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From Palliation to Cure: Two Case Reports on Methylene Blue Benefits in Elderly, Frail, and Critically Ill COVID-19 Patients

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Abstract

In frail subjects, the SARS-CoV-2 virus can trigger a severe hyperactive inflammatory response, with acute respiratory distress and multi-organ damage. Hyperactive inflammation is sustained by the excessive production of cytokines ("*cytokine storm*") and oxidants such as free oxygen and nitrogen radicals. There are still no drugs able to effectively counteract the unfavorable hyperactive inflammatory status when an infected individual is unresponsive to the available therapies. The old and versatile drug methylene blue (MB), which reduces free radicals and cytokine production and directly inhibits the inflammasomes, emerged as a potential adjuvant in mitigating the hyper inflammatory response involved in both the severe discomfort and the unfavorable clinical evolution of COVID-19 disease. We reported two cases of elderly, frail, critically ill COVID-19 patients with acute respiratory distress syndrome. To reduce the discomfort and agitation secondary to the hyperactive inflammatory response, we added intravenous MB to maximal medical treatments including non-invasive ventilation (NIV). In both cases, MB treatment was associated with an evident reduction of symptoms, followed by an unexpected clinical improvement, followed by discharge without residual "*long COVID*" syndrome. The pleiotropic activity of MB, especially the reduction of free radicals and cytokines, could contribute to potentiating the efficacy of other anti-COVID-19 therapies. The two reported cases support the potential of MB as an adjuvant agent in the management of patients with severe COVID-19 disease.

Introduction

The SARS-CoV-2 virus can trigger a severe hyper inflammatory response sustained by the overproduction of cytokines (e.g., IL-1β, IL-2, IL-6, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1α, and TNF-α) the so-called cytokine storm (CS) and oxidants including oxygen free radicals (ROS) and nitrogen free radicals (RNS) [1-6]. CS is supposed to be the main cause of morbidity and mortality when leading to systemic inflammatory response syndrome. Particularly in frail subjects, the response to COVID-19 is associated with acute respiratory distress and multi-organ damage [1].

The uncontrolled replication of SARS-CoV-2, mainly in type II pneumocytes, induces apoptosis or pyroptosis with the release of large quantities of pro-inflammatory factors leading to respiratory decompensation and hypoxia with possible evolution toward shock, acute respiratory distress syndrome (ARDS), and metabolic acidosis [1,6]. Oxidative stress contributes to alveolar cell death, endothelial injury, and eventually to multi-organ dysfunction [2,7]. Uncontrolled viral replication also promotes the activation of the NLRP3 inflammasome, which contributes to cytokine excess [6,8]. Interestingly, Carcaterra and Caruso [9] postulated the existence of an inflammation vicious cycle sustained by M1 pro-inflammatory macrophages, cytokine release, and NF-κB pathway occurring in type II alveolar epithelial cells, which are considered the main targets of SARS-CoV-2. Therefore, NF-κB represents an additional therapeutic target to hamper disease progression.

Although mass vaccination and new treatments active in the early stages of COVID-19 have significantly reduced the unfavourable course of infection [10], effective therapies for frail patients are still lacking. The unfavourable inflammatory excess of advanced disease may actually be unresponsive to the available therapies, which include steroids, NSAIDs, and various anticitokinic agents [1,6]. Severe dyspnea can hardly be controlled using the available artificial, non-invasive respiratory supports such as high-flow nasal cannula oxygen therapy (HFNC), continuous positive airway pressure therapy (CPAP), and non-invasive ventilation (NIV), which are often poorly tolerated. New strategies able to limit the cytokine-mediated hyperinflammatory reaction and free radical-induced damage could implement the action of specific drugs and regulate immune system function, leading to better control of the oppressive symptoms related to therapeutic supports [2,6]. In this context, methylene blue (MB), discovered in the late 1800s, could represent a versatile adjuvant agent in the management of patients with severe COVID-19 disease. The drug is currently registered for methaemoglobinaemia and used as an adjuvant in urinary tract inflammation, drug-resistant malaria, and extreme cases of shock of various aetiologies [11-14]. The kinetic and dynamic profiles of MB are safe and, with adverse effects recorded for very high doses, cautions are requested only in case of combination with selective serotonin reuptake inhibitors for the risk of serotonergic crisis and in patients with glucose-6-phosphate dehydrogenase deficiency for risk of haemolytic anaemia [13, 14].

