

## Review article



# Effectiveness of Mavrilimumab in Viral Infections Including SARS-CoV-2 Infection - A Brief Review

Kinal Bhatt <sup>1</sup>, Radhika Garimella <sup>2</sup>, Rahima Taugir <sup>3</sup>, Isha Mehta <sup>4</sup>, Muhammad Jamal <sup>5</sup>, Rupalakshmi Vijayan <sup>6</sup>, Rita Offor <sup>7</sup>, Kanayo Nwankwo <sup>8</sup>, Uroosa Arif <sup>9</sup>, Khurram Waheed <sup>10</sup>, Priyanka Kumari <sup>11</sup>, Maulik Lathiya <sup>12</sup>, George Michel <sup>13</sup>, Naushira Pandya <sup>14</sup>, John Halpern <sup>14</sup>, Hassan Nasir <sup>14</sup>, and Marcos A. Sanchez-Gonzalez <sup>1</sup>

## OPEN ACCESS

Received: Sep 15, 2020

Accepted: Feb 17, 2021

### Corresponding Author:

**Kinal Bhatt, MD, MPH**

Division of Clinical & Translational Research,  
Larkin Health System, 7031 SW 62nd Ave South  
Miami, FL 33124, USA.

Tel: (928) 225 0273

E-mail: kinalbhatt@gmail.com

Copyright © 2021 by The Korean Society of Infectious Diseases, Korean Society for Antimicrobial Therapy, and The Korean Society for AIDS

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ORCID iDs

Kinal Bhatt

<https://orcid.org/0000-0003-0261-9643>

Radhika Garimella

<https://orcid.org/0000-0002-0726-6923>

Rahima Taugir

<https://orcid.org/0000-0001-5769-6203>

Isha Mehta

<https://orcid.org/0000-0002-6628-1365>

Muhammad Jamal

<https://orcid.org/0000-0003-2294-3299>

Rupalakshmi Vijayan

<https://orcid.org/0000-0002-8419-3238>

<sup>1</sup>Division of Clinical & Translational Research, Larkin Health System, South Miami, FL, USA

<sup>2</sup>Dr. NTR University of Health Sciences, Andhra Pradesh, India

<sup>3</sup>Medical University of the Americas, St. Kitts and Nevis

<sup>4</sup>Windsor University School of Medicine, St. Kitts and Nevis

<sup>5</sup>Beihua University, Jilin City, China

<sup>6</sup>Kasturba Medical College, Mangalore, India

<sup>7</sup>Texas A and M University, College Station, Texas, USA

<sup>8</sup>Ebonyi State University, Abakaliki, Nigeria

<sup>9</sup>Khyber Teaching Hospital, Peshawar, Pakistan

<sup>10</sup>Lady Willingdon Hospital, Lahore, Pakistan

<sup>11</sup>Chandka Medical College, Larkana, Pakistan

<sup>12</sup>Jeevandip Hospital, Surat, India

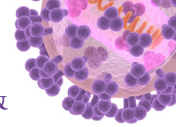
<sup>13</sup>Department of Internal Medicine, Larkin Health System, South Miami, FL, USA

<sup>14</sup>Larkin Health System, South Miami, FL, USA

## ABSTRACT

Hyperinflammation and cytokine storm has been noted as a poor prognostic factor in patients with severe pneumonia related to coronavirus disease 2019 (COVID-19). In COVID-19, pathogenic myeloid cell overactivation is found to be a vital mediator of damage to tissues, hypercoagulability, and the cytokine storm. These cytokines unselectively infiltrate various tissues, such as the lungs and heart, and nervous system. This cytokine storm can hence cause multi-organ dysfunction and life-threatening complications. Mavrilimumab is a monoclonal antibody (mAb) that may be helpful in some cases with COVID-19. During an inflammation, Granulocyte-macrophage colony-stimulating factor (GM-CSF) release is crucial to driving both innate and adaptive immune responses. The GM-CSF immune response is triggered when an antigen attaches to the host cell and induces the signaling pathway. Mavrilimumab antagonizes the action of GM-CSF and decreases the hyperinflammation associated with pneumonia in COVID-19, therefore strengthening the rationale that mavrilimumab when added to the standard protocol of treatment could improve the clinical outcomes in COVID-19 patients, specifically those patients with pneumonia. With this review paper, we aim to demonstrate the inhibitory effect of mavrilimumab on cytokine storms in patients with COVID-19 by reviewing published clinical trials and emphasize the importance of extensive future trials.

**Keywords:** COVID-19; SARS-CoV2; Mavrilimumab; Cytokine storm; Monoclonal antibody



Rita Offor 

<https://orcid.org/0000-0002-1671-2008>

Kanayo Nwankwo 

<https://orcid.org/0000-0002-4355-1991>

Uroosa Arif 

<https://orcid.org/0000-0003-3229-5790>

Khurram Waheed 


<https://orcid.org/0000-0002-0665-1061>

Priyanka Kumari 

<https://orcid.org/0000-0002-6656-3637>

Maulik Lathiya 


<https://orcid.org/0000-0002-3593-3850>

George Michel 


<https://orcid.org/0000-0002-9899-8205>

Naushira Pandya 

<https://orcid.org/0000-0001-9388-9504>

John Halpern 

<https://orcid.org/0000-0002-1006-7220>

Hassan Nasir 

<https://orcid.org/0000-0002-3544-1944>

Marcos A. Sanchez-Gonzalez 

<https://orcid.org/0000-0002-7585-708X>

#### Conflict of Interest

No conflicts of interest.

