theory that SARS-CoV-2 cox2 overexpression and prostaglandin E2 is responsive to dose dependent inhibition by celecoxib. The combination of two paracrine inhibitors; high dose famotidine and high dose celecoxib’s clinical, biomarker, and radiographic results provide further evidence for randomized clinical trials with this adjuvant therapy in covid-19.