In reducing the production of free radicals and cytokines and exerting a direct action on the inflammasome, MB has the potential to modulate the hyper inflammatory response responsible for both the severe discomfort and the unfavorable clinical evolution of COVID-19. Notably, several studies have shown that MB may contribute to reducing the inflammation triggered by the activation of alveolar macrophages by inhibiting ROS production via the blockade of superoxide anion synthesis; counteracting the formation of RNS and reducing cytokine release [12-14]. The anti-inflammasome activity of MB can also rely upon its ability to down modulate the expression of gene coding for inflammasome components via inhibition of NF-κB signaling [15].

Moreover, in in vitro models, MB was shown to exert antiviral activity against SARS-CoV-2 by inhibiting the binding of the spike protein to the ACE2 receptor [11, 13, 16-18]. Other studies have shown that MB was able to restore the mitochondrial respiratory chain damaged by SARS-CoV-2 infection [12, 19, 20].

Overall, experimental and preliminary clinical data support the "*repositioning*" of MB in the management of SARS-CoV-2 infection according to its antiradical, anticytokine, and anti-inflammasome actions [13, 14, 18]. The pleiotropic activity of MB could contribute to potentiating the efficacy of anti-COVID-19 therapeutics. Indeed, antiviral drugs are effective only if administered before the onset of the inflammatory cascade [10] and anticitokinic drugs (e.g., anakinra, tocilizumab) impact only a few cytokines and do not block the activity of free radicals [4].

In this study, we report two cases of elderly frail patients with COVID-19 ARDS, with severe and difficult-to-control respiratory distress. We added intravenous administration of MB to the maximal medical treatment to reduce the patients' severe discomfort. In both reported cases, MB together with anti-COVID-19 therapeutics was associated with an initial improvement in symptoms followed by an unexpected and relevant improvement in the global clinical picture, with recovery and discharge. We previously presented these findings as a meeting abstract at the National Congress SIAARTI XX ACD on December 9-11, 2021, in Rome, Italy.

Case Series

We treated two patients, Pt1 and Pt2, who had contracted COVID-19. They were cared for since March 2021 in the Infectious Diseases II Ward of the San Paolo Hospital in Milan, Italy, for acute respiratory distress.

Overall, we used the following therapies in both cases: MB 100 mg/10 ml ampoules (administered at a dosage of 1 mg/kg i.v. bid in 4-5-day cycles), tocilizumab, dexamethasone, enoxaparin, benzodiazepines, antipsychotics, morphine (10-15 mg/day i.v.), remdesivir (only in Pt1), hyper immune plasma (only in Pt2), celecoxib (only in Pt2). As oxygen delivery devices, we used a Continuous Positive Airway Pressure (CPAP), Venturi mask (VM), Nasal Cannulae for oxygen (CN) , and Mask with Reservoir (MR). Acronyms include FiO2 (fraction of inspired oxygen), PEEP (positive end-expiratory pressure), and P/F ratio (ratio of PaO2, or arterial oxygen partial pressure, to FiO2).

Case 1: Male, 80 Years Old, Hypertensive, Obese, with Hepatic Steatosis.

The patient was admitted to the emergency department (ED) after four days of fever with hypoxia and dyspnea (SO2 89% AA). The nasopharyngeal polymerase chain reaction (NP PCR) sample was positive for SARS-CoV-2 and the chest computed tomography (CT) scan showed "*bilateral shaded ground-glass areas more evident in the left upper lobe and right lower lobe*." Owing to the rapid worsening of the interstitial pneumonia, the patient started CPAP at high oxygen concentration and was admitted to the Infectious Diseases Ward. The initial treatment included dexamethasone, enoxaparin, remdesivir, and tocilizumab, with no real improvement (Figure 1).