#### Author Contributions

Conceptualization: KB, KW. Data curation:

KB. Investigation: KB. Methodology: KB.

Project administration: KB, KW. Resources:

KB. Supervision: KB, GM, NP, JH, HN, MASG.

Validation: KB, MASG. Visualization: KB, MJ,

MASG. Writing - original draft: KB, RG, RT, IM,

MJ, RV, RO, KN, UA, PK, ML. Writing - review &

editing: KB, IM, KW, MASG.

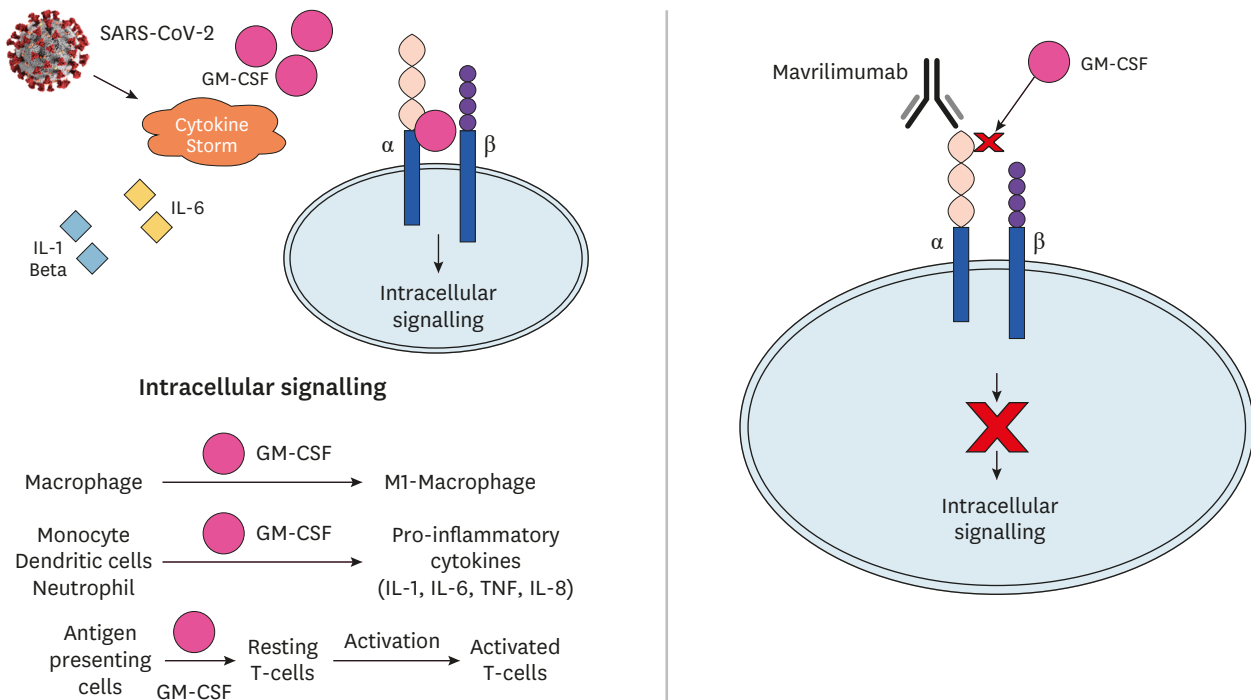
## BACKGROUND

The Angiotensin Converting Enzyme-2 (ACE2) receptor enzyme is expressed is broadly expressed on the cell membranes of cells, an endogenous membrane protein that promotes COVID-19 infection with the extracellular peptidase domain enabling virus entry, using most prominent Spike glycoprotein (S), which is responsible for receptor attachment and allowing the virus to enter the host cell via membrane fusion. [1, 2]. Most of the lung damage leading to respiratory failure needing mechanism ventilation is contributed to inflammatory cytokines [Interleukin-6, interferon- $\gamma$ , and granulocyte-macrophage stimulating factor (GM-CSF)]. GM-CSF is produced by many cells, including macrophages, T-cells, fibroblasts, endothelial cells, epithelial cells, and tumor cells; found to be increased in COVID-19 patients in comparison to healthy controls. Therefore, inhibition of GM-CSF or GM-CSF receptor is beneficial to reduce lung inflammation and therefore found to have a direct impact on improved oxygenation, reduced hospitalization, and mortality rate [3].

COVID-19 intensive care unit (ICU) patients are found to have increased levels of several inflammatory cytokines: interleukin (IL)-2, IL-6, IL-7, ferritin, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage stimulating factor (GM-CSF), interferon- $\gamma$ -inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1- $\alpha$  (MIP1- $\alpha$ ), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [3]. So far, increased IL-6 and ferritin are associated with the worst prognostic factor in these patients. Researchers have discovered increased IL-1 $\beta$  and IL-6 are found along with increased ferritin. A phase 3 trial of IL-1 receptor antagonist, Anakinra, has shown a significant survival rate compared to a placebo group [3]. As a myeloid cell growth factor and pro-inflammatory cytokine, GM-CSF might be the most important factor in immunopathological sequelae of COVID-19. GM-CSF is also an important agent that maintains pulmonary function and lung sentinel cell-mediated immunity. Pulmonary GM-CSF stimulates PU.1 transcription factor in alveolar macrophage enabling their maturation and differentiation. This helps in the prevention of infection of alveolar macrophages by promoting virion clearance and destruction. Interruption of GM-CSF signaling can impair the GM-CSF receptor, and in turn, interrupt alveolar macrophage maturation, exposing to infections [4]. GM-CSF can also trigger the overexpression of IL-1, IL-6, TNF, and chemokines. A GM-CSF-targeted treatment strategy might have broader effects in restricting the overactive immunity than other immunomodulatory modalities [5].

