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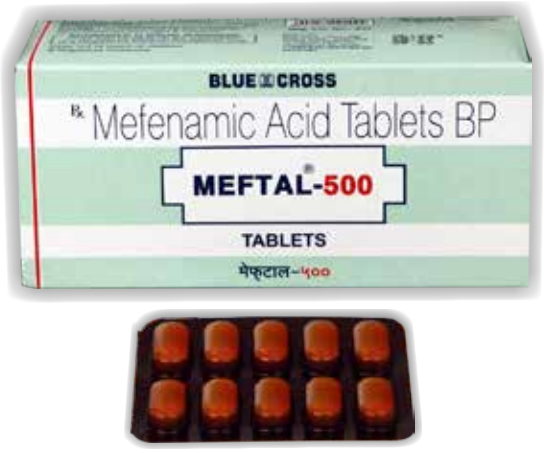

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Mefenamic Acid as Steroid-sparing Anti-inflammatory Drug During Viral Phase of COVID-19: 5 Case Reports

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ABSTRACT

The diverse disease manifestations in coronavirus disease 2019 (COVID-19) patients are an enigma since some cases display little to no symptoms, whereas others develop severe fever and pneumonia, leading to acute respiratory distress syndrome and eventually death. Given the excessive inflammatory activity, there is a need to target a regulator of cellular inflammation while leaving the antiviral pathways intact. Corticosteroids are used as potent anti-inflammatory agents; however, it may also be linked with attenuation of viral clearance leading to nonuniform benefits across the disease spectrum. Mefenamic acid can be used as a steroid-sparing, long-term drug in the management of COVID-19 and post-COVID inflammation. In this article, the management of 5 mild-to-moderate COVID-19 cases using steroid-sparing anti-inflammatory agents is described.

Keywords: Mefenamic acid, steroid-sparing anti-inflammatory drugs, COVID-19, fenamates, NLRP3 inflammasome

One of the greatest enigmas around COVID-19 is the varied disease trajectories among COVID-19 patients. While some of the patients may develop little to no symptoms, others develop severe fever and pneumonia, resulting in acute respiratory distress syndrome and eventually death. The key to overcoming excessive inflammatory activity is to target a critical regulator of cellular inflammation while the antiviral pathways are left intact.[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the lung cell damage triggers a local immune response, utilizing macrophages and monocytes responding to infection that release cytokines and prime adaptive T- and B-cell immune responses. In a dysfunctional immune response, hyperinflammation and cytokine storm occur, eventually leading to severe lung injury and even systemic pathologies. It is equally significant to control the inflammatory response as well as targeting the virus. Therapies inhibiting viral infection and regulating dysfunctional immune response may act in synergy to block pathologies at different steps.[2] The available evidence has shown that the anti-inflammatory effects of nonsteroidal anti-inflammatory drugs (NSAIDs) like mefenamic acid reduce acute symptoms such as fever.[3] Mefenamic acid can be used along with the different antiviral drugs being currently tried for the treatment of COVID-19.[4]

In this retrospective case study, 5 COVID-19 patients were managed with steroid-sparing anti-inflammatory therapy. The article discusses the role of treating COVID-19 with an anti-inflammatory approach using mefenamic acid with or without colchicine.

CASE PRESENTATIONS

Participants and Sources of Data

All patients treated at Heart Care Foundation of India (HCFI) OPD between November 01 and December 01, 2020, diagnosed with COVID-19 and treated with mefenamic acid were considered, and of these cases, 5 patients treated with mefenamic acid were randomly selected. The indication criteria for mefenamic acid use was a mild-to-moderate symptomatic case of COVID-19 with C-reactive protein (CRP) levels above 10 mg/L. Mefenamic acid was given along with the other standard of care treatment as recommended by the Ministry of Health and Family Welfare, Government of India. The Institutional Review Board of HCFI approved this report and waived the need for informed consent from individual patients due to the absence of identifying images or personal or clinical details that could

President, CMAAO and HCFI

compromise anonymity. Table 1 provides details of all the patients included in the study.