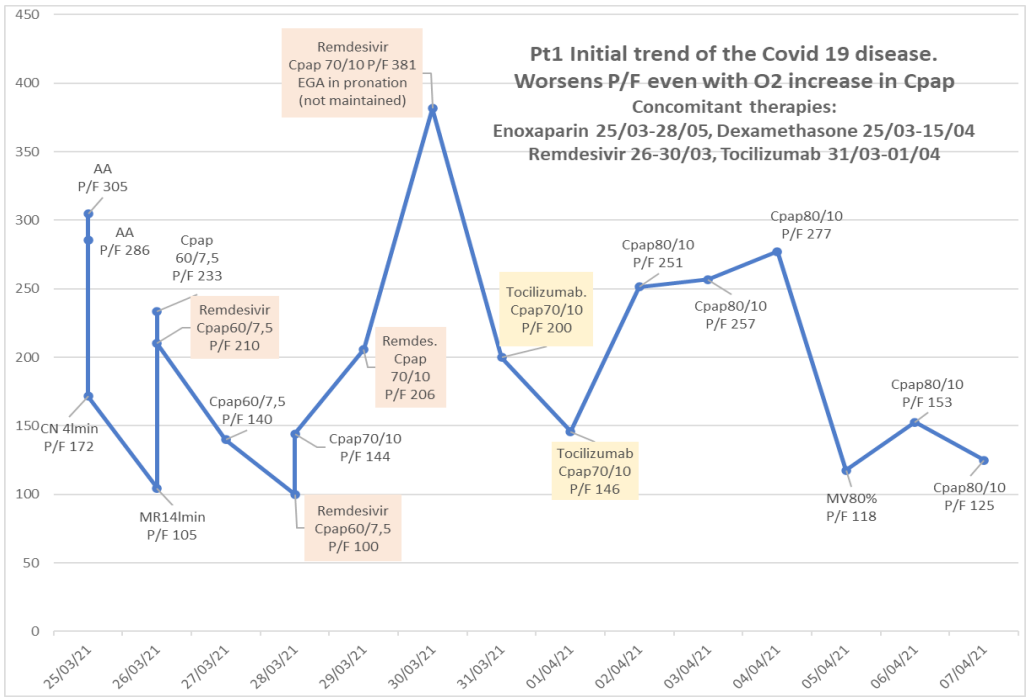

Figure 1: Pt1 initial COVID-19 disease trend.

Despite maximal medical treatment, the patient suffered severe worsening of respiratory symptoms, a critical decrease in P/F, delirium, and severe agitation leading to repeated spontaneous removal of respiratory aids. In this setting, we added MB as a symptomatic-palliative treatment. Unexpectedly, a steady, progressive, and constant general improvement was evident, which allowed us to wean the patient off the artificial NIV support (Figure 2).