## MECHANISM OF ACTION OF MAVRILIMUMAB IN VIRAL INFECTIONS

Mavrilimumab formerly known as (CAM-3001) is a human mAb (IgG4), inhibits granulocyte-macrophage colony-stimulating factor receptor alpha (GM-CSFR- $\alpha$ ) and thus antagonizes GM-CSF signaling (**Fig. 1**) [6]. GM-CSFR is a heterodimer that consists of two subunits, alpha and beta chain. The alpha subunit is a binding site for GM-CSF and the beta chain is involved in signal transduction. The association of alpha and beta subunit results in receptor activation and downstream activation of multiple signaling pathways [7, 8]. GM-CSF, a hematopoietic growth factor that has a role in immunomodulation. GM-CSF when bind to its receptor, leads to an increase in the release of inflammatory cytokines from monocytes (macrophages) and polymorphonuclear leucocytes (neutrophils). The resulting activation of ERK1/2 (extracellular signal-regulated protein kinase) and NF- $\kappa$ B (Nuclear factor- $\kappa$ B) pathway leads to inflammatory



**Figure 1.** The immunological response induced by an antigen upregulating GM-CSF in inflamed tissue [6]. SARS-CoV-2, severe acute respiratory syndrome Coronavirus 2; GM-CSF, granulocyte-macrophage colony-stimulating factor.

response as well. GM-CSF signaling leads to activation of several other pathways such as recruitment and activation of Janus kinase 2 (JAK-2)-signal transducer and activator of transcription 5 (STAT-5), mitogen-activated protein kinase (MAPK) and Phosphoinositide 3 Kinase (PI3K)-Akt pathways, thus initiating the immune and inflammatory reactions, resulting in a cytokine storm [9, 10].

Mavrilimumab, a potential antagonist of (GM-CSFR- $\alpha$ ) was used in patients with rheumatoid arthritis. The previous phase 2 studies of mavrilimumab in patients with rheumatoid arthritis showed that mavrilimumab was effective in these patients due to its dampening effect on inflammation along with good safety and tolerability outcomes.

SARS-CoV-2 induces a cytokine and chemokine mediated immune response, the resulting virus-induced hyperinflammatory response cause detrimental damage to the lungs due to recruitment of inflammatory neutrophils and proinflammatory macrophages in the lung tissue resulting in progressive respiratory failure and acute respiratory distress syndrome (ARDS) [11]. Histological findings of COVID-19 lung tissue showed diffuse alveolar damage with giant cell and pneumocyte hyperplasia, hyaline membrane formation, and, edema [12]. Patients with severe COVID-19 have increased plasma levels of C-reactive protein (CRP), Ferritin, D-dimers, Lactate dehydrogenase (LDH) [12]. The cytokine release syndrome (CRS) in SARS-CoV-2 patients resemble the secondary hemophagocytic lymphohistiocytosis syndrome (SHLH) or Macrophage activation syndrome (MAS) with an increased level of inflammatory cytokines including GM-CSF, G-CSF, IL-7, IL-10, IL-6 and, TNF- $\alpha$  [12].

GM-CSF is an inflammatory cytokine mostly produced at the site of inflammation by macrophages, T-cells as well other cells such as epithelial cells, endothelial cells, and many

others [13, 14]. GM-CSF receptor activation and resulting downstream activation of multiple pathways result in differentiation of macrophages including alveolar macrophages (AM) as well activation and proliferation of other immune cells; resulting hyperinflammation-induced lung damage seen in patients with severe COVID-19 can be blunted by targeting GM-CSF signaling [9]. Mavrilimumab by targeting GM-CSF-R $\alpha$  prevents the downstream activation of inflammatory pathways and ultimately dampening the hyperinflammatory response seen in patients with severe COVID-19 [15].

## ROLE OF MAVRILIMUMAB IN REDUCING INFLAMMATION

The concentration of circulating GM-CSF is low during standard physiological conditions, while their concentrations are elevated during the inflammation process. Several cell types together with fibroblasts, macrophages, dendritic cells, endothelial cells, neutrophils, helper T (TH) cells, eosinophils, and tumor cells serve as the source for GM-CSF. Their production multiplies locally at the site of inflammation, thus increasing feed-forward inflammatory response [16]. During an inflammation, GM-CSF release is crucial to driving both innate and adaptive immune responses. The GM-CSF immune response is triggered when an antigen attaches to the host cell and induces the signaling pathway. GM-CSF can act locally in inflamed tissue or systemically to induce the survival, proliferation, and differentiation of myeloid cells, together with monocytes, macrophages, and neutrophils. Categorically, GM-CSF activates mature myeloid cells to release proinflammatory cytokines (IL-1, IL-6, and TNF) and chemokines (CCL2, IL-8, and CCL17); recruit immature myeloid cells from the circulation for differentiation and stimulate dendritic cells to attain the adaptive immune response. Activated lymphocytes (TH cells) migrate to the diseased tissue and within the circulation to function as a source of GM-CSF, to further recruit and activate new myeloid cells, therefore resulting in heightened GM-CSF-dependent inflammatory response in inflamed/diseased tissue. The wide range of immunological activities of GM-CSF can form part of positive-feedback loops that can initiate and maintain disease-causing hyperactive or chronic immune responses. Therefore, it has been proposed that GM-CSF functions as a key communication channel between inflammatory lymphoid and myeloid cells [16]. Mavrilimumab, a GM-CSF antagonist, has anti-inflammatory and immunomodulatory properties that may prevent or reduce the disease-driving hyperactive immunological response [16]. The pathogenic overactivation of myeloid cells is a primary mediator of tissue damage, cytokine storm, and hypercoagulation in COVID-19 and various other coronavirus-mediated diseases [16].

