Case Report

Colchicine, Aspirin, and Montelukast – A Case of Successful Combined Pharmacotherapy for Adult Multisystem Inflammatory Syndrome in COVID-19

Sean Downing, Vivek Chauhan[1], Irshad H. Chaudry[2], Sagar Galwankar[3], Pushpa Sharma[4], Stanislaw P. Stawicki[5]

Departments of Medicine and [3]Emergency Medicine, Sarasota Memorial Hospital, Sarasota, Florida, [2]Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama, [4]Department of Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, MD, [5]Department of Research and Innovation, St. Luke's University Health Network, Bethlehem, Pennsylvania, USA, [1]Department of Medicine, IGMC, Shimla, Himachal Pradesh, India

Abstract

Since the beginning of the COVID-19 pandemic, many therapeutic strategies have been tried, with mixed results, to prevent and treat adult multisystem inflammatory syndrome in COVID-19 (AMIS-COVID-19). The reason behind this may the complex web of highly intertwined pathophysiologic mechanisms involved in the SARS-CoV-2 infection and the corresponding human systemic response, leading to end-organ damage, disability, and death. Colchicine, high-dose aspirin, and montelukast are being investigated currently as potential modulators of AMIS-COVID-19 in patients who fail to improve with traditional therapeutic approaches. Here, we present a patient who presented with high fevers, extreme fatigue and dyspnea, and ongoing deterioration. As part of our clinical approach, we used the simultaneous combination of the three agents listed above, capitalizing on their different respective mechanisms of action against AMIS-COVID-19. Following the initiation of therapy, the patient showed symptomatic improvement within 24 h, with the ability to return to daily activities after 72 h of continued triple-agent approach. Based on this experience, we have reviewed the immunomodulatory basis of this regimen, including potential avenues in which it may prevent the development of cytokine release syndrome (CRS) and its clinical manifestation, AMIS-COVID-19. By blocking the early stages of an inflammatory response, via diverse mechanistic pathways, the regimen in question may prove effective in halting the escalation of CRS and AMIS-COVID-19 in acutely symptomatic, nonimproving COVID-19 patients.

Keywords: Coronavirus, cytokine release syndrome, prevention, SARS-CoV-2, systemic inflammatory response

Introduction

The management of adult multisystem inflammatory syndrome caused by COVID-19 (AMIS-COVID-19) is based on a multipronged approach aimed at supporting pulmonary, cardiac, renal, and hematological systems, along with the targeted therapy of any associated infectious complications.[1] Approximately 15% of all COVID-19 cases will require hospitalization. Of these patients, 5%–10% will require long-term ICU level care for AMIS-COVID-19.[2,3] Researchers and clinicians have attempted to implement a plethora of many possible individual treatments which are intended to address AMIS-COVID-19 in the setting of an already-activated systemic inflammatory cascade.

The authors of this report postulate that if used early, a novel combination of drugs with primarily anti-inflammatory activity aimed at different target sites along the inflammatory cascade can prevent the development of cytokine release syndrome (CRS) and the resulting AMIS-COVID-19. Here, we present the case of a COVID-19 patient who described his initial symptoms as a "day from hell," characterized by spiking fevers, myalgias, and dyspnea. These symptoms are known to portend a poor prognosis in COVID-19 cases.[3] The patient showed a good response to a novel combination of

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Address for correspondence: Dr. Vivek Chauhan, Department of Medicine, IGMC, Shimla, Himachal Pradesh, India. E-mail: drvivekshimla@yahoo.com

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triple therapy – colchicine, aspirin, and montelukast (CAM) – within 24 h of its initiation.

Case Report

A 51-year-old man (Mr. W.) without any preexisting illness, medical or history, was evaluated in teleconsultation for the complaints of fevers, myalgias, and dyspnea. He had just completed a long car trip from Florida to rural Vermont, USA, immediately before the appearance of the current complaints. He reported taking several stops along the way, including brief stays at several restaurants and car fueling stations. When he arrived in Vermont, he began experiencing extreme fatigue. Being an avid athlete who participates in marathons, he was not worried as he attributed his fatigue to the physical exhaustion associated with this long interstate trip. The first night after arrival, he was abruptly awakened by a high fever and headache. The following morning, his temperature spiked to 104°F, with simultaneous complaints of scalp tenderness and persistent headache. He slept most of the day but became increasingly concerned due to the appearance of mild dyspnea with any exertion and dry cough associated with deep inspiration. His wife became concerned as she had not seen him this ill during their entire marriage. After her urging, Mr. W. contacted his primary care clinic by phone. It was quickly determined that his symptoms were highly suggestive of SARS-CoV-2 infection. Given that he was in a remote rural area of Vermont, it was decided to treat him empirically with an anti-inflammatory regimen. The goal of therapy was to prevent the development of AMIS-COVID-19 before obtaining laboratory confirmation of SARS-CoV-2 infection, which could be significantly delayed given the logistics of the remote area. Mr. W. was placed on a combination of CAM therapy, consisting of 650 mg of aspirin every 4 h, colchicine 0.6 mg every 12 h, and montelukast 10 mg daily. He was not given hydroxychloroquine as the evidence at that time did not support its use.[3,4] To control his febrile spikes, acetaminophen 1000 mg was advised at 8-h intervals.