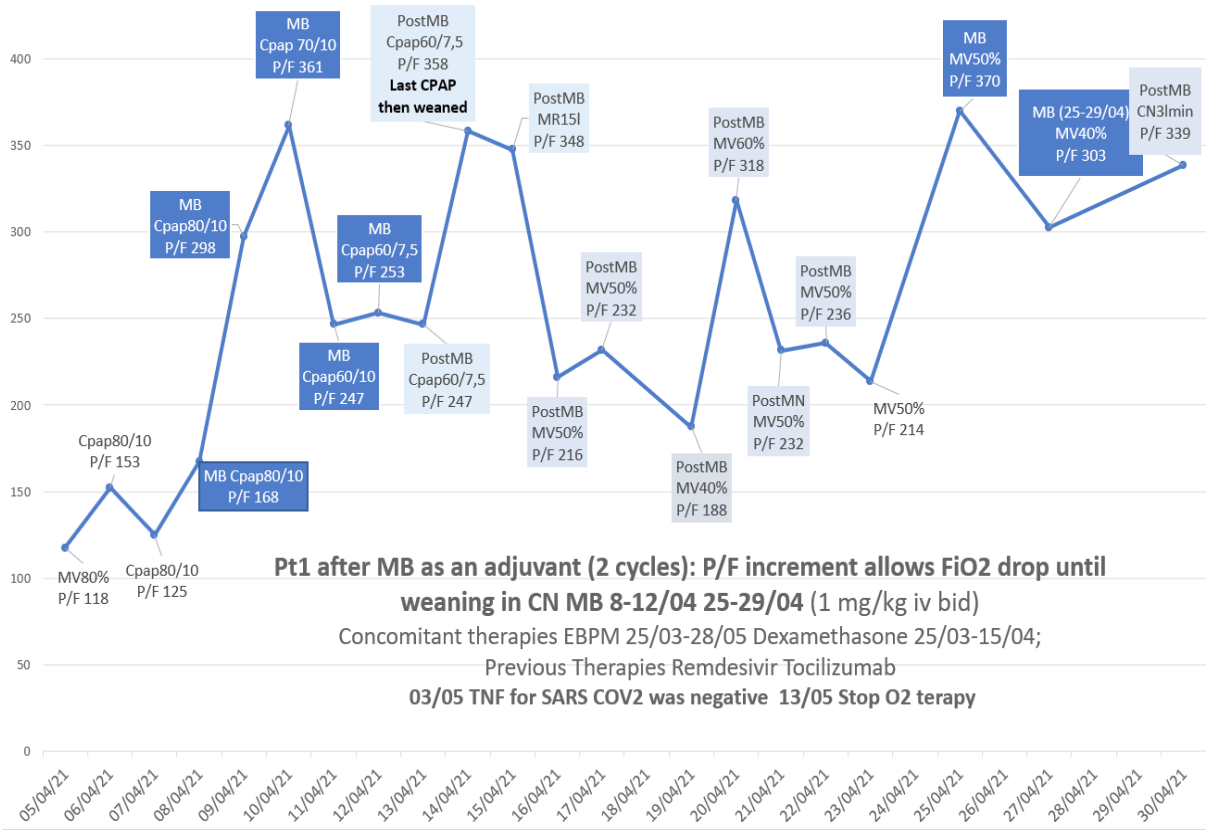

Figure 2: Pt1 COVID-19 disease trend after MB administration as adjuvant.

MB administration lasted four days at a dose of 1 mg/Kg e.v. bid, with blue and green urine for 10 days. There was a significant increase in P/F (from 168 to 298 in CPAP 80/10) the morning after the first MB infusion, confirmed in the following days, which allowed us to wean the patient off CPAP and switch to the VM. Seven days later, the CT scan excluded pulmonary thromboembolism but revealed a still-present severe pulmonary impairment secondary to SARS-CoV-2: "*increased bilateral parenchymal thickening (involvement of about 70% of the lung parenchyma)*." Given the good response to the first MB cycle, the persistence of severe pulmonary impairment, and the need to maintain the VM, we administered a further MB cycle (100 mg e.v. bid for weight loss) for four days, after which we switched the VM to CN 3 L/min without P/F drop, stable at 339. On the fourth day, NP PCR for SARS-CoV-2 was negative, and after 10 days, we discontinued oxygen therapy. Surprisingly, during the following two weeks the patient experienced a progressive complete recovery of cognitive and motor functions and was able to go home.

Subsequent hospital checks revealed good general condition and the absence of symptoms referable to "*long COVID*." A CT scan six months later showed "*no frank sequelae or outcomes of interstitial pneumonia from SARS-CoV-2 infection*."

Case 2: Female, 80 Years Old, Major Comorbidities (Arterial Hypertension, Obesity, Diabetes Type 2, Metabolic Syndrome).

