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# Immunomodulation in COVID-19: A Review of Literature

Chunnu Kumar Yadav[1*], Bishal Pratap Shah[1], Mayank Kumar Mishra[1], Dipesh Jha[1], Binod Mehta[2], Pramodman Singh Yadav[2]

[1]Department of General Medicine, AIIMS, Rishikesh, India
[2]B.P Koirala Institute of Health Sciences, Nepal

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***Corresponding author:** Chunnu Kumar Yadav
Department of General Medicine, AIIMS, Rishikesh, India

**Abstract** **Review Article**

The outbreak of novel corona virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 in Wuhan, China caused a worldwide pandemic. Both symptomatic and asymptomatic carriers were responsible for the transmission of the diseases. Many studies showed high infectivity of the virus. It is therefore urgent to control the transmission of the virus and treat patients infected with SARS-CoV-2 virus. Many evidences have suggested that involvement of human hyperactivation and severe acute respiratory syndrome plays an important role in pathogenesis of critically ill patients with COVID-19. Therefore, repurposing of approved drugs has been used to tackle COVID-19 as the pharmacokinetic and safety profile of these drugs are known. Several immunomodulatory drugs such as disease modifying anti-rheumatic drugs (DMARD) have been proposed as potential therapies for treatment of COVID-19. In this Review we discuss human immune response to virus, pathogenesis of COVID-19 and potential drugs for COVID-19.

**Keywords:** Covid-19, Human Immunology, Immunomodulation.



## IMMUNITY IN BODY

The human body has two types of immune mechanisms in response to internal and external pathogens. They are innate immunity and adaptive immunity. Innate immunity depends on the recognition of conserved molecular patterns found in micro-organisms while the production of antibodies and T cells against particular pathogens is referred to as adaptive immunity. Our body's host defense acts differently to different kinds of pathogens like bacteria, viruses, fungi, parasites, etc. In this article, we will be mainly concerned with our host responses to viruses.

Innate immunity in response to the virus is mainly mediated by seven molecules. They are TLR-3, TLR-7, TLR-9, RIG-1, MDA-5, cGAS sting pathway, and AIM-2 [1]. TLR-3, TLR-7, and TLR-9 are present on the endosomal cell surface while RIG-1 and MDA-5 are present in the endosomal cytoplasm. cGAS pathway and AIM-2 occur in the cytoplasm. These molecules recognize viruses on basis of their nucleic acids and proteins present in the virus. TLR-3, TLR-7, RIG-1, and MDA-5 recognizes RNA viruses while TLR-9, cGAS sting pathway and AIM 2 recognize DNA viruses. When any viral antigen interacts with these molecules, these receptors are stimulated which leads to a common pathway that leads to the formation of IFN-α and IFN-β along with the production of NF-KB and pro-inflammatory cytokines (IFN-y, IL-6, TNF α). Further these IFN-α and IFN-β signal through Janus Kinase (JAK) to signal transduction and activator of transcription (STAT) pathway to stimulate gene expression that regulates CD8 cell which in association with Antigen-presenting Cell (APC) produces antibodies against the virus [2].

Adaptive response is very important for the defense against viral infections. It mainly consists of antibodies and lymphocytes. There are two types of lymphocytes- B cells and T cells. They, both are derived from pluripotent stem cells present in bone marrow but have different sites of maturation and development. T cells in the thymus undergo different stages to form mature T lymphocytes. Pre-T cell with the help of IL 2/7 stimulates the expression of RAG 1/2 and tdT which results in 1st and 2nd burst of proliferation to form TCR β and TCR α rearrangement respectively. A T cell then undergoes positive and negative selection to form mature antigen recognizing T

cells and without being self-reactive and causing auto-immunity [3]. The ability of T cells to moderately bind MHC complex to receive survival signal is known as the positive selection however, T cells whose T cell receptor (TCR) bind too strongly to MHC complexes will likely be self-reactive and are killed in process of negative selection. These cells then recognize and kill virus-infected cells. The development of B cells mainly occurs in lymphoid follicles. Like T cells with the help of RAG 1/ 2 and tdT B cell undergo heavy chain and light chain recombination to form B cell receptor (BCR) which is known as an immature B cell. These immature B cells either undergo apoptosis or anergy when failing to receptor editing or go into the spleen to form transitional B cell stage 1 which is converted to transitional B cell stage 2 through an increase in co-receptor expression and cell-surface IgM and IgD expression. These cells then enter secondary lymphoid organs and on antigen exposure undergo somatic hypermutation and class switch signaling to form plasma cells which produce antibodies that generally bind to virus particles in the blood and mucosal surfaces blocking the spread of infection. One of the most peculiar features of adaptive immunity is memory. Memory is maintained by B and T lymphocyte which remains in the body for long duration. The primary adaptive response takes many days to mature while repeated same viral infections are immediately met with a strong and specific response that develops within hours of infection. Memory response also decreases the reliance on innate immunity. Vaccination in children prevents many adult infections through this memory response of adaptive immunity.