Procedures

All 5 patients in the study received mefenamic acid 500 mg thrice a day for a maximum duration of 14 days. COVID-19 diagnosis was confirmed through the reverse transcription polymerase chain reaction (RT-PCR) test. All the required tests were done at the baseline, and blood hemogram and CRP were repeated after the intervention. CRP values served as an important biomarker for the measurement of the inflammatory response of the patients. Vital statistics were assessed at the time of examining the patients.

RESULTS

Case 1

A 43-year-old male presented with moderate grade fever and body pain. His vitals were normal, CRP 13.55 mg/L. His chest X-ray was done, and the results were normal. On examination, he confessed to being a chain smoker and an alcoholic. The chest X-ray did not reveal any abnormalities. The patient was started on mefenamic acid 500 mg, thrice a day, ivermectin 12 mg, twice a day for 3 days, doxycycline 100 mg twice a day for 5 days, and multivitamin capsules. Symptomatic relief was seen in 8 days. His CRP levels reduced to 8.07 mg/L in 8 days, and the treatment was discontinued. The patient has not come back with any post-COVID syndrome.

Case 2

A 27-year-old female with a mild fever and runny nose presented to the clinic. She had traveled to Mumbai for an official meeting. She had no other comorbidities and was not on any other prior medications. There were no abnormalities seen in the chest X-ray. Her CRP was 12.43 mg/L. She was started on mefenamic acid 500 mg thrice a day for 10 days, doxycycline 100 mg twice a day for 5 days. Her CRP was reduced to 10.16 mg/L on the 11th day. Symptoms were relieved after 3 days of treatment.

Table 1. Details of Patients Included in the Study

Patient	Patient characteristics	Symptoms	Baseline assessment	Treatment approach	Post-treatment assessment	Patient outcome	Post-COVID symptoms
1	43 years, male	Moderate grade fever and body pain	Vitals normal, CRP: 13.55 mg/L; chest X-ray normal without abnormalities	Mefenamic acid 500 mg thrice a day; ivermectin 12 mg twice a day; doxycycline 100 mg twice a day; multivitamins	CRP: 8.07 mg/L	CRP reduced in 8 days	None
2	27 years, female	Mild fever and runny nose	CRP: 12.43 mg/L. No abnormalities in chest X-ray	Mefenamic acid 500 mg thrice a day; doxycycline 100 mg twice a day	CRP: 10.16 mg/L	Symptom relief in 3 days	None
3	43 years, female	Fever, cough and body aches	Normal vitals CRP: 4.78 mg/L Chest X-ray clear without any abnormality	Mefenamic acid 500 mg thrice a day Multivitamins	CRP: 2.47 mg/L	CRP reduced after 6 days of treatment	Fatigue and persistent cough after 10-12 days
4	25 years, male	Loss of taste and smell	CRP: 6.78 mg/L; Chest X-ray: normal	Mefenamic acid 500 mg, thrice a day	CRP: 3 mg/L	Regained his sense of taste and smell CRP reduced in 5 days	None
5	35 years, female	Headache, nose block, lethargy, cough, shortness of breath and loose motions	Normal vitals CRP: 12.56 mg/L Chest X-ray score 2	Mefenamic acid 500 mg thrice a day; ivermectin 12 mg twice a day; doxycycline 100 mg twice a day for 5 days; oral multivitamins	CRP: 9.47 mg/L	Symptom relief in 6 days CRP reduced in 7 days of treatment	None

Case 3

A 43-year-old female presented with fever, cough and body aches. Her vitals were normal, and her CRP levels were 4.78 mg/L. The chest X-ray was clear without any abnormalities. She was given mefenamic acid 500 mg thrice a day and multivitamins. Her CRP was reduced to 2.47 mg/L after 6 days. However, she complained of fatigue and persistent cough after 10-12 days. Her CRP values rose again, and she was given colchicine along with mefenamic acid and ivermectin.

Case 4

A 25-year-old male complained of loss of taste and smell. He had no other debilitating symptoms. Otherwise, a healthy male, he did not smoke or drink. He had been given favipiravir previously. His CRP level was tested to be 6.78 mg/L. The chest X-ray score was normal. He was given mefenamic acid 500 mg thrice a day for 5 days. His CRP was reduced to 3 mg/L after 3 days. He regained his sense of taste and smell. He has not reported back with any post-COVID symptoms.