The patient was admitted to the ED for dyspnea and desaturation seven days after pyrexia and diarrhea with positive NP PCR for SARS CoV-2. She was treated with steroids, low-molecular-weight heparins, and antibiotics. A CT scan showed *"ground-glass parenchymal thickenings in submantellar and peribronchial arrangement in all lung segments, with a tendency to consolidation at the level of the lower lobes, with parenchyma involvement of about 25-50%, already in a rather advanced phase."* We did not administer remdesivir because it was too late in the course. We gave her CPAP for severe respiratory failure and admitted her to the Infectious Diseases Ward. The therapy included celecoxib 200 mg, enoxaparin, dexamethasone, tocilizumab, morphine, and anxiolytics for severe dyspnea and anxiety. Hyper immune plasma did not produce benefits (Figure 3).

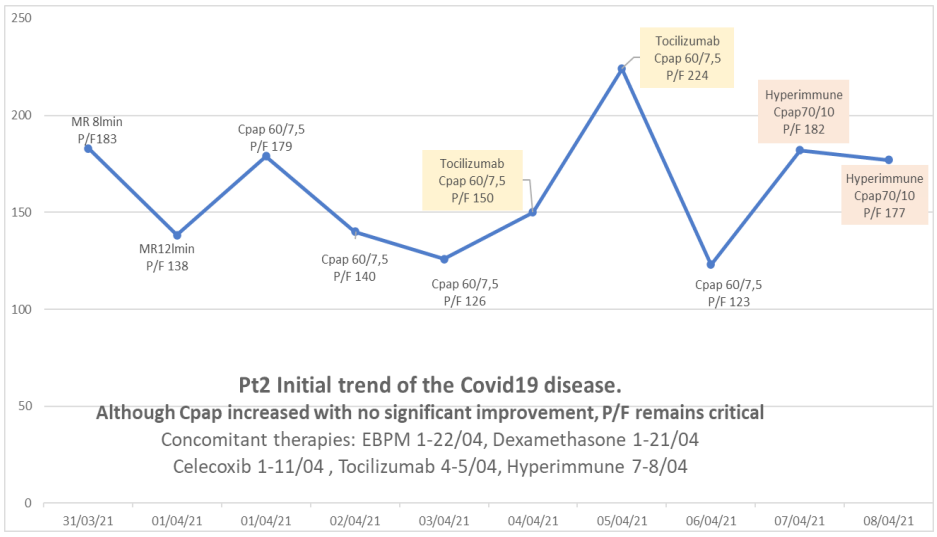

Figure 3: Pt2 initial COVID-19 disease trend.

Since the patient did not tolerate CPAP because of severe panic and agitation despite the maximal medical treatment, we administered MB for palliation. Again, we recorded a gradual constant improvement in respiratory symptoms and agitation, weaned the patient off CPAP (now tolerated), shifted her to CN, and then weaned her off oxygen (Figure 4). After testing negative for NP PCR SARS-CoV-2, she was discharged in autonomy. Improvement was also maintained in this case, with no reported symptoms attributable to "long COVID."