Epigenetic modulation in a cell regulates development and adaptations during the life of an organism [4]. In humans, it mainly occurs by TLR/NLR activation. This leads to various immunometabolic alterations like decrease transcription of IRG-1, inhibitions of various TCA cycle genes and activation of cholesterol biosynthesis. These alter methylation and demethylation in various transcription factors which directly or indirectly result in an anti-inflammatory response.

## IMMUNOPATHOGENESIS OF COVID-19 PNEUMONIA

Corona virus is enveloped, positive sense, single stranded RNA virus that belongs to the family of coronaviridae. It is also known as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) which is a highly contagious virus that can be transmitted from person to person [5]. Most of the nuclear pattern of SARS-CoV-2 is similar to SARS-CoV. SARS-CoV-2 enters the human cell through Angiotensin Converting Enzyme-2 (ACE-2) [6]. ACE-2 expression in humans is found in the tissues of the oral and nasal mucosa, nasopharynx, lungs, stomach, small intestine, colon, blood vessels, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidneys in the brain [7]. One of the prospective studies showed that COVID infections have three unique stages. The first stage is characterized by mild symptoms like fever, cough and other flu like symptoms that resolve spontaneously. The second stage is again accompanied by fever but with moderate to severe intensity and with hypoxemia and pneumonia like symptoms. The final stage is the most severe life-threatening stage in which the patient develops acute respiratory distress syndrome (ARDS). However, it was found that viral load in humans usually peaks on day 10 of infections. The deterioration of disease after that is supposed to be associated with the immune response of the host. Pathological findings in patients who died of COVID infections showed extensive lung consolidation, diffuse alveolar injury, robust macrophage infiltration, alveolar hyaline membrane formation and respiratory distress. These findings are similar to finding in ARDS.

In most studies, it has been found that the cause of ARDS changes is due to cytokine storm. Cytokine storm also known as cytokine release syndrome is a severe excessive immune response caused by a positive feedback loop between cytokine and immune cells. It is characterized by fever, erythema, edema, extreme fatigue and eventually leads to multiple organ damage and death [8]. The innate response is the first response against viral infections. A study showed the interaction of SARS-CoV-2 to receptors in host cell results in the production of low levels of the antiviral cytokines IFN-α and IFN-β, moderate levels of the proinflammatory cytokines tumor necrosis factor (TNF) and IL-6 and high level of inflammatory chemokines CCL3, CCL5, CCL2 and CXCL10 [9]. These cytokines/chemokines induce chemotaxis of neutrophils, monocytes and activated T-cells and their excessive production result in the dysregulation of the immune response to cause unwanted and deteriorating injury to lung epithelial cells, and thus causing acute respiratory distress syndrome. It was found that the serum levels of proinflammatory cytokines (IFN-Y, IL-1, IL-6, IL-12, Transforming growth factor β (TGF β) and chemokines (CCL2, CXCL10, IL-8) were found significantly higher in patients with severe ARDS than in non-ARDS patients. Similarly in another study, there was a significant rise in the level of IL-18, IFN-Y, inducible protein 10 (IP-10), monokines induced by IFN-Y, and monocyte chemotactic protein-1 (MCP-1) in patients who died of COVID-19 than who survived suggesting that IFN-Y-related cytokine storm are involved in immunopathological injury in SARS [10]. Such cytokine storm is related to poor prognosis in COVID-19 patients.

## INFLAMMATORY MARKERS IN COVID-19

Progression of COVID-19 is related to dysregulated immune response and inflammation in our body. These responses are triggered by rapid viral replications and cellular destruction which leads to the