## ROLE OF MAVRILIMUMAB IN RHEUMATOID ARTHRITIS

GM-CSF plays an important role within the pathogenesis of rheumatoid arthritis (RA) through the activation, differentiation, and survival of neutrophils and macrophages. The patients with RA have elevated levels of this cytokine in synovial fluid from joint spaces. A study shows that antagonism of GM-CSF can exceedingly cut back the established disease in mouse models of arthritis [17]. Rheumatoid arthritis is a systemic chronic autoimmune disease involving persistent and erosive inflammatory polyarthritis. It can also harm other organs like the lungs, skin, cardiovascular system, and eyes. If RA is not well-treated, then it leads to progressive destruction of joints with a succeeding disability, loss of function and mobility, work incapacity, and diminished quality of life and life expectancy. Traditionally disease-modifying

antirheumatic drugs (DMARDs) have become the primary standard of treatment for RA, with methotrexate (MTX) considered as the "gold standard" in RA monotherapy or as an adjuvant with alternate drugs. However, patients with refractory symptoms and an inadequate response to treatment with traditional DMARDs or MTX could also be treated with biologic agents targeting TNF and interleukins (IL-6 and IL-1), which play a crucial role throughout pathological processes active in RA, and with biologic agents targeting T- and B-cells (*e.g.*, abatacept, rituximab). Biologic DMARDs (including tocilizumab, TNF, rituximab,) have shown to have larger efficacy than traditional DMARDs (methotrexate, sulfasalazine) in controlling joint damage. The recent study shows an emergence of biologic agents that focus on GM-CSF related to the pathogenesis of RA through the activation, differentiation, and survival of neutrophils and macrophages that additionally cause synovitis through the release of cytokines, chemokines, reactive oxygen and nitrogen intermediates, proteases, and microparticles. Mavrilimumab is a biologic agent that selectively antagonizes and neutralizes GM-CSF. This mechanism of action leads to inhibition of what may be a central pathogenetic pathway underlying inflammation in RA [18].

## ROLE OF MAVRILIMUMAB IN COVID-19

The unnatural expression of GM-CSF is may drive excessive inflammation, pain, chemotaxis, and tissue damage and enhance the production of alternate pathogenic cytokines. At the interface of lymphoid and myeloid cells, it has been urged that the GM-CSF network promotes disease processes by persistently driving and hyper-activating inflammatory responses. This network is defined as a positive-feedback loop leading to secretion of GM-CSF and consequent pro-inflammatory cytokines and chemokines across monocytes, macrophages, and TH cells. The cytokines most conspicuously implicated in this network are IL-1, IL-6, and TNF, which have been targeted with success in numerous inflammatory and infectious diseases and have now been suggested as potential targets in COVID-19 [18]. Agents that block GM-CSF may prove helpful in treating the cytokine storm and inflammatory myeloid cell tissue infiltration seen in moderate-to-severe COVID-19. The GM-CSF blockade could have broad immunomodulatory effects to inhibit the secretion of multiple pro-inflammatory cytokines and chemokines by myeloid cells. Looking at the broad range functioning of GM-CSF in numerous disease and inflammatory processes, GM-CSF-based therapies are worth investigational approaches during the pressing global requirement for effective COVID-19 therapeutics [18].

Siddiqi HK et al. (2020) proposed a clinical staging system to launch a classification system identifying that COVID-19 illness exhibits 3 stages of increasing severity [19]. This system correlates with different clinical findings, response to therapy, and clinical outcome. The three stages of COVID-19 illness are mild, moderate, and severe respectively, and each stage shows different symptoms. Stage I includes early infection, fever, cough, and other relatively mild symptoms accompanying an increase in viral load. Furthermore, stage II comes with severe pneumonia that persists, regardless of a decline in viral load, due to a hyperactive immune response (IIA) without and (IIB) with hypoxia. Finally, stage III includes the symptoms of systemic hyper inflammation-significant immune dysregulation resulting in pulmonary destruction, cardiac instability, multiorgan failure, and death.

It is getting more understood that the characteristic hyperactive immune response driving COVID-19 progression consists of a 'cytokine storm' [20]. In the later phases (stage IIb and

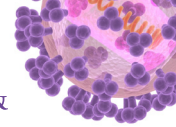
III), the rise in GM-CSF levels as part of the cytokine storm during the onset of COVID-19 pneumonia suggests that GM-CSF may be harmful at this stage of the disease. Huang, C. et al. (2020) in a prospective study found that plasma concentrations of GM-CSF, amongst other cytokines, were elevated in ICU patients than non-ICU patients [21]. In another study by Zhou, Y. et al. (2020) peripheral blood samples from patients with severe pneumonia were collected for immune analysis. CD8+ T-cells had a higher expression of GM-CSF in the ICU patients as compared to their counterparts. It is imperative to state that blockade of GM-CSF signaling may be beneficial in the most severe cases of COVID-19 [22]. This can be achieved through receptor-mediated antagonism of the GM-CSF or by binding to it in plasma. A therapeutic trial of this drug may be able to reduce the primary pathology of the cytokine storm and the myeloid cell-induced lung destruction in the later stages of COVID-19.