One day after starting the CAM regimen, his fever, myalgia, and cough had resolved. He still had slight fatigue but felt almost back to his preillness baseline. He was able to make his scheduled appointment at the local hospital for SARS-CoV-2 testing and had some routine laboratory blood work completed. This work-up included a complete blood count (CBC, see below) with differential; C-reactive protein (CRP, 2.18 mg/L); lactate dehydrogenase (143 U/L); ferritin (92 μg/L); and D-dimer (0.35 mg/L). His CBC with differential showed mild leukopenia (4,370 cells/μL) with elevated monocyte fraction (17.4%) and low absolute lymphocyte count (1,000 cells/μL). His neutrophil-to-lymphocyte ratio was noted to be 2.6, which combined with his age placed him at approximately 10% risk of severe illness.[3,5]

The next day, although he reported the loss of the sense of smell, his headaches had resolved and fatigue was significantly improved. After approximately 2 days, he wanted to restart his regular exercise regimen and also was asking if he could stop taking the CAM medications. He was advised to continue the medical regimen and was instructed to carefully and gradually resume physical activity. As part of the CAM triple therapy de-escalation, the aspirin was weaned off over 2 weeks, with gradually increasing interval between consecutive doses (q6 h for 4 days, then q8 h for 4 days, then q12 h for the balance of time, then stopped). Montelukast and colchicine were continued for a total of 1 month. His SARS-CoV-2 RNA nasopharyngeal swab came back positive 6 days after the initial appearance of his initial symptoms.

Discussion

SARS-CoV-2 produces clinical symptoms by either direct (virus-induced) mechanisms or through indirect (immune-based) mechanisms.[6] Remdesivir, an RNA polymerase inhibitor, has received emergency use authorization for symptomatic SARS-CoV-2 infection and is the only antiviral agent being used to stop the direct effects of this virus.[7] Most other pharmacological agents in use are directed at the modulation of the immune-based effects of the novel coronavirus.

From a pathophysiological perspective, virus-infected cells undergo pyroptosis. This process involves the release of both cellular and viral components collectively called "damage-associated molecular patterns" (DAMPs) and "pathogen-associated molecular patterns" (PAMPs).[8,9] In the context of acute illness, DAMPs and PAMPs are recognized by the components of the innate immune system and the antigen-presenting cells (APCs) resulting in the release of interleukin (IL)-1β from the activated neutrophils and macrophages.[6] IL-1β initiates local inflammation, which further stimulates the recruitment and activation of neutrophils, lymphocytes, and macrophages that release cytokines such as IL-6, interferon-γ, inducible protein-10, and monocyte chemoattractant protein-1 (MCP-1).[6] Pulmonary tissue damage secondary to SARS-CoV-2 pneumonia also contributes to asymptomatic or minimally symptomatic hypoxemia,[10] which itself is a potent inducer of IL-6 and other cytokines.[6] All these processes combine to produce a CRS potentiating the inflammatory damage in the lungs, kidneys, heart, brain, and gastrointestinal tract and leading to AMIS-COVID-19.[6] Nuclear factor-kappa B (NF-κB) plays an important role in cellular synthesis and development of CRS.[11] Inactivation of NF-κB has been shown to effectively dampen CRS and prevent the development of AMIS-COVID-19[12] [Figure 1].

The first step in the COVID-19-related inflammatory cascade is IL-1β production that is initiated upon recognition of PAMPs and DAMPs by a multiprotein cytosolic complex called the inflammasome. The inflammasome activation is known to be inhibited by colchicine, an agent used to treat acute attacks of gout and familial Mediterranean fever[13,14] [Figure 1]. In the context of the current case report, the patient showed significant improvement within 24 h of the initiation of a colchicine-based