recruitment of macrophages and monocytes and induces the release of cytokines and chemokines. In various autopsy analyses and critically ill COVID-19 patient, it was seen that both cellular and host immunity was involved. There is a significant decrease in circulating T lymphocytes, CD4 T cells and CD8 T cells in association with increased disease severity [11]. A study showed COVID-19 infection is related to an increase in neutrophil count along with a decline in lymphocyte count, and in parallel levels of both inflammatory (IL-6, IL-2) and anti-inflammatory cytokines (IL-4, IL-10) were increased [12]. One of the studies conducted in China showed the inflammatory markers including interleukin-6(IL-6), D-dimer, neutrophil to lymphocyte ratio (NLR) and high sensitivity C- reactive protein (hsCRP) were found to be indicative of severe COVID-19 infections. However, their association with mortality was not reviewed in that article. In another study by Cheng *et al*., inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein and IL-6 have been associated with high risks of development of severe COVID-19 infection [13]. This study also showed serum amyloid A (SAA) to be involved in COVID-19 pathogenesis and may serve as a potential biomarker for monitoring disease progression. Further, a metanalysis study conducted by Zeng *et al.*, showed inflammatory markers especially CRP, IL-6 and ESR were positively correlated with the severity of COVID-19. However, the association of SAA and serum ferritin with the severity of COVID-19 needs to be further classified. Most COVID-19 patients have intrapulmonary infiltrates primarily of macrophages; therefore, serum Macrophage Chemoattractant Protein - 1 (MCP-1) may be used as an alternative indicator of disease severity [13]. Cytokine storm is major pathophysiology in severe COVID-19 infections and IFN-Y is a key factor causing cytokine storm. Therefore IFN-Y can also be used to assess disease severity. Some studies also showed Interferon-gamma inducible protein (IP-10) and Interferon stimulated gene (ISG) suitable for assessment of disease severity.

Thus, inflammatory markers such as IL-6, hsCRP, D-dimer and NLR is used as markers for COVID-19 severity.

## DRUGS ON COVID-19

The manifestations of COVID-19 infection are based on the host body's inflammatory response against the virus. Therefore, severity depends on how strong does body's immune reaction to pathogens. The best way to tackle these immune responses is through different immunomodulatory drugs. Several drugs have been studied for the treatment of COVID-19 infections and many other drugs are still on trial and some are left to be studied. We will categorize drugs based on studies done and the efficacy of the drug.

### Drugs with proven efficacy

### Glucocorticoids

Glucocorticoids and their analogs are the most common drugs which are used to combat inflammation. These are widely used in the treatment of hyperimmune state such as Rheumatoid arthritis, ARDS, vasculitis disease, etc. It has been found that in a patient with ARDS, glucocorticoid treatment improves oxygen saturation, inflammatory markers, length of ICU stay and ventilator-free days. However, they can also inhibit pathogen clearance leading to potential side effects. The mode of action of glucocorticoids is of two types: genomic and non-genomic. In genomic glucocorticoid binds to glucocorticoid receptor and then its activated glucocorticoid and receptor complex is rapidly translocated into the nucleus where it binds as a dimer to specific sites in DNA stimulating transcription of a large variety of target genes (transactivation) while the same glucocorticoid and glucocorticoid receptor complex interacts with transcriptional factors (such as activator protein 1, interferon regulatory factor 3, and nuclear factor-kB) as monomer leading to inhibition of binding of these factors to their consensus sites of DNA (transrepression). It is supposed that adverse effects of glucocorticoids may be predominantly due to transactivation whereas anti-inflammatory effects may be mostly due to transrepression. The non-genomic mechanism targets specific receptors and exerts effect directly without any transcription factors. In non-genomic glucocorticoid binds to glucocorticoid receptor which after activation exert effect without the need of transcription. Various trials have been done in COVID-19 patients in response to glucocorticoid. One of the famous trials is the RECOVERY trial [14]. In this trial, a total of 2104 patients were assigned to receive dexamethasone (a dose of 6 mg daily) for up to 10 days and 4321 to receive usual care. The primary outcome was 28 days mortality. It was found that mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 out of 2104 patients (22.9%) and 1110 of 4321 patients (25.7%) respectively. Patients in the dexamethasone group also had a shorter duration of hospitalization than those in the usual care group. The timing of corticosteroids plays a vital role in improving the mortality of COVID-19 patients. In a study conducted by Bahl *et al*., it was found that patients receiving the first dose of corticosteroid > 72 hours into hospitalization had a lower risk of death compared to patients with 1st dose at an earlier time interval. There was a mortality benefit in patients with > 7 days of symptoms onset to initiation of corticosteroid. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) working group also found that administration of systemic corticosteroid was associated with lower 28 days all-cause mortality to placebo. Thus, corticosteroid was found to be beneficial in COVID-19 treatment.