## REVIEW OF STUDIES ON THE USE OF MAVRILIMUMAB IN TREATMENT OF COVID-19 INFECTIONS

Mavrilimumab has shown promise for early clinical improvements in respiratory outcomes for hospitalized patients. Professor Lorenzo Dagna and his team at San Raffaele Hospital in Milan in a prospective, single-center pilot experience carried out a treatment protocol with mavrilimumab. A total of 6 Patients with severe pulmonary involvement of COVID-19, acute respiratory distress, fever, clinical and biological markers of systemic hyper inflammation status were treated with a single intravenous dose of mavrilimumab. All the patients responded to treatment, and 50% (n = 3) were discharged in less than a week. As reported in Lancet Rheumatology [23] -A 28-day clinical outcomes data from the open-label treatment protocol with mavrilimumab in non-mechanically ventilated patients with severe COVID-19 pneumonia and hyperinflammation.

The main aim of the treatment protocol was to determine whether mavrilimumab in addition to standard of care therapy could improve clinical outcomes in patients with severe COVID-19 pneumonia. A total of 13 patients were placed on mavrilimumab 6 mg/kg and 26 receiving standard care were matched for age, sex, comorbidities, baseline inflammatory markers: C-reactive protein, ferritin levels, and respiratory dysfunction. All patients upon admission received standard of care with hydroxychloroquine, azithromycin, and lopinavir/ritonavir, and respiratory support with supplemental oxygen and/or non-invasive ventilation with continuous positive airway pressure. Throughout the 28-day follow-up period, there was no mortality in the mavrilimumab group *vs.* 27% (n = 7), in the standard care group ( $P = 0.86$ ) 86% of deaths occurred in week 1; the rest were on day 8. There was >25% PaO<sub>2</sub>: FiO<sub>2</sub> improvement in all the mavrilimumab group 100% *vs.* 65% in the standard care group. Patients treated with mavrilimumab also showed faster improvement defined as median time to discharge of 10 days versus 20 days for the standard of care, and reduced frequency of progression to mechanical ventilation. Whilst these studies have shown benefits in the mavrilimumab-treated group as reported across multiple clinically relevant endpoints which strengthen the rationale for immunomodulation in hyperinflammatory settings, there are still valid concerns about the potential for selection bias and placebo effect due to the unavailability of the drug, patients were not randomly assigned to receive mavrilimumab or the institutional standard of care.

The relatively short follow-up of 28 days during the hospitalization may be limited to assess the longer-term efficacy and safety of the investigational medication. Furthermore, given the



fact that anti-viral immunity is required to recover from COVID-19, the pros and cons of using an immunosuppressant on these patients require careful assessment. Lastly, the timing of treatment is important to reduce the side-effects of immunosuppression as GM-CSF could be beneficial for maintaining alveolar macrophage function during the viral assault in the early disease phase [16]. The findings reported in this study need to be considered in the light of several important limitations and further testing in controlled trials is warranted. A more robust study designed to evaluate the efficacy and safety of the use of mavrilimumab relative to placebo in addition to standard of care therapy in the treatment of patients with severe COVID-19 pneumonia and hyper inflammation is needed. There is an active investigational new drug (IND) [24] (IND) application with the U.S. Food and Drug Administration (FDA) for the second phase trial evaluating mavrilimumab in severe COVID-19 pneumonia.

Cheng et al. (2020) completed a randomized clinical trial to assess the effect of recombinant human granulocyte-colony stimulation factor (rhG-CSF) in 200 patients with COVID-19 and lymphopenia to determine whether this therapy may increase peripheral blood leukocyte and lymphocyte counts, which may then lead to clinical improvement [25]. The trial took place across 3 centers in China. Trial patients were divided into two groups: usual care alone, or usual care with 3 doses of the-CSF subcutaneously at days 0 - 2. While the researchers did not find a difference in clinical improvement between the usual care group (median of 13 days) and rhG-CSF group (median of 12 days), a clinically significant decrease was seen in respiratory distress syndrome, sepsis, and septic shock in the rhG-CSF group. The mortality rate was also lower in the rhG-CSF group at day 21 (2%) compared to the usual care group (15%). Researchers also noted the reduced rate of serious adverse events (*e.g.* sepsis or septic shock, respiratory failure, and ARDS) in the rhG-CSF group (14.5%) compared to the usual care group (21%).

Cavilli et al. (2020) conducted a retrospective cohort study in Milan, Italy in patients aged  $\geq 18$  years of age with moderate to severe ARDS and hyperinflammation (defined as CRP  $\geq 100$  mg/L, ferritin  $\geq 900$  ng/mL, or both) secondary to COVID-19 [26]. These patients were managed with non-invasive ventilation and received 200 mg of hydroxychloroquine twice a day orally, 400 mg lopinavir with 100 mg ritonavir twice a day orally. Patients were divided into two groups: A standard treatment group who received the treatment listed above and the other group received Anakinra (either 5 mg/kg twice a day intravenously (high dose) or 100 mg twice a day subcutaneously (low dose). On day 21, researchers compared all groups to assess survival, mechanical ventilation-free survival, changes in CRP, and respiratory function. The treatment group with high dose Anakinra showed clinical improvement in 72% of patients. This data showing dampening of inflammatory markers like IL-1 $\alpha$  and IL-1 $\beta$  released by epithelial and endothelial cells and monocytes, macrophages, and neutrophils respectively was detrimental for patient survival. This also allowed researchers evidence-based data that showed various inflammatory cytokines need to be tested for and be treated as the need arises. However, this also requires further confirmation of efficacy in controlled trials.