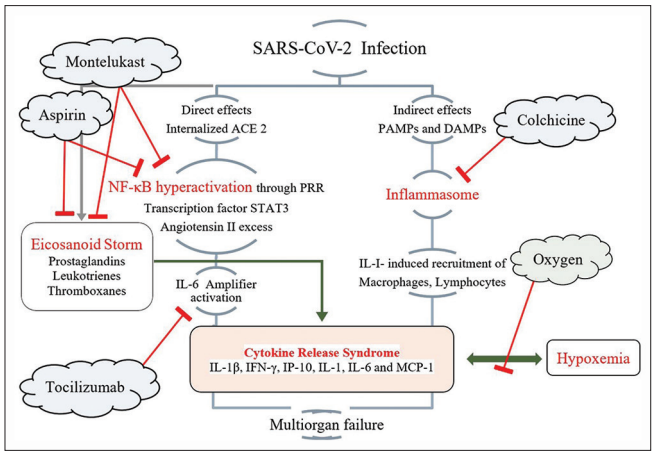

Figure 1: Immunopathogenesis of adult multi-organ dysfunction syndrome of COVID-19 and its early modulation by colchicine, aspirin, montelukast, and oxygen supplementation. ACE-2: Angiotensin-converting enzyme-2, NF-κB: Nuclear factor-kappa B, PRR: Pattern recognition receptor, STAT3: Signal transducer and activator of transcription 3, IL-6: Interleukin-6, CRS: Cytokine release syndrome, SARS: Severe acute respiratory syndrome, PAMPs: Pathogen-associated molecular patterns, DAMPs: Disease-associated molecular patterns, IL-1β: Interleukin-1β, IL-1: Interleukin-1, IFN-γ: Interferon-γ, IP-10: Inducible protein-10, MCP-1: Monocyte chemoattractant protein-1

regimen. The potential efficacy of colchicine in the setting of COVID-19 was reported in a case series from Italy, involving 9 consecutive patients who had spiking fevers unresponsive to 3–5-day courses of acetaminophen and antibiotics. In those cases, colchicine led to universal defervescence within 72 h, and only one patient required hospitalization. Besides, all patients in that report survived COVID-19.[15]

Aspirin is the second in the proposed regimen that acts through its anti-inflammatory action mediated by irreversible inhibition of cyclooxygenases 1 and 2. The antiplatelet action of aspirin is mediated through the inhibition of thromboxane A2 production. Aspirin also has proven antiviral effects against RNA viruses of the respiratory tract including rhinoviruses and influenza A viruses by its action on the modulation of the NF-κB pathway.[16-18] The transcription factor NF-κB is critical for the inducible expression of multiple cellular and viral genes involved in inflammation and infection. These factors include IL-1, IL-6, and cell adhesion molecules (CAMs) and cytokines. Therefore, the antiviral action of aspirin is explained by its modulatory action on NF-κB[16] [Figure 1].

The third agent in the regimen is montelukast, a cysteinyl leukotriene 1 receptor antagonist that is used to reduce bronchial inflammation in asthma.[19] Montelukast can also modulate the production of IL-6, tumor necrosis factor-alpha, and MCP-1 through inhibition of NF-κB[20] [Figure 1]. Montelukast may also have a direct antiviral effect on the SARS-CoV-2 main protease enzyme. Computer modeling studies suggest that montelukast should have high-affinity binding to the active pocket of the main protease enzyme.[21] Therefore, montelukast may have a bimodal action as a leukotriene antagonist and a protease inhibitor.

Eicosanoid storm is a potential mechanism that may be a significant and somewhat unrecognized contributor to the development of CRS in COVID-19.[22,23] The potent synergistic action of aspirin and montelukast on eicosanoid may constitute an important inhibitory influence in the development of CRS in SARS-CoV-2 infection [Figure 1]. Hypoxia is another factor responsible for the development of CRS, and it needs to be proactively identified and aggressively treated in COVID-19 patients along the entire care continuum, including both prehospital/ambulatory and early hospitalization stages.[6,24,25]

Within the broader context of our discussion, colchicine is currently being studied in a large (n = 6000) randomized placebo-controlled trial (RCT) COLCORONA [Figure 1], primarily for its efficacy in preventing hospitalization and death within 30 days of randomized treatment.[26] Aspirin and montelukast individually are also being studied using RCTs and their results on a large patient population may soon be available.[27,28] Tocilizumab, a monoclonal antibody to IL-6, another agent working downstream in the CRS pathway, is already approved for use in severe illness from SARS-CoV-2.[29]

Limitations

We discourage the use of the current combination therapy for COVID-19 outside of a formal clinical trial or close supervision by an experienced health-care provider. Although the drugs colchicine, aspirin, and montelukast have been in clinical use for many decades and have a proven safety profile, the authors advise physicians to exercise caution and clinical judgment while using them either as monotherapy or combination therapy in the setting of SARS-CoV-2. When used, physicians must closely monitor for any known or suspected side effects and possible drug–drug interactions.[30-32]

Conclusion

Prevention of CRS and subsequently AMIS-COVID-19 in patients who are SARS-CoV-2 positive should be the priority in the management of this illness. We recommend an evidence-based and mechanism-targeted regimen of aspirin, colchicine, montelukast, and supplemental oxygen (if hypoxemic) aimed primarily at prevention of AMIS-COVID-19. Unlike most of the current treatments for COVID-19, this regimen is affordable and easily available. Although obtaining laboratory confirmation of SARS-CoV-2 infection is highly variable, the 7–14 days of wait time for test results may allow the inflammatory cascade to become irreversibly activated. This regimen should be started empirically in patients under investigation for SARS-CoV-2 infection as prevention of AMIS-COVID-19 and to reduce morbidity and mortality.

Declaration of patient consent

The authors certify that they have obtained patient consent before submitting this case report. As part of the consent process, the patient has given his consent for the clinical information reported herein to be published. The patient

understands that due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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