Case 5

A 35-year-old female complained of headache, nose block, lethargy, cough, shortness of breath and loose motions. Her vitals were normal; she had suffered from allergic rhinitis 3 months back. Her CRP at the time of presentation was 12.56 mg/L. Her chest X-ray score was 2. She was immediately started on mefenamic acid 500 mg thrice a day, ivermectin 12 mg twice a day, doxycycline 100 mg twice a day for 5 days and oral multivitamins. Her CRP was reduced to 9.47 mg/L after 7 days of treatment; treatment was discontinued after 10 days. Symptoms were relieved in 6 days.

DISCUSSION

Early monitoring of crucial indicators forms a critical basis to make decisions on treatment approaches. Early evaluation of the severity of the patient's condition has great significance.[5]

CRP levels are correlated with the level of inflammation, and its concentration level remains unaffected by factors including age, sex and physical condition. At the early stage of COVID-19, CRP levels are positively correlated with lung lesions, hence reflect disease severity, and should be employed as a key indicator for disease monitoring.[5]

Serum CRP has been found to be an important marker that alters significantly in severe patients with COVID-19. It serves as an early marker of infection and inflammation. CRP preferably binds to phosphocholine expressed highly on the surface of damaged cells.[6]

This binding leads to the activation of the classical complement pathway of the immune system and modulates the phagocytic activity to clear microbes and damaged cells from the organism. With the resolution of the inflammation or tissue damage, CRP concentration reduces, making it a useful marker for monitoring the severity of COVID-19.[7]

It has also been suggested that interleukin (IL)-6 acts as the primary inducer of CRP gene expression, with IL-1β augmenting the effect. On the other hand, growing evidence has shown that CRP plays an important role in the inflammatory process and host responses to infection, including the complement pathway, apoptosis, phagocytosis, nitric oxide release and the production of cytokines, especially IL-6 and tumor necrosis factor (TNF)-α.[8]

In COVID-19 disease, the initial viral infection and subsequent host inflammatory response may lead to the excessive release of pro-inflammatory cytokines, IL-6 and IL-8, as well as TNF-α, eventually leading to hypercytokinemia. In order to address this hyperimmune-inflammatory pathogenesis, anti-inflammatory medicines targeting specific cytokines are a useful treatment approach.[9]

NLRP3 inflammasome has been implicated in a plethora of diseases. It is also involved in antiviral responses and virus-associated illnesses. As a mechanism to intensify disease pathogenesis, inflammasome activation can trigger cellular pyroptosis, which is a kind of programmed cell death. Pyroptosis of macrophages that have phagocytosed viruses rapidly releases multiple alarmins, including viral particles, cytokines, chemokines, lactate dehydrogenase (LDH), ATP and reactive oxygen species (ROS) prompting an immediate reaction from surrounding immune cells and thus inducing a pyroptic chain reaction. Besides, pyroptosis may lead to the generation of immune complex and circulation and deposition of viral antigens and RNA in target organs to initiate inflammatory cascade.[1]

SARS-CoV-2-induced inflammasome activation and pyroptosis in alveolar macrophages and recruited monocyte-derived macrophages, could drastically aggravate pneumonia symptoms, including acute respiratory distress syndrome and fever. Widespread and uncontrolled pyroptosis could lead to excessive tissue inflammation, organ failure and even death.[1]

The use of NLRP3 suppressors offers a viable solution to the treatment of hyperinflammatory responses in

virus infections. The benefits of NLRP3 inflammasome inhibitors like fenamates reduce local inflammation and ameliorate comorbidities associated with COVID-19, including hypertension, chronic obstructive pulmonary disease, type 2 diabetes mellitus and cardiovascular diseases as NLRP3 inflammasome activation is implicated in these diseases. In the management of COVID-19, there are two anti-inflammatory approaches: steroids and steroid-sparing agents like mefenamic acid with or without colchicine. However, early initiation of steroids is associated with a risk of increasing viral load.[1]