De Luca Et al. (2020) completed a single-center prospective cohort study of patients 18 years or older admitted to a hospital in Milan, Italy with severe COVID-19 pneumonia, hypoxia, and systemic hyperinflammation [27]. A single dose of 6 mg/kg of IV Mavrilimumab was added to the standard of care, compared to the control group who had similar baseline characteristics. The primary outcome of the study was clinical improvement defined as an improvement of two or more points on the seven-point ordinal scale of clinical status. At 28-day follow-up, patients in the Mavrilimumab group and the control groups showed clinical improvement;

8 days *vs.* 19 days respectively. The researchers discussed some limitations to their study such as they were trying to find a lifesaving medication and how it would affect the disease process rather than trying to do an investigative type of study [27]. De Luca Et al 2020 The study lacked randomization of who was receiving the drug which possibly can introduce bias into the study. However, in this study, indeed, both patients treated with mavrilimumab and standard care had comparable baseline clinical characteristics, including inflammatory markers, LDH levels, lung function, and need for supplemental oxygen. Thus, even though not-randomized, the matching of baseline demographics and clinical characteristics likely reduced the risk of bias and provided important clinical information during the overwhelming COVID-19 pandemic. It is important to do more studies where Mavrilimumab goes through more rigorous testing such as multicenter, double-blind studies, and randomized treatment groups with patients who are suffering from severe lung inflammation from COVID-19.

There are at least three ongoing clinical trials of Mavrilimumab in COVID-19 patients: 1) A prospective, phase 2, multi-center, blinded randomized placebo-controlled study (NCT04492514) at the University of Cincinnati, designed to demonstrate early treatment with mavrilimumab prevents progression of respiratory failure in patients with severe COVID-19 pneumonia and clinical and biological features of hyper-inflammation. The primary endpoint of the study is to measure proportions of subjects alive and off oxygen at day 14 [28]; 2) A phase 2/3, randomized, double-blind, placebo-controlled study (NCT04447469) to evaluate the efficacy and safety of Mavrilimumab (KPL-301) treatment in adult subjects hospitalized with severe COVID-19 pneumonia and hyperinflammation. For the primary outcome of the study, there are two cohorts. Cohort 1 will look at the proportion of participants alive and without respiratory failure at Day 15. Respiratory failure is defined as the need for high flow oxygen (HFO), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO). Cohort 2 will assess mortality rate at day 15, defined as the proportion of participants who die [29]; 3) A prospective, phase 2, multi-center, blinded randomized placebo-controlled study (NCT04463004) is designed to demonstrate that early treatment with Mavrilimumab prevents progression of respiratory failure in patients with severe COVID-19 pneumonia and clinical and biological features of hyperinflammation. The primary outcome measure of the study is to assess the proportion of subjects alive and off oxygen at day 14 [30].

## MAIN CONCERNS REGARDING THE EFFICACY, SAFETY, AND ADVERSE EFFECTS

Mavrilimumab has proven efficacy and a considerable safety profile, established in patients with Rheumatoid arthritis; demonstrated in multiple clinical trials at dosages as high as 150mg [15, 31-33]. To determine the right dose and route of administration in COVID-19 patients, De Luca et al. (2020) relied on the data from previous efficacy and safety evaluation studies of mavrilimumab in RA patients. A combination of data from these studies and the pathophysiology of COVID-19 led to the selection of a single dose of 6mg/kg of mavrilimumab given intravenously. Mavrilimumab can be safely used in COVID-19 patients; Luca et al reported no deaths in patients receiving mavrilimumab for COVID-19 as compared to the placebo group [27]. Burmester et al. (2018) reported adverse events of Mavrilimumab 100mg in 442 patients, as Treatment-emergent adverse events (TEAEs), Treatment-emergent serious adverse events (TESAEs), and Treatment-emergent adverse events (TEAEs) of special



interest. Most common adverse effects among the TEAE group were nasopharyngitis (n = 69), bronchitis (n = 51) and hypertension (n = 38). Osteoarthritis (n = 4) and bronchitis (n = 4) were among the common adverse events reported in the TESAEs category. Pulmonary events (defined as a reduction in lung function [FEV1 and FVC] of >20% from baseline and  $\geq 80$  predicted which is clinically relevant) were reported as the TEAEs of special interest; 83 out of 442 patients experienced either reduction in FEV1 or FVC [33].

## LIMITATIONS OF MAVRILIMUMAB IN COVID-19

In a randomized, double-blind, placebo-controlled study determining the effects of Mavrilimumab on Rheumatoid Arthritis, investigation methods such as chest x-ray, forced vital capacity, diffusing capacity of the lung for carbon monoxide (DLCO) were monitored to ensure the pulmonary function is stable with Mavrilimumab treatment. The protocol in this study indicated discontinuation of the treatment if pulmonary function declined >20% of baseline spirometry or DLCO values and for the changes to be reported as adverse events [30].

In a prospective cohort study in patients admitted to San Raffaele Hospital (Milan, Italy), the limitation of the absence of a pre-established randomization process was encountered. This, therefore, can introduce risks such as selection bias, treatment bias, or placebo effect [27]. Other limitations to the use of mavrilimumab include: the onset of COVID-19 pneumonia symptoms >14 days, PaO<sub>2</sub>/FiO<sub>2</sub> <100 mmHg, total neutrophil count <1,500mm<sup>3</sup>, severe hepatic cirrhosis, history of chronic hepatitis B virus and hepatitis C virus infection, known or active tuberculosis (TB), or a history of incompletely treated TB, Moderate or severe Heart Failure (New York Heart Association class 3 or 4), any prior or concurrent use of immunosuppressive therapies, pregnancy or lactation (women of childbearing age should use effective contraception/ abstinence after treatment with mavrilimumab and for 3 months after dosing).

