Special Reprint

Repurposing Mefenamic Acid in the Management of COVID-19

Dr
©

Largest
Circulated
Medical Journal
in India

Visit us at https: // onlinejima.com

<u>Review Article</u>

Repurposing Mefenamic Acid in the Management of COVID-19

K K Aggarwal[1], Yeh Woei Chong, Rajan Sharma, Marthanda Pillai, Ravi Naidu, Alvin Yee-Shing Chan,
Marie Uzawa Urabe, Debora Cavalcanti, Prakash Budhathoky, Qalsar Sajjad, Russel D'Souza,
N Ganabaskaran, Md Jamaluddin Chowdhary, Prakash, R V Asokan, Ramesh K Datta,
Jayakrishnan Alapet, V K Goel, Brijendra Prakash, Shashank Joshi, Ashok Gupta, Suneela Garg,
Alex Thomas, D R Rai, J A Jayalal, P N Arora, K Kalra, A K Aggarwal, Anita Chakravarti,
Atul Pandya, Shantanu Tripathi, Bejon Mishra, T S Jain, Anil Pachnekar, Shivkumar S Utture,
Ketan Mehta, R P Pareek, Alok P Nachane, Ambanna Gowda, Shilpa Karande

With the growing understanding of coronavirus disease-2019 (COVID-19) pathogenesis, different therapeutic targets are being considered for the management of COVID-19. The development of new drugs is a time-consuming process; hence, many drugs acting on similar therapeutic targets/sites in the COVID-19 treatment are repurposed in COVID-19.

In this article, an expert panel deliberated on the existing evidence on the immunopathogenesis, therapeutic targets under consideration for treatment of COVID-19, and the place of mefenamic acid in the therapy landscape of COVID-19. The expert panel has also provided recommendations regarding the dose and regimen of mefenamic acid in different phases of the COVID-19 disease.

In the coronavirus disease 2019 (COVID-19) pandemic scenario, there are no specific agents against severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), while COVID-19 continues to be a public health emergency affecting millions of people across the globe. Given this, experts have identified and recommended some therapies such as a combination of two HIV drugs, antimalarial drugs, and an experimental antiviral compound remdesivir to be used in the management of COVID-19[1]. Even though the search for new agents is continuing, the demands for new effective agents and therapies is enormous. Hence, several drugs already available for other indications have undergone clinical trials to repurpose against COVID-19. With increasing knowledge about the pathogenicity of the disease, different therapeutic targets are being considered, and drugs acting on the virus-related or host-related targets are repurposed for COVID-19[2]. The SARS-CoV-2 infection has aggressive inflammatory responses strongly implicated in the resulting damage to the airways and several other body organs. Here, we have considered

> **Editor's Comment :**
> - **Many old drugs are being repurposed for Covid-19 with varying Success.**
> - **Mefenamic acid, an NSAID, inhibits the NLRP3 inflammasome.**
> - **This can theoretically inhibit cytokine over activation.**
> - **This is also useful for Post-Covid Myalgia**

repurposing mefenamic acid in COVID-19 for its antipyretic, anti-inflammatory, and antiviral properties.

Methodology :

The present review examines the existing evidence on the immunopathogenesis of COVID-19 and the role of mefenamic acid in its management. The review presents evidence-based and clinical experience-based recommendations on the use of mefenamic acid in the management of COVID-19.

To inform the highest possible evidence base for the use of mefenamic acid in COVID-19, a systematic review of the literature was conducted on PubMed, Cochrane database, and Google Scholar. Existing guidelines, meta-analysis, systematic reviews, randomized controlled trials (RCTs), non-RCT studies, and experimental studies relating to the benefits of mefenamic acid and the immunopathogenesis of COVID-19 were searched, scanned, selected, and reviewed. Only articles in English and COVID-19, experimental, clinical studies, or review on mefenamic

acid were included. Articles in other foreign languages and focusing on other respiratory disorders were excluded from the selection.

Recommendations for the use of mefenamic acid are based on the available evidence and preliminary discussions among expert groups. Several rounds of discussions ensued with the Confederation of Medical Associations of Asia and Oceania (CMAAO) group of experts, the Indian Medical Association (IMA) panel, and the committee of experts, including clinicians treating or undertaking research in COVID-19 management, which was specially formed to delve into the available evidence and relevant clinical experience on mefenamic acid.

The expert panel then discussed the recommendations formulated above, put forth in this article. Where there was little or no evidence, the panel relied on logical empiricism and consensus to generate the recommendations about the rational use of mefenamic acid in the management of COVID-19.

Immunopathophysiology of COVID-19 :

The virus —

The virus responsible for COVID-19 disease belongs to the family Coronaviridae. Inhumans, most coronavirus infections lead to mild respiratory symptoms and may be attributed to causing almost 20-30% of common colds[3]. The virus has too high transmissibility and a degree of lethality comparatively lesser than the SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus). However, the situation is currently evolving, and the degree of lethality is yet to be established globally[4].