**TOCILIZUMAB**

Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody of the immunoglobulin IgG1k (gamma 1 kappa) subclass with a typical H2L2 polypeptide structure. IL-6 is one of the key cytokines which is involved in inflammatory cytokine storm and is usually elevated in COVID-19 patients. This drug has been used in the treatment of many auto-immune diseases such as rheumatoid arthritis. In 2020 Guaraldi *et al*., conducted a retrospective cohort study on Tocilizumab in a patient with COVID-19. The study included adults more than 18 years with severe COVID pneumonia who were admitted to tertiary centers in bologona and reggioemilia, Italy between February 21 and March 24, 2020, and in a tertiary care center in Modena, Italy, between Feb 21 and April 30, 2020. All patients were treated with the standard of care (ie, supplemental oxygen, hydroxychloroquine, azithromycin, antiretrovirals, and low molecular weight heparin), and a non-randomly selected subset of patients also received Tocilizumab. Tocilizumab was given either intravenously at 8 mg/kg body weight (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh (ie, 324 mg in total), when the intravenous formulation was unavailable. The primary endpoint was a composite of invasive mechanical ventilation or death. They found that treatment with Tocilizumab, whether administered intravenously or subcutaneously, might reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia. In another study conducted by Salama *et al.*, on Tocilizumab in hospitalized COVID-19 pneumonia, they randomly assigned (in a 2:1 ratio) patients hospitalized with COVID-19 pneumonia who were not receiving mechanical ventilation to receive standard care plus one or two doses of either Tocilizumab (8 mg per kilogram of body weight intravenously) or placebo. The primary outcome was mechanical ventilation or death by day 28. It was found that in hospitalized patients with COVID-19 pneumonia who were not receiving mechanical ventilation, Tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival. Thus, the above studies showed the use of Tocilizumab may be beneficial in severe COVID pneumonia. However, there are some safety concerns with blocking a major regulatory cytokine like IL-6. Due to the blocking of IL-6 general immunomodulatory effects like infections, IL-6 related effects (abnormalities in liver enzymes, lipid profiles) and drugs specific infusion reactions may occur.

**PEGYLATED INTERFERON LAMBDA**

It is one of the newer drugs used in the treatment of COVID-19. It is also known as type III interferon. It has the same antiviral properties as that of IL-α and IL-β but has a distinct receptor complex with a high expression level limited to epithelial cells in the lungs, liver and intestine which results in fewer side effects. It has been found that it controls respiratory viral responses without the risk of promoting cytokine storm syndrome. There are very few studies on this drug in the treatment of COVID. One of the famous studies on this drug was done by Feld *et al*., [14] as Peginterferon lambda for the treatment of outpatient with COVID-19. This was a double-blind, placebo-controlled trial, outpatients with laboratory-confirmed COVID-19 were randomly assigned to a single subcutaneous injection of peginterferon lambda (180 μg) or placebo within 7 days of symptoms onset or first positive swab if asymptomatic. The primary endpoint was the proportion of patients who were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA on day 7 after the injection. After the end of the study, it was found that Peginterferon lambda accelerated viral decline in outpatients with COVID-19, increasing the proportion of patients with viral clearance by day 7, particularly in those with high baseline viral load and Peginterferon Lambda has also potential to prevent clinical deterioration and shorten the duration of viral shedding. However, there need more studies to be effectively used in COVID-19.

**BARICITINIB**

Baricitinib is a small molecule inhibitor of Janus kinase 1 (JAK 1) and Janus Kinase 2 (JAK 2). These JAK 1 and JAK 2 belong to the tyrosine protein kinase family and play an important role in the proinflammatory pathway signaling. This pathway signaling is an important step in the innate response of our body to anti-viral response. One famous trial has been done with Baricitinib plus Remdesivir for a hospitalized adult with COVID-19. The trial is known as the Adaptive COVID-19 Treatment trial (ACTT-1) which was done by Kalil *et al*., [15]. It was a double-blind, randomized, placebo-controlled trial evaluating Baricitinib plus Remdesivir in hospitalized adults with COVID-19. All the patients received Remdesivir (≤10 days) and either Baricitinib (≤14 days) or placebo (control). The primary outcome was the time to recovery with the secondary outcome as clinical status at day 15. The study showed Baricitinib plus Remdesivir was superior to Remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, notably among those receiving high flow oxygen or non-invasive ventilation. However, Baricitinib may be associated with some side effects like infections, transient and usually mild elevation in serum aminotransferase level.