## CONCLUSION

Mavrilimumab is a mAb that may be helpful in some studies with COVID-19. Mavrilimumab seems to have promising results when it comes to treating Covid-19 and should be explored further with more randomized double-blinded trials and a larger sample size. Patients who have been infected with SARS-CoV2 have shown high levels of inflammatory cytokines in their blood counts. With the world trying to contain the COVID-19 pandemic with no concrete treatment option, GM-CSF inhibition may be the key to limiting the severity of the viral infection and shortening the disease duration in COVID-19 patients. A few research studies have shown mavrilimumab antagonizes the action of GM-CSF and decreases the hyperinflammation associated with pneumonia seen in COVID-19, therefore strengthening the conclusion that Mavrilimumab when added to the standard protocol of treatment could improve the clinical outcomes in COVID-19 patients, specifically those patients with pneumonia. Research studies conducted of mavrilimumab in COVID-19 patients have mostly proved that mavrilimumab is well tolerated in patients as well as the associated adverse effects are minimal.

## REFERENCES

1. Singh Tomar PP, Arkin IT. SARS-CoV-2 E protein is a potential ion channel that can be inhibited by Gliclazide and Memantine. *Biochem Biophys Res Commun* 2020;530:10-4.  
[PUBMED](#) | [CROSSREF](#)
2. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271-80.e8.  
[PUBMED](#) | [CROSSREF](#)
3. Bonaventura A, Vecchié A, Wang TS, Lee E, Cremer PC, Carey B, Rajendram P, Hudock KM, Korbé L, Van Tassell BW, Dagna L, Abbate A. Targeting GM-CSF in COVID-19 Pneumonia: Rationale and Strategies. *Front Immunol* 2020;11:1625.  
[PUBMED](#) | [CROSSREF](#)
4. Trapnell BC, Carey BC, Uchida K, Suzuki T. Pulmonary alveolar proteinosis, a primary immunodeficiency of impaired GM-CSF stimulation of macrophages. *Curr Opin Immunol* 2009;21:514-21.  
[PUBMED](#) | [CROSSREF](#)
5. Bhattacharya P, Budnick I, Singh M, Thiruppathi M, Alharshawi K, Elshabrawy H, Holterman MJ, Prabhakar BS. Dual Role of GM-CSF as a pro-inflammatory and a regulatory cytokine: implications for immune therapy. *J Interferon Cytokine Res* 2015;35:585-99.  
[PUBMED](#) | [CROSSREF](#)
6. Burmester GR, Feist E, Sleeman MA, Wang B, White B, Magrini F. Mavrilimumab, a human monoclonal antibody targeting GM-CSF receptor- $\alpha$ , in subjects with rheumatoid arthritis: a randomised, double-blind, placebo-controlled, phase I, first-in-human study. *Ann Rheum Dis* 2011;70:1542-9.  
[PUBMED](#) | [CROSSREF](#)
7. McClure BJ, Hercus TR, Cambareri BA, Woodcock JM, Bagley CJ, Howlett GJ, Lopez AF. Molecular assembly of the ternary granulocyte-macrophage colony-stimulating factor receptor complex. *Blood* 2003;101:1308-15.  
[PUBMED](#) | [CROSSREF](#)
8. Broughton SE, Dhagat U, Hercus TR, Nero TL, Grimbaldeston MA, Bonder CS, Lopez AF, Parker MW. The GM-CSF/IL-3/IL-5 cytokine receptor family: from ligand recognition to initiation of signaling. *Immunol Rev* 2012;250:277-302.  
[PUBMED](#) | [CROSSREF](#)
9. Hamilton JA. GM-CSF as a target in inflammatory/autoimmune disease: current evidence and future therapeutic potential. *Expert Rev Clin Immunol* 2015;11:457-65.  
[PUBMED](#) | [CROSSREF](#)
10. Hamilton JA. GM-CSF in inflammation and autoimmunity. *Trends Immunol* 2002;23:403-8.  
[PUBMED](#) | [CROSSREF](#)
11. Cardone M, Yano M, Rosenberg AS, Puig M. Lessons learned to date on COVID-19 hyperinflammatory syndrome: considerations for interventions to mitigate SARS-CoV-2 viral infection and detrimental hyperinflammation. *Front Immunol* 2020;11:1131.  
[PUBMED](#) | [CROSSREF](#)
12. Nicholls JM, Poon LL, Lee KC, Ng WF, Lai ST, Leung CY, Chu CM, Hui PK, Mak KL, Lim W, Yan KW, Chan KH, Tsang NC, Guan Y, Yuen KY, Peiris JS. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003;361:1773-8.  
[PUBMED](#) | [CROSSREF](#)
13. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934-43.  
[PUBMED](#) | [CROSSREF](#)
14. Griffin JD, Cannistra SA, Sullivan R, Demetri GD, Ernst TJ, Kanakura Y. The biology of GM-CSF: regulation of production and interaction with its receptor. *Int J Cell Cloning* 1990;8(Suppl 1):35-44; discussion 44-5.  
[PUBMED](#) | [CROSSREF](#)
15. Crotti C, Biggioggero M, Becciolini A, Agape E, Favalli EG. Mavrilimumab: a unique insight and update on the current status in the treatment of rheumatoid arthritis. *Expert Opin Investig Drugs* 2019;28:573-81.  
[PUBMED](#) | [CROSSREF](#)
16. Lang FM, Lee KM, Tejjaro JR, Becher B, Hamilton JA. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. *Nat Rev Immunol* 2020;20:507-14.  
[PUBMED](#) | [CROSSREF](#)