Coronaviruses possess single-stranded positive RNA, spike-S, membrane-M, and envelope-E proteins in the virus envelope. Nucleocapsid-N is present inside the virion that covers the RNA. From 5' to 3', genes for the replicases ORF1a,b are located on the viral genome,occupying two-thirds of the genome, and code for the polyproteins pp1a and pp1b. Towards the 3' end, the genes for structural proteins S,E,M, and N are present[4].

Protein S contains the receptor-binding domain for the ligand on the host cell membrane and the epitopes recognized by T and B cells, which trigger antibodies' production. The primary receptor for the SARS-CoV-2 on the host membrane is the angiotensin-converting enzyme 2 (ACE2). It is present on the membrane of many cells, including type I and II pneumocytes, small intestine enterocytes, kidney proximal tubule cells, the endothelial cells of arteries and veins, and the arterial smooth muscle. Receptor-binding domain essential for ACE2 binding mobilises conformational changes on S leading to cleavage of S1 and S2 proteins, mediated by the transmembrane *serine protease* 2 (TMPRSS2), enabling S2 to facilitate the fusion of the virus envelope with the cell membrane thus permitting viral entry into the cytoplasm of the host cell. Inside the cell, viral RNA serves as a template for the translation of the polyprotein pp1a and pp1b that are split into 5-16 nonstructural proteins (nsp2-nsp9), leading to a reshuffling of the membranes to form the vesicles where viral replication and transcription complexes are secured. The virions are gathered in the ER-Golgi, and the secretory pathways eventually release mature virions[4].

The Innate Immune Response :

During the SARS-CoV-2 infection, the virus is recognized by pattern recognition receptors (PRR) such as toll-like receptor (TLR)-7 and TLR8, retinoic acid-inducible gene-I-like receptors (RLRs) and NOD (nucleotide binding and oligomerization domain)-like receptor (NLR) expressed by epithelial cells as well as by local cells of the innate immune response, such as alveolar macrophages. After binding to the ligand, PRRs recruit adaptor proteins activating crucial downstream transcription factors, including interferon regulatory factor (IRF), nuclear factor kappa B (NF-κB), and AP-1 leading to the production of type I and typeIII antiviral interferons (IFNs) and different chemokines[5]. These chemokines attract more innate response cells, polymorphonuclear leukocytes, monocytes, NK cells, dendritic cells, which also produce chemokines. SARS-CoV-2-induced five cytokines: IL-6, MCP1, CXCL1, CXCL5, and CXCL10/IP10. SARS-CoV-2 induces a specific signature featured by decreased IFN-I and IFN-III responses and significant induction of multiple pro-inflammatory chemokines, IL-1β, IL-6, tumor necrosis factor (TNF-α), and IL1RA. These findings have been supported by the increased serum levels of these cytokines in COVID-19 patients[4].

The Adaptive Immune Response :

The transition from innate to adaptive response is crucial because, at this juncture, the immune regulatory events will lead to the development of either a protective immune response or an exacerbated inflammatory response. The protective response is T cell-dependent, with CD4 helping B cells help in producing specific neutralizing antibodies and cytotoxic CD8 cells eliminate infected cells. It has been found that in COVID-19, 80% of the infiltrating cells are CD8[6]. In the case of a dysfunctional response, an exacerbated inflammatory response leads to a cytokine

storm, clinically manifested by severe acute respiratory distress syndrome (ARDS) and systemic results like disseminated intravascular coagulation[4]. The disease is hypothesized to be divided into two phases; an early phase dependent on viral replication and a later viral-independent, immune-dependent phase accompanied by an exacerbated inflammatory component.

Prostaglandins Involvement :

Arachidonic acid (AA) possesses potent antimicrobial activity via leakage and lysis of microbial cell membranes, viral envelope disruption, amino acid transportation, inhibition of respiration, and uncoupling of oxidative phosphorylation[7]. It is also suggested that reduced concentration of AA may be the causative factor for the absence of inhibition of SARS-CoV-2 replication in COVID-19 patients[8]. On the contrary, a decrease of AA levels has also been observed in COVID-19 patients, who could be attributed to the conversion of AA into prostaglandins via up-regulated gene expression of cyclooxygenase (COX)-1, COX-2, and PTGES3 and increased PGE2levels. Also, cytosolic phospholipase A2α (cPLA$_2\alpha$) genes,which are highly expressed in the endothelial and epithelial cells of the human lung, are up-regulated in COVID-19 patients[9].

Infection with SARS-CoV-2 ligates various pathogen recognition receptors such as TLR and/or RLRs and triggers transcription factors such as IFN regulatory factor 3 (IRF3) and NF-κB that are responsible for the expression of type I and III IFNs and pro-inflammatory mediators, including TNF-α, IL-6, and PGE2, respectively. NF-κB is the vital transcription factor responsible for the induction of pro-inflammatory cytokines. Activation of NF-κB can stimulate gene expression of inducible COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1) in many cell types bringing about the production of COX-2-dependent PGE2.This PGE2acts autocrinally and/or paracrinally on NF-κB stimulation to expand pro-inflammatory cytokines and chemokines through the E-type prostanoid receptor (EP)-2 receptors. In humans, PGE2 promotes IL-1β-dependent production of IL-6, macrophage colony-stimulating factor (M-CSF), and vascular endothelial growth factor (VEGF) from human fibroblasts via EP4 receptors. It also enhances induction of IL-6 and other pro-inflammatory cytokines upon many stimuli in monocytes, macrophages, fibroblasts, and airway epithelial cells through both EP2 and EP4 receptors. Besides, IL-6 also up-regulates COX-2 gene expression and increases PGE2 production, working together for normalized production of other inflammatory factors such as MMP9. PGE2 can also trigger IL-6 production in a paracrine way[10].