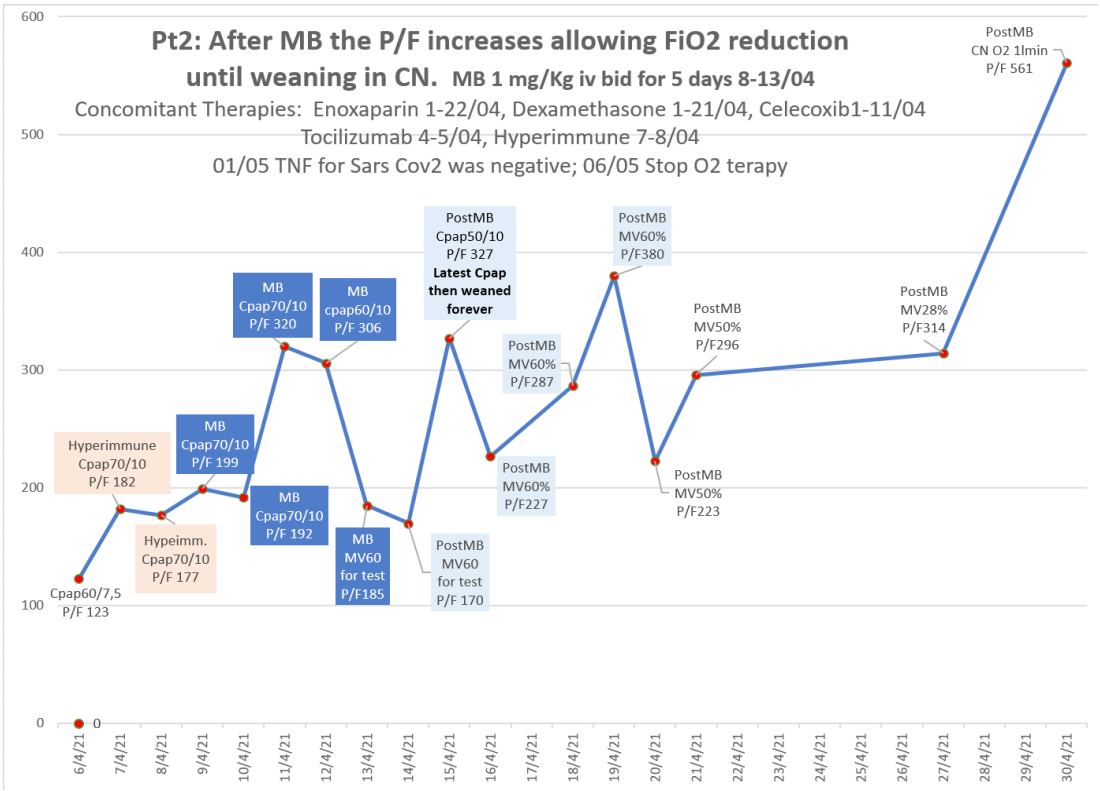

Figure 4: Pt2 COVID-19 disease trend after MB administration as adjuvant.

We administered MB 1 mg/Kg ev (bid for a total of 11 administrations) for five days. The patient exhibited persistent greenish urine in the following week. Slight improvement started from the first administration and was more evident from day 3 (in CPAP 70/10, P/F 319 versus 17), allowing us to wean her definitively off CPAP in the four following days. After one week the patient was transferred to the Rehabilitation Unit, where she was switched to CN and finally to room air over the next 10 days.

Cases 1 and 2: Pre-post MB in Same CPAP Respiratory Setting.

In the two cases, Figures 5 and 6 depict the evolution of the respiratory parameters during the one-week period before and after the introduction of MB. They show the P/F changes in CPAP alone that occurred in a homogeneous respiratory setting, not considering early weaning changes in different respiratory settings.