17. Ramani T, Auletta CS, Weinstock D, Mounho-Zamora B, Ryan PC, Salcedo TW, Bannish G. Cytokines: the good, the bad, and the deadly. *Int J Toxicol* 2015;34:355-65.  
[PUBMED](#) | [CROSSREF](#)
18. Di Franco M, Gerardi MC, Lucchino B, Conti F. Mavrilimumab: an evidence based review of its potential in the treatment of rheumatoid arthritis. *Core Evid* 2014;9:41-8.  
[PUBMED](#) | [CROSSREF](#)
19. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant* 2020;39:405-7.  
[PUBMED](#) | [CROSSREF](#)
20. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev* 2020;54:62-75.  
[PUBMED](#) | [CROSSREF](#)
21. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.  
[PUBMED](#) | [CROSSREF](#)
22. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, Sun R, Tian Z, Xu X, Wei H. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Natl Sci Rev* 2020 Mar 13:nwaa041.  
[CROSSREF](#)
23. Lisi L, Lacial PM, Barbaccia ML, Graziani G. Approaching coronavirus disease 2019: Mechanisms of action of repurposed drugs with potential activity against SARS-CoV-2. *Biochem Pharmacol* 2020;180:114169.  
[PUBMED](#) | [CROSSREF](#)
24. U.S National Library of Medicine. Mavrilimumab in severe COVID-19 pneumonia and hyper-inflammation (COMBAT19). Available at: <https://clinicaltrials.gov/ct2/show/NCT04397497>. Accessed 25 December, 2020.
25. Cheng LL, Guan WJ, Duan CY, Zhang NF, Lei CL, Hu Y, Chen AL, Li SY, Zhuo C, Deng XL, Cheng FJ, Gao Y, Zhang JH, Xie JX, Peng H, Li YX, Wu XX, Liu W, Peng H, Wang J, Xiao GM, Chen PY, Wang CY, Yang ZF, Zhao JC, Zhong NS. Effect of Recombinant Human Granulocyte Colony-Stimulating Factor for Patients With Coronavirus Disease 2019 (COVID-19) and Lymphopenia: A Randomized Clinical Trial. *JAMA Intern Med* 2021;181:71-8.  
[PUBMED](#) | [CROSSREF](#)
26. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Tassan Din C, Boffini N, Tomelleri A, Farina N, Ruggeri A, Rovere-Querini P, Di Lucca G, Martinenghi S, Scotti R, Tresoldi M, Ciceri F, Landoni G, Zangrillo A, Scarpellini P, Dagna L. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020;2:e325-31.  
[PUBMED](#) | [CROSSREF](#)
27. De Luca G, Cavalli G, Campochiaro C, Della-Torre E, Angelillo P, Tomelleri A, Boffini N, Tentori S, Mette F, Farina N, Rovere-Querini P, Ruggeri A, D'Aliberti T, Scarpellini P, Landoni G, De Cobelli F, Paolini JF, Zangrillo A, Tresoldi M, Trapnell BC, Ciceri F, Dagna L. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol* 2020;2:e465-73.  
[PUBMED](#) | [CROSSREF](#)
28. U.S. National Library of Medicine. Mavrilimumab to reduce progression of acute respiratory failure in COVID-19 pneumonia and systemic hyper-inflammation. NCT04492514. Available at: <https://clinicaltrials.gov/ct2/show/NCT04492514?term=Mavrilimumab&draw=2&rank=5>. Accessed 25 December, 2020.
29. U.S. National Library of Medicine. Study of Mavrilimumab (KPL-301) in participants hospitalized with severe corona virus disease 2019 (COVID-19) pneumonia and hyper-inflammation. NCT04447469. Available at: <https://clinicaltrials.gov/ct2/show/NCT04447469?term=Mavrilimumab&draw=2&rank=7>. Accessed 25 December, 2020.
30. U.S. National Library of Medicine. Mavrilimumab to reduce progression of acute respiratory failure in COVID-19 pneumonia and systemic hyper-inflammation. NCT04463004. Available at: <https://clinicaltrials.gov/ct2/show/NCT04463004?term=Mavrilimumab&draw=2&rank=9>. Accessed 25 December, 2020.
31. Takeuchi T, Tanaka Y, Close D, Godwood A, Wu CY, Saurigny D. Efficacy and safety of mavrilimumab in Japanese subjects with rheumatoid arthritis: findings from a Phase IIa study. *Mod Rheumatol* 2015;25:21-30.  
[PUBMED](#) | [CROSSREF](#)

32. Burmester GR, McInnes IB, Kremer JM, Miranda P, Vencovský J, Godwood A, Albulescu M, Michaels MA, Guo X, Close D, Weinblatt M. Mavrilimumab, a fully human granulocyte-macrophage colony-stimulating factor receptor  $\alpha$  monoclonal antibody: long-term safety and efficacy in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2018;70:679-89.  
[PUBMED](#) | [CROSSREF](#)
33. Weinblatt ME, McInnes IB, Kremer JM, Miranda P, Vencovsky J, Guo X, White WI, Ryan PC, Godwood A, Albulescu M, Close D, Burmester GR. A Randomized Phase IIb Study of Mavrilimumab and Golimumab in Rheumatoid Arthritis. *Arthritis Rheumatol* 2018;70:49-59.  
[PUBMED](#) | [CROSSREF](#)