**CONVALESCENT PLASMA THERAPY**

This therapy is a form of passive immunotherapy. Passive immunity is provided when preformed antibodies are given to a person rather than produced by the body itself. This therapy is very popular from back in history. It has been used since the

19th century when this therapy was found effective in controlling diphtheria infections. In present days the use of immunoglobulins has been found established in many infections like a respiratory syncytial virus, cytomegalovirus, hepatitis as well as in acute respiratory distress syndrome (ARDS), Middle East Respiratory Syndrome (MERS) and Ebola virus disease. In the same way, various studies showed plasma with high titer of convalescent plasma therapy against SARS-CoV-2 to mild COVID pneumonia reduced progression of the severity of the disease. A study was done in which patients received convalescent plasma and placebo group less than 72 hours after symptoms onset with the intention-to-treat population. A primary end-point event (progression to predefined severe disease during follow-up) occurred in 16% (13 of 80 patients) and 31% (25 of 80 patients) of the well-matched convalescent plasma and placebo groups, respectively [16]. A dose-dependent effect relative to the antibody titers after the infusion was observed, and this effect was larger after the exclusion of 6 patients who had a primary end-point event before infusion. No serious adverse events were observed. The authors conclude that "early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of COVID-19. However, this therapy was not seen as beneficial in moderate to severe COVID pneumonia. The Infectious Diseases Society of America and the AABB (formerly known as the American Association of Blood Banks) recommends that the use of convalescent plasma be limited to clinical trials, that critically ill patients and those in the intensive care unit (ICU) are unlikely to benefit from transfusions of convalescent plasma, and that convalescent plasma should be used as early as possible in the course of infection (preferably within 3 days after diagnosis) to achieve the best outcome. The collection of convalescent plasma is troublesome. Only those convalescent plasma are appropriate which are of high antibody titers which are determined by different guidelines. There may be risks of plasma transfusion like fluid overload, allergic and hypersensitivity reactions and transfusion-associated acute lung injury (TRALI).

## DRUGS WITH ENOUGH STUDIES BUT WITHOUT PROVEN EFFICACY

### HYDROXYCHLOROQUINE

Hydroxychloroquine which was initially commonly used in the treatment of malaria has been commonly used in several other diseases like HIV, Q fever, fungal infections, Systematic lupus Erythematous, Anti-phospholipid antibody syndromes, rheumatoid arthritis and Sjogren syndrome. Chloroquine (CQ) and hydroxychloroquine (HCQ) are similar in structure which is derived from plant alkaloid known as quinine and quinoline containing compound. These compounds are weak bases that increase the pH of intracellular organelles like lysosomes/endosomes. Lysosomes/endosomes require low pH for maturation and function thus chloroquine and hydroxychloroquine impair their activity. Despite this, CQ was found to cause changes in glycosylation of ACE 2 spike protein and receptor that ultimately inhibits entry step and the post-entry phase of SARS-CoV-2. In one of the studies done by Fantini *et al*., in 2020, it was found that SARS-CoV-2 starts its replication by attaching to the spike (S) viral protein of respiratory cells. The S protein utilizes sialic acids and ACE-2receptor connected to host cell surface gangliosides for entry. The study showed that CQ (or its more active derivative, HCQ) has a high affinity for binding to gangliosides and sialic acids. By these all mechanisms of CQ and HCQ it seemed they will be effective in SARS-CoV-2 treatment but many studies showed against it. In the review by Saghir *et al*., [17] who studied different trials and in-vitro experiments on CQ and HCQ, it was confirmed that CQ/HCQ regimen does not provide any clinical benefits for COVID-19 patients. However, in one of the multi observational studies conducted by Andrew Ip *et al*., [18] that aimed to explore the role of HCQ therapy in mildly symptomatic patients diagnosed in OPD setting, it was found that SARS-CoV-2 infected non hospitalized patient HCQ exposure was associated with a decrease rate in subsequent hospitalization but the cure rate was not determined. The toxicity of HCQ/CQ was found to be dose-dependent. A high dose of CQ was associated with reduced visual acuity, retinal toxicity, bilateral vision loss, hallucinations, paranoia and suicidal ideations. Other adverse effects were pruritus, photosensitivity and seizures. HCQ is safer than CQ due to its more solubility and less toxic metabolites.

## DRUGS WITHOUT ADEQUATE RESPONSE

### ANAKINRA

It is one of the newer drugs that can be used in the treatment of COVID-19. It is a recombinant, non-glycosylated homolog of IL-1R. It differs from native IL-1R by the addition of single methionine at its amino-terminal. Therefore, it competitively inhibits the binding of IL-1 to IL-1R and blocks the activity of IL-1. It has been approved in the treatment of Rheumatoid arthritis, Still's diseases and cryopyrin-associated periodic syndrome. IL-1 was reported to be increased in some patients with COVID-19, therefore blockade of IL-6 can beneficial in the treatment of these patients. Not many studies have been done on this drug in the prevention of COVID pneumonia. In a study conducted by Kooistra *et al*., [19], 21 critically ill patients were treated with Anakinra compared to a group of standard care. It was found that the drug was effective in reducing clinical signs of hyperinflammation. One study also showed a decrease in ferritin concentration and reduced mortality with the use