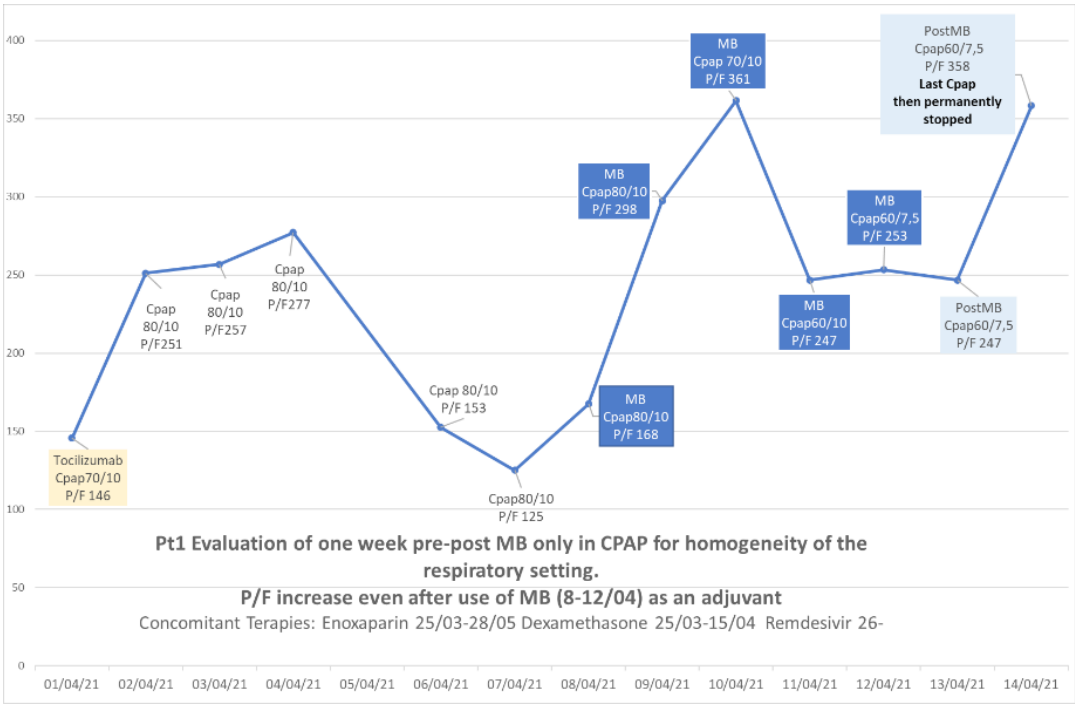

Figure 5: Pt1 P/F variations in CPAP alone pre-post MB.