Corticosteroids are potent anti-inflammatory agents suggested to check the deleterious effects of cytokine storm in COVID-19.[10] Initial reports from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial showed that dexamethasone improved 28-day mortality compared to placebo in patients needing invasive mechanical ventilation (IMV) and those requiring oxygen therapy.[11] It strengthened the recommendation to use corticosteroids in hospitalized COVID-19 patients. However, it is essential to understand here that steroids in viral infection can behave like a double-edged sword, where the corticosteroid therapy may lead to attenuation of viral clearance as seen in the case of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) influenza and hence worsen clinical outcomes. It may also increase the probability of bacterial infections and mortality. Hence, the risk:benefit ratio of corticosteroid use may not be consistent across the varying disease severity of COVID-19, thereby leading to more harm than benefits. Hence, it becomes necessary to look for nonsteroid agents that exhibit much-needed anti-inflammatory properties to reduce cytokine storm and improve patient outcomes. In this context, mefenamic acid is an essential NSAID acting via selective NLRP3 inflammasome inhibition.[10]

The management of mild-to-moderate cases currently comprises antiviral agents, symptomatic treatment, and anti-inflammatory drugs. Doxycycline and ivermectin combination is given to symptomatic and asymptomatic COVID-19 patients for symptomatic relief and viral clearance.[12] Studies have shown that ivermectin is effective for the treatment of early-onset mild COVID-19 in adult patients causing early viral clearance of SARS-CoV-2 in treated patients; however, remission of fever, cough and sore throat is not attributed to the use of ivermectin.[13] Nonsteroidal anti-inflammatory agents have well-known anti-inflammatory activity and are suggested to be beneficial for both the early control of inflammation and prevention of thromboembolism, thereby theoretically restricting COVID-19 progression.[14] Mefenamic acid is one such NSAID that is known to provide significant protection against increased levels of TNF-α and IL-1β in radiation-induced genotoxicity of human lymphocytes.[15,16] Mefenamic acid has also been reported to be beneficial in patients who do not respond to paracetamol. Besides, paracetamol is a particular NSAID with no or almost negligible anti-inflammatory and antiplatelet activity and there are evident concerns about paracetamol-induced toxicty.[14,17]

In the cases presented above, early initiation of treatment with mefenamic acid provided symptomatic relief to the patients, who were not hypoxic, in reducing fever. The use of mefenamic acid alone led to the lowering of the CRP levels, which can also prevent cytokine storm, reflecting the significant anti-inflammatory activity of mefenamic acid in COVID-19 patients. The anti-inflammatory activity of mefenamic acid is very well-established, and it inhibits cyclooxygenase enzymes in the synthesis of prostaglandins and has been widely used to treat pain and inflammation. It is also a selective inhibitor of NLRP3 inflammasome and IL-1β release.[4]

As seen in one of the cases, in patients with cough, it is advisable to prescribe mefenamic acid along with other anti-inflammatory agents such as colchicine, as the cough could be due to viral pneumonia. In all mild-to-moderate cases of COVID-19 (CRP levels between 10 and 14 mg/L), mefenamic acid can be prescribed as an effective anti-inflammatory and antipyretic agent with careful monitoring and regular assessment of CRP values. Besides, nonsteroidal anti-inflammatory agents like mefenamic acid may be given in the case of post-COVID myalgia till the CRP level reduces below 1. Mefenamic acid is continued until two consecutive CRP readings <1 is achieved in an interval of 3-7 days.

CLINICAL PEARLS

- Mefenamic acid with or without colchicine can be used early to manage mild and moderate COVID-19 cases for combating cytokine inflammation (rising CRP) as a steroid-sparing potent anti-inflammatory drug during the early high viral load state of the disease.
- Mefenamic acid may also be used as a steroid-sparing long-term drug in post-COVID inflammation till CRP levels below 1 mg/L are achieved.

Mefenamic acid is a repurposed antipyretic and anti-inflammatory agent (selective NLRP3 inflammasome inhibitor) in treating mild-to-moderate COVID-19 patients.

CONCLUSION

Considering the clinical effect of mefenamic acid in mild-to-moderate COVID patients, it can be repurposed as an antipyretic and anti-inflammatory agent in treating COVID-19. Owing to its role as an antipyretic and anti-inflammatory drug, mefenamic acid plays a significant role in reducing fever and inflammation and can be used as a steroid-sparing medicine in treating COVID-19. Even though these case studies determine the potential usefulness of mefenamic acid in COVID-19 patients, larger clinical trials are needed to corroborate further the evidence seen in the cases mentioned above.

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