NLRP3 Inflammasome :

It has been observed that several external and internal stimuli, including viral RNA (E protein and ORF3a of SARS-CoV), trigger the activation of NLRP3 inflammasome through mechanisms including formation of pores with ion redistribution and lysosomal disruption, leading to inflammation and associated cell death. Once NLRP3is activated, procaspase-1 is converted to the active effector protease caspase-1, which leads to cleavage and maturation of pro-inflammatory cytokines like pro-IL-1β into its active form IL-1β and that of IL-18. These pro-inflammatory cytokines stimulate a cascade of other downstreammediators of inflammation, including IL-6, TNF-α, prostaglandins, and leukotrienes[11].

Abnormal activation and triggered cascade of downstream mediators may lead to pathological tissue injury during infection, as is s-αeen in the case of SARS-CoV-2 infection[12]. Infection with SARS-CoV notably induces a storm of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α, all of which play a vital role in the progression of tissue inflammation causing ARDS and eventually leads to death[13]. Based on this strong inflammatoryability of the NLRP3 inflammasome, it forms an important target in the treatment strategy of COVID-19.

Cytokine Storm and COVID-19 :

Mortality in COVID-19 patients has been associated with the presence of the "cytokine storm" induced by the virusand the hyper-inflammatory immune response of the host. Excessive formation of pro-inflammatory cytokines causes aggravation of ARDSand widespread tissue damage resulting in multi-organ failure and death. The cytokine storm in COVID-19 is related directly to lung injury, multi-organ failure, and unfavorable prognosis of severe COVID-19. Three of the most critical pro-inflammatory cytokines of the innate immune response are IL-1β, TNF-α, and IL-6. These cytokines are produced by tissue macrophages, mast cells, endothelial and epithelial cells during the innate immune response. A sudden acute boost in circulating levels of different pro-inflammatory cytokines (such as IL-6, IL-1β, TNF-α, and IFN). The increase in cytokine levels leads to the recruitment of several immune cells like macrophages, neutrophils, and T cells from blood circulation into the infection site with the destructive effects on human tissue resulting from the destabilization of endothelial cell to cell interactions, damage of vascular barrier, capillary damage, diffuse

alveolar damage, multi-organ failure, and eventual death. Lung injury is a severe manifestation of the cytokine storm that can progress into ARDS. Given the above discussion, the early detection and prompt treatment can lead to a better outcome of COVID-19[14].

Fever in COVID-19 :

The first presentation of fever during the first week in COVID-19, during the viral phase of the illness, is probably a manifestation of the body's immune reaction to the replication of the virus to enhance immunity. However, when the infection does not resolve indue course, it leads to a complicated disease process stimulated by the viral activated state of dysregulated inflammation referred to as cytokine storm or secondary hemophagolymphocytosis, foreshadowed by chronic fever[15]. In these cases, where fever occurs due to severe inflammation, it may be counter productive. Here, fever is not beneficial at this stage, as it may promote further inflammation and non-advantageous immune activation. Hence, fever may have a differential impact on the prognosis during the viral and inflammatory stage of the disease marking the use of antipyretics in different stages of COVID-19 infection[16].

Post-COVID Myalgia :

Myalgia reflects generalised inflammation and cytokine response and may even be the onset symptom in 36% of patients with COVID-19. It has been noted that common myalgia caused by COVID-19 is more prolongedand severe when compared with other viral infections and may be unresponsive to traditional painkillers. It is also seen that as the viral load is reduced with treatment, muscle pain may subsequently reduce[17].

As the acute COVID-19 infection has been alleviated, some patients experience long-term adverse effects similar to those of chronic fatigue syndrome or myalgic encephalomyelitis with symptoms including persistent fatigue, diffuse myalgia, depressive symptoms, and non-restorative sleep. Due to the build-up of cytokines in the central nervous system maybe the cause of post-viral symptoms because of the pro-inflammatory cytokines passing through the blood-brain barrier in circumventricular organs such as the hypothalamus, leading to autonomic dysfunction[18].

Repurposing Mefenamic Acid in COVID-19 Management :

Antiviral Activity —

Angiotensin-converting enzyme 2 is the host cell receptor for the S protein of SARS-CoV-2, and TMPRSS2 is required for S protein priming of SARS-CoV-2. Their inhibition may prevent cell entry of the SARS-CoV-2[19]. Mefenamic acid inhibits the formation of M28, thereby acting as a protease inhibitor. The inhibition of the protease has been reported to be of significance in the treatment of COVID-19[20].

Earlier studies have also shown that mefenamic acid possesses antiviral activity. The inhibitory effect of mefenamic acid against RNA viruses has been assessed as 90% at a concentration of 30 µM[21]. Mefenamic acid is thus a drug with protease inhibitory action in conjunction with other antiviral drugs or even on its own[22].

A study was performed to assess the potential antiviral activity of nonsteroidal anti-inflammatory drugs (NSAIDs) under the assumption that active compounds with potential antiviral and anti-inflammatory activities could be used in human subjects to treat chikungunya virus (CHIKV) infections. The results showed that mefenamic acid possessed potential antiviral activity both *in vitro* and *in vivo*. A better activity was reported when it was administered in combination with the common antiviral drug, ribavirin. The combination of the antiviral and anti-inflammatory effects of mefenamic acid was beneficial in significantly reducing the pathological signs. The viral titer quantification revealed in the blood of CHIKV-infected mice through the plaque formation assay showed that treatment with the combination of ribavirin and mefenamic acid exhibited a 6.5-fold reduction compared with untreated controls. There are suggestions that these findings might lead to the use of combination against other viral infections[23].

An older study has demonstrated that mefenamic acid, along with doxycycline, had antiviral activity. The inhibitory effect of mefenamic acid against RNA viruses is estimated to be 90% at a concentration of 30 µM[21].

Anti-inflammatory and antipyretic activity :

Cyclooxygenase Inhibition —

There are two COX isoforms, COX-1 and COX-2, which catalyse the first two steps of prostaglandin biosynthesis from AA and are the pharmacological targets of NSAIDs. Mefenamic acid depicts selective inhibition of 2-arachidonylglycerol (2-AG) oxygenation by COX-2[24].

Action on Prostaglandins :

PGE2 has multifaceted effects on the modulation of T-cell responses. PGE2 suppresses T-cell receptor-dependent T-cell activation and proliferation via EP2/EP4 receptor-mediated cyclic adenosine 3',5' -monophosphate (cAMP)-PKA (protein kinase A) pathway, but this suppressive effect is weakened by

enhancing CD28 co-stimulation through augmentation of phosphatidylinositol 3 kinase (PI3K) signalling. Following SARS-CoV-2 infection, the pathway related to CD28 signalling in T helper cells was significantly down-regulated, while the PKA pathway and PGE2 biosynthesis pathway were significantly up-regulated. Thus, PGE2–cAMP-PKA signalling is likely to inhibit antigen-dependent activation of antiviral T-cell responses in COVID-19 patients. On this basis, the use of NSAIDs by inhibiting endogenous PGE2 production may enhance antiviral T-cell responses in COVID-19 patients[10]. The fenamates (like mefenamic acid) possess a dual inhibitory action; they rapidly neutralize the effects of preformed prostaglandins as well as prevent the continuing synthesis of prostaglandins by inhibiting the synthetase enzyme system[25].

Action on NLRP3 Inflammasome :

Fenamate NSAIDs (mefenamic acid) selectively inhibit the NLRP3 inflammasome and IL-1β release by blocking the membrane volume regulated anion [chloride] channel (VRAC). This blockade acts independently of its COX-mediated anti-inflammatory activity. It has also been established that there is a synergy between inhibitors in inflammatory pathways to bring about different levels of inhibition much more than observed singly[26]. Hence, molecules such as mefenamic acid, which modulate several points in a pathway, have an increased probability of leading to enhanced protective effects as compared to molecules that act on a single target[27]. This also allows them to confer greater efficacy at lower doses. Another advantage of this blockade is that the use of fenamates would avoid compromising NLRC4 or AIM2 inflammasome-dependent host responses to infection[26].

In the SARS-CoV-2 infection, there is a role of NLRP3 inflammasome inhibitors in terms of the inflammatory manifestations; this draws attention towards mefenamic acid[22].

Mefenamic Acid and Other NSAIDs :

Studies demonstrated that unlike other NSAIDs, fenamates (mefenamic acid, flufenamic acid) selectively inhibit the NLRP3 inflammasome and IL-1β release[11]. In a study, it was shown that indomethacin led to small intestinal damage through NLRP3 inflammasome-derived IL-1β via TLR4- and P2X7-dependent signalling pathways[28]. Paracetamol overdose triggers the release of danger-associated molecular proteins (DAMPs), which bring about transcriptional activation of pro-inflammatory cytokines in macrophages through TLRs and inflammasome activation, causing liver damage[29]. Other than one study which showed that naproxen in low doses inhibits NFκB activity[30], there was no other clinical study mentioning the association of naproxen with NLRP3 inflammasome inhibition.

NSAIDs block prostaglandin and may exhibit antiplatelet effects and hence are clinically useful in the management of COVID-19[10]. Mefenamic acid possesses a dual inhibitory effect of neutralising the effects of prostaglandinas well as inhibiting its synthesis[25]. Fenamates have a direct inhibitory effect on PGE receptor binding at the usual therapeutic

---

5 important points regarding Mefenamic Acid :

1. Mefenamic acid inhibits cyclooxygenase (COX-1 and COX-2) and has analgesic, anti-inflammatory, and antipyretic properties, as it is a potent inhibitor of prostaglandin synthesis.

2. Mefenamic acid is indicated for

(a) mild to moderate pain in patients = 14 years of age (when therapy will not exceed one week)

(b) For treatment of primary dysmenorrhea

3. This drug should not be started in back ground of thrombotic events (post MI, post CABG, stroke) and patients with GI Ulcer, bleeding. Need to aware of the risk factors like hepatotoxicity, hypertension, acute kidney injury, hyperkalemia, heart failure, pedal edema, skin reactions and anaphylaxis while using mefenamic acid.

4. Known hypersensitivity, History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs, In the setting of coronary artery bypass graft (CABG) surgery - mefenamic acid is strictly contraindicated.

5. While using to treat acute pain in adults and adolescents ≥14 years of age, the recommended dose is 500 mg as an initial dose followed by 250 mg every 6 hours as needed, usually not to exceed one week.

For the treatment of primary dysmenorrhea, the recommended dose is 500 mg as an initial dose followed by 250 mg every 6 hours, given orally, starting with the onset of bleeding and associated symptoms. Clinical studies indicate that effective treatment can be initiated with the start of menses and should not be necessary for more than 2 to 3 days.

dosage. Other prostaglandin synthetase inhibitors have not shown such a dual mode of action, and no effect was reported for acetylsalicylic acid[31].

Indomethacin is a potent nonselective COX inhibitor that was widely used as an anti-inflammatory medication. However, it has become unfavorable because of its tendency toward adverse events compared with other commercially available NSAIDs. Owing to the adverse events, its indication and duration of use are limited[32]. It is already mentioned that indomethacin use also led to the damage of the small intestine along with the promotion of caspase-1 and IL-1β maturation underlying the role of IL-1β in indomethacin-induced enteropathy. However, IL-18 activated by inflammasomes with pro-inflammatory activities was not activated[28]. Contrary to this, another study using a mice model showed that indomethacin could protect pancreatic acinar cells from injury by inhibiting the NLRP3 inflammasome pathway and hence reduce the severity of severe acute pancreatitis[33]. Such contradictory results have created ambiguity around the role of indomethacin in NLRP3 inflammasome activation, and more research is required to comprehend its role in the NLRP3 pathway. Currently, there are no reports suggesting the action of ibuprofen or diclofenac on the NLRP3 inflammasome action.

Acetaminophen (paracetamol) is in use as an antipyretic agent for a long time. It reduces prostaglandin synthesis in the brain. However, it does not inhibit prostaglandin synthesis in the periphery and hence does not have any anti-inflammatory action. Along with potential side effects, it might also lead to severe hypersensitivity reactions. Even though considered a dependable antipyretic, there have been reports where paracetamol has failed to control fever leading to the search for other antipyretics. Paracetamol and NSAIDs have essential differences, including the former's weak inflammatory effects and its generally poor ability to inhibit COX in the presence of a high concentration of peroxides as are found at sites of inflammation[32]. Hepatic injury and subsequent hepatic failure due to both intentional and nonintentional overdose of paracetamol have affected patients for decades. It is considered to be one of the most common pharmaceutical products to cause drug-induced liver injury[34]. Acetaminophen has also displayed hepatotoxicity in many combination medications; hence caution is needed with its use[32].

Table 1 — *Action of Different NSAIDs on the Various Immunopathogenesis of COVID-19*

Cytokine	Paracetamol	Naproxen	Indomethacin	Nimesulide	Mefenamic acid
IL-1β		↓ +	↑	↓	↓++
IL-6	☞	↓+	↓+	↓+	↓+++
IL-18	✗	✗	✗	✗	↓+
TNF-α	↓	↑	☞	↓	↓++
NLRP3	✗	✗	Ambiguity ☞	✗	✓
Viral load	✗	Prevents viral entry & replication	Inhibits viral replication at a higher dosage	✗	Inhibits the serine protease and viral replication

Nimesulide also possesses analgesic and antipyretic properties and has comparable efficacy to naproxen, acetylsalicylic acid, paracetamol, and mefenamic acid; however, it is associated with fulminant hepatitis[35].

As is clear from the discussion in previous sections, mefenamic acid is a potent COX inhibitor and causes both central and peripheral analgesic action. In a study comparing the efficacy and safety of paracetamol and mefenamic acid in the treatment of fever, it was reported that both paracetamol and mefenamic acid were effective antipyretic drugs. In the study findings, the body temperature reduced more in the mefenamic acid compared with the paracetamol group, six hours after the treatment. Also, the fall in temperature at 1 hour was better in the mefenamic acid group. Mefenamic acid thus exhibited a highly significant reduction in the body temperature baseline to the sixth hour compared with paracetamol in pediatric patients with fever (p<0.01)[35]. Comparable results were seen in a previous study, which demonstrated that mefenamic acid was more potent antipyretics than paracetamol[36]. Based on the above evidence, Table 1 had been formulated to depict the effect of different NSAIDs on different aspects of the immunopathogenesis of COVID-19.

Recommendations of the Expert Panel :

1. COVID-19 can be classified into two phases: a viral phase and the second immune-inflammatory phase. Since there are no treatments for the disease currently, several pre-existing drugs with antiviral action or action on different regulators of the inflammatory phase can be repurposed in the management of COVID-19.

2. While both NSAIDs and acetaminophen

(paracetamol) can be used as antipyretic agents in the management of fever, given the understanding of the fever in COVID-19, it is important to note that paracetamol does not possess the same anti-inflammatory features that NSAIDs possess. Experts also opined that anti-inflammatory drugs like ibuprofen could act as an aggravating factor for the infection.

3. Mefenamic acid with established antipyretic action is one such NSAID that can be used safely right from the first day of infection.

4. Mefenamic acid can be used at any stage of COVID-19, contradictory to steroids,which should be avoided during the viremic phase of the infection.

5. An additional advantage of mefenamic acid is that it possesses anti-inflammatory, analgesic, and antiviral effects as well. When used in the inflammatory phase of the disease, mefenamic acid acts on the NLRP3 inflammasome and inhibits it, thereby reducing IL-1β, IL-18, IL-6, and TNF-α.

6. In individuals with persistently high C-reactive protein (CRP) (persistent inflammation), mefenamic acid can be given in a dose of 500 mg thrice a day for long-term (up to 3 months), in post-COVID syndrome along with oral anticoagulants to break the cycle of inflammation and inflammation begetting thrombosis.

7. Mefenamic acid possesses antipyretic action for both the thermodysregulation of the hypothalamus and fever associated with cytokine storm.

8. Mefenamic acid is effective in a fever, not responding to paracetamol. It also possesses antipyretic action in those cases where fever is not responding to steroids.

The recommendations for the use of mefenamic acid in the management of COVID-19 adult patients are:

1. 500 mg mefenamic acid 2-3 times a day for 7-10 days

2. In case of high CRP levels persisting in the inflammatory phase, may continue with mefenamic acid (500 mg, three times a day) for up to three months or till the CRP value optimize, for managing inflammation.

3. In post-COVID syndrome, mefenamic acid may be considered in a dose of 500 mg, three times a day for up to three months.

Precautions :

In the case of patients with estimated glomerular filtration rate (eGFR) 30 to <60 mL/min/1.73m^2, mefenamic acid should be temporarily discontinued, while in those with eGFR<30 mL/min/1.73m^2, mefenamic acid should be avoided. When used in elderly or geriatric patients, caution should be exercised in patients above 65 years of age; in patients over 75 years or receiving concomitant oral/parenteral corticosteroids, anticoagulants or antiplatelets has increased risk of gastrointestinal bleed; or if transaminase elevation is increased over 2-3 folds. Mefenamic acid is pregnancy category C; it should only be used with caution if benefits outweigh risks. However, it should be avoided in the third trimester. Mefenamic acid is a safe antipyretic in children; however, in COVID-19, it is not advisable in children under 14 years of age due to lack of clinical evidence.

Conclusion :

Blocking the viral entry and replication and inhibiting the cytokine storm via blocking various immune-inflammatory pathways are essential therapeutic targets in COVID-19 treatment. IL-1β, IL-6, and TNF-α are the three most important pro-inflammatory markers leading to tissue inflammation, ARDS, and eventual death.

Mefenamic acid is an NSAID with antiviral, anti-inflammatory, analgesic, and antipyretic activities. It is a known COX-inhibitor,which also has an inhibitory action on the NLRP3 inflammasome and additionally inhibits the serine proteases of the virus.It has shown potent action in blocking all the three implicated pro-inflammatory biomarkers responsible for causing cytokine storm.

Various members from the expert panel shared their anecdotal experience on the effectiveness of mefenamic acid as an antipyretic, analgesic, and anti-inflammatory agent in the management of COVID-19 patients.Thus, the expert panel has recommended the use of mefenamic acid (500 mg, thrice a day) in the management of COVID-19 in adults. However, more extensive clinical trials are warranted to establish the samein the management of COVID-19.

REFERENCES

1 Harrison C — Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol* 2020; **38(4):** 379-81.

2 Singh TU, Parida S, Lingaraju MC, Kesavan M, Kumar D, Singh RK — Drug repurposing approach to fight COVID-19. *Pharmacol Rep* 2020: 1-30.

3 Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G — Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. *Cell Stress* 2020; **4(4):** 66-75.

4 García LF — Immune response, inflammation, and the clinical spectrum of COVID-19. *Front Immunol* 2020; **11:** 1441.

5 Hur S — Double-stranded RNA sensors and modulators in innate immunity. *Annu Rev Immunol* 2019; **37(1):** 349-75.

6 Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, *et al* — Coronavirus infections and immune responses. *J Med Virol.* 2020; **92(4):** 424-32.

7 Das UN — Arachidonic acid and other unsaturated fatty acids and some of their metabolites function as endogenous antimicrobial molecules: a review. *J Adv Res* 2018; **11:** 57-66.

8 Das UN % Can bioactive lipids inactivate coronavirus (COVID-19)? *Arc Med Res* 2020; **51(3)**: 282-6.

9 Yan Q, Li P, Ye X, Huang X, Mo X, Wang Q, *et al* — Longitudinal peripheral blood transcriptional analysis of COVID-19 patients captures disease progression and reveals potential biomarkers. *medRxiv.* Published online May 8, 2020:2020.05.05.20091355.

10 Robb CT, Goepp M, Rossi AG, Yao C — Non-steroidal anti-inflammatory drugs, prostaglandins, and COVID-19. *Br J Pharmacol* 2020; **177(21):** 4899-920.

11 Shah A % Novel coronavirus-induced NLRP3 inflammasome activation: a potential drug target in the treatment of COVID-19. *Front Immunol* 2020; **11:** 1021.

12 da Costa LS, Outlioua A, Anginot A, Akarid K, Arnoult D — RNA viruses promote activation of the NLRP3 inflammasome through cytopathogenic effect-induced potassium efflux. *Cell Death Dis* 2019; **10(5):** 346.

13 Nieto-Torres JL, Verdiá-Báguena C, Jimenez-Guardeño JM, Regla-Nava JA, Castaño-Rodriguez C, Fernandez-Delgado R, *et al* — Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. *Virology* 2015; **485:** 330-9.

14 Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R — The COVID-19 cytokine storm; what we know so far. *Front Immunol* 2020; **11:** 1446.

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

16 Gul MH, Htun ZM, Inayat A — Role of fever and ambient temperature in COVID-19. *Expert Rev of Respir Med.* Published online September 9, 2020: 1-3.

17 Kucuk A, Cumhur Cure M, Cure E — Can COVID-19 cause myalgia with a completely different mechanism? A hypothesis. *Clin Rheumatol* 2020; **39(7):** 2103-4.

18 Perrin R, Riste L, Hann M, Walther A, Mukherjee A, Heald A — Into the looking glass: Post-viral syndrome post-COVID-19. *Medical Hypotheses* 2020; **144:** 110055.

19 McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C — Candidate drugs against SARS-CoV-2 and COVID-19. *Pharmacol Res* 2020; **157:** 104859.

20 Ghosal A, Yuan Y, Tong W, Su AD, Gu C, Chowdhury SK, *et al* — Characterization of human liver enzymes involved in the biotransformation of boceprevir, a hepatitis C virus protease inhibitor. *Drug Metab Dispos* 2011; **39(3):** 510-21.

21 Inglot AD — Comparison of the antiviral activity in vitro of some non-steroidal anti-inflammatory drugs. *J Gen Virol.* 1969;**4(2):** 203-14.

22 Pareek R — Use of mefenamic acid as a supportive treatment of COVID-19: A repurposing drug. *Int J Sci Res* 2020; **9(6):** 69-73.

23 Rothan HA, Bahrani H, Abdulrahman AY, Mohamed Z, Teoh TC, Othman S, *et al* — Mefenamic acid in combination with ribavirin shows significant effects in reducing chikungunya virus infection in vitro and in vivo. *Antiviral Res* 2016; **127:** 50-6.

24 Prusakiewicz JJ, Duggan KC, Rouzer CA, Marnett LJ — Differential sensitivity and mechanism of inhibition of COX-2 oxygenation of arachidonic acid and 2-arachidonoylglycerol by ibuprofen and mefenamic acid. *Biochemistry* 2009; **48(31):** 7353-5.

25 Jakubowicz DL, Wood C — The use of the prostaglandin synthetase inhibitor mefenamic acid in the treatment of menorrhagia. *Aust New Zealand J Obstet Gynaecol* 1978; **18(2):** 135-8.

26 Daniels MJ, Rivers-Auty J, Schilling T, Spencer NG, Watremez W, Fasolino V, *et al* — Fenamate NSAIDs inhibit the NLRP3 inflammasome and protect against Alzheimer's disease in rodent models. *Nat Commun* 2016; **7:** 12504.

27 Small BG, McColl BW, Allmendinger R, Pahle J, López-Castejón G, Rothwell NJ, *et al* — Efficient discovery of anti-inflammatory small-molecule combinations using evolutionary computing. *Nat Chem Biol* 2011; **7(12):** 902-8.

28 Higashimori A, Watanabe T, Nadatani Y,Takeda S, Otani K, Tanigawa T, *et al* — Mechanisms of NLRP3 inflammasome activation and its role in NSAID-induced enteropathy. *Mucosal Immunol.* 2016; **9(3):** 659-68.

29 Woolbright BL, Jaeschke H — Role of the inflammasome in acetaminophen-induced liver injury and acute liver failure. *J Hepatol.* 2017; **66(4):** 836-48.

30 Hsueh MF, Bolognesi MP, Wellman SS, Kraus VB — Anti-inflammatory effects of naproxen sodium on human osteoarthritis synovial fluid immune cells. *Osteoarth Cartil* 2020; **28(5):** 639-45.

31 Rees MC, Cañete-Solér R, López Bernal A, Turnbull AC — Effect of fenamates on prostaglandin E receptor binding. *Lancet* 1988; **2(8610):** 541-2

32 William BS — Nonopioid analgesics. In: *Essentials of Pain Medicine.* 2018:457-68. Accessed October 16, 2020. https://sci-hub.st/10.1016/B978-0-323-40196-8.00051-6

33 Lu G, Pan Y, Kayoumu A, Zhang L, Yin T, Tong Z, *et al* — Indomethacin inhabits the NLRP3 inflammasome pathway and protects severe acute pancreatitis in mice. *BiochemBiophys Res Commun* 2017; **493(1):** 827-32.

34 Yoon E, Babar A, Choudhary M, Kutner M, Pyrsopoulos N — Acetaminophen-induced hepatotoxicity: A comprehensive update. *J Clin Transl Hepatol* 2016; **4(2):** 131-42.

35 Rahul K, Aishwarya S, Chavva AK — Evaluation of efficacy and tolerability of acetaminophen (paracetamol) and mefenamic acid as antipyretic in pediatric patients with febrile illness: A comparative study. *Int J Med Res Health Sci* 2013; **2(1):** 23-9.

36 Keinänen S, Similä S, Kouvalainen K — Oral antipyretic therapy: Evaluation of the N-aryl-anthranilic acid derivatives mefenamic acid, tolfenamic acid and flufenamic acid. *Eur J Clin Pharmacol.* 1978;**13(5):** 331-4.

Contributor List

K K Aggarwal MBBS, MD. President, Heart Care Foundation of India

Yeh Woei Chong MBBS, MRCP. Senior Consultant Physician (Internal Medicine), Vice Chairperson-CMAAO

Rajan Sharma MS (Ortho). National President, Indian Medical Association

Marthanda Pillai MS (Neuro), MNAMA (Neuro), FRCS. Managing Director, Ananthapuri Hospitals and Research Institute, Trivandrum

Ravi Naidu CEO and Managing Director, CRC Care, Malaysia

Alvin Yee-Shing Chan MBBS, MRCP, DCH, FHKCP, FHKAM, MR CPCH, FRCP. Vice Chairman, HKMACF, Hong Kong

Marie Uzawa Urabe President, Uzawa Kokusai Gakkan, Japan

Debora Nobrega Cavalcanti Director of Parliamentary Affairs, Brazilian Medical Association

Prakash Budhathoky MDS. Senior Dental Surgeon, HOD of Eyes, Nose, Ear and Throat, Dept. of Health Services, Kathmandu, Nepal

Qaisar Sajjad MBBS, DLO-MS. ENT Surgeon, Doctor Plaza, Karachi

Russel D'Souza MBBS, MD. Chair, Dept. of Education, UNESCO Chair in Bioethics, Malaysian Medical Association

N Ganabaskaran Immediate Past President, Malaysian Medical Association

Md Jamaluddin Chowdhary Senior Central executive Committee Member, Bangladesh Medical Association

R V Asokan Deen Hospital, Punalur, Kerala

Ramesh K Datta MBBS, DCH (Paediatrics). Child Specialist (Paediatrician)

Jayakrishnan Alapet MS, MCh, FRCS. Professor and HOD, Amala Institute of Medical Sciences, Kerala

V K Goel MBBS. General Physician, Goel Clinic, New Delhi

Brijendra Prakash DMRD. Consultant Radiologist, CARE Super Speciality Hospital, Telangana

Shashank Joshi MD, DM, FACP, FRCP, FACE. Endocrinologist, Joshi Clinic, Lilavati Hospital, Mumbai

Ashok Gupta MD, MCh, DNB, FRCS, FNAMS, DSc, MPhil. Consultant Plastic Surgeon, Bombay Hospital, Mumbai

Suneela Garg MBBS, MD, FIPHA, FIAGP, FIAP SM. Director, Professor and Head Community Medicine, Maulana Azad Medical College and Associated Hospitals, New Delhi

Alex Thomas MBBS, MD. President, Association of National Board of Accredited Institutions

J A Jayalal MS, FRCS. Consultant General and Laparoscopic Surgeon; Senior Vice-President, National IMA

P N Arora MBBS, MD-Dermatology, Venereology and Leprosy. Consultant Dermatologist, Sukhmani Hospital, New Delhi

K Kalra MD. Paediatrician, New Delhi

A K Aggarwal Medical Advisor, Innovations and Medical Education Apollo Group of Hospitals; Ex-Dean, Maulana Azad Medical College, New Delhi

Anita Chakravarti MD, MNAMS, FIMSA. Professor and Head, Dept. of Microbiology, Maulana Azad Medical College, New Delhi

Atul Pandya MD Pathologist. President, IMA, Rajkot

Shantanu Tripathi MD, DM. Professor and Head, Dept. of Clinical and Experimental Pharmacology, Calcutta School of Tropical Medicine

Bejon Mishra BBM. Founder, Partnership for Safe Medicines (PSM), India

T S Jain MBBS, MD. Paediatrician, Max Super Speciality Hospital, New Delhi

Anil Pachnekar MBBS. General Physician, President, IMA Maharashtra

Shivkumar S Utture MBBS, MS. General Surgeon, Shushrusha Citizens Co-operative Hospital, Mumbai

Ketan Mehta MD (Medicine). Consulting Physician, Health Harmony Clinic, Mumbai

R P Pareek MD (Medicine). Professor, BITS, Pilani, Rajasthan

Alok P Nachane MD (Pharmacology). RMO, ESIS Hospital, Mumbai

Ambanna Gowda MD (Pharmacology). Consulting Physician and Diabetologist, Fortis Hospital, Bangalore

Shilpa Karande MD (Medicine). Associate Professor, Nair Hospital, Mumbai

BLUE CROSS

World Class Quality Medicines At Affordable Prices