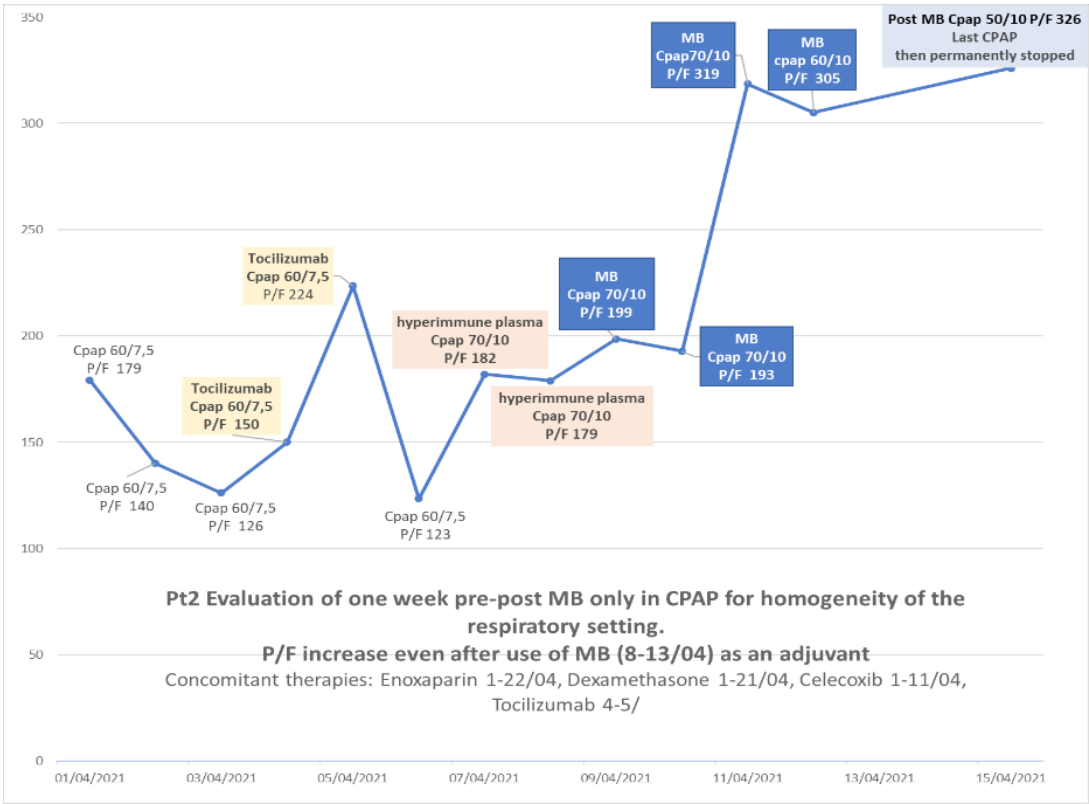

Figure 6: Pt2 P/F variations in CPAP alone pre-post MB.

Discussion

The administration of MB over the concomitant maximal medical treatment was associated in the two cases with an overall improvement of the clinical picture and a consistent reduction of severe discomfort from dyspnea and agitation. Administered for palliation, MB, which modulated the hyper inflammatory response, might have contributed to the reduction of distressing symptoms.

However, the conventional palliative drugs, including morphine used at appropriate dosages to avoid a negative clinical impact in an acute disease, and the maximal medical therapy for frail elderly patients were unable to control either the symptoms or the disease. Indeed we had also already considered the decision to suspend treatment and "do-not-resuscitate" due to a highly probable negative outcome owing to the worsening clinical conditions.

Instead, in these elderly frail patients with advanced CO-VID-19 disease, MB administration may have contributed to improving the severely impaired respiratory function associated with poor clinical conditions. Actually, in both cases the symptomatic remission was followed by a stable general improvement of the clinical picture including agitation and respiratory discomfort, resulting in the resolution of the COVID-19 disease. Although these two anecdotal but clinically complex cases do not allow a direct correlation between the use of MB and the clinical results, the impressive changes observed after MB administration might support the potential benefits of using MB on top of the available medical treatments.

In particular, the ability of MB to modulate inflammasome activation and cytokine production in different clinical settings [8, 12-14] might support in selected cases an early use of the dye to counteract the virus-induced hyperinflammatory status. Beyond its broad-spectrum anti-inflammasome activity, MB's ability to restore mitochondrial function [12, 19] could also have contributed to improving the overall clinical picture in our cases. Moreover, whereas the anticytokine drugs (anakinra, tocilizumab) used for the treatment of COVID-19-related ARDS can restrain the action of a few cytokines, MB exhibits multitargeting/pleiotropic activities [4, 6]. Indeed, MB reduces cytokine excess and has antioxidant activity both on RNS (lowering nitric oxide bioavailability) and on ROS (inhibition of xanthine oxidase action) without inducing serious adverse effects and immune depression [11, 13, 14]. Owing to its pharmacological profile, and in spite of the advanced stages of the COVID-19 disease, MB may have

contributed in both cases to limiting hyper inflammation, crucial in worsening both objective (i.e., severe hypoxia) and subjective (i.e., dyspnea, discomfort, severe agitation) symptoms, thus acting synergistically with the maximal medical treatment and the non-invasive respiratory support.

Conclusion

The two reported cases might support MB's potential as an adjuvant agent in the management of patients with severe COVID-19 disease. Owing to its antioxidant, anticytokine, and anti-inflammasome activities, MB may in fact modulate the inflammatory excess involved in both the severe discomfort and the highly probable unfavorable clinical evolution of the COVID-19 disease. Further studies are needed to evaluate the addition of the dye to the available therapeutic agents, not only in the advanced stages of COVID-19 disease as a "*last resort*" but perhaps better, in the early stages of illness in frail patients to prevent clinical worsening. Notably, MB's low cost and safety profile represent an additional value, particularly in low-income countries where the availability of "expensive" drugs is reduced, leading to suboptimal epidemic control.

Additional information

The authors disclose no potential conflicts of interest.

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All patients provided written informed consent to use the clinical data for scientific purposes in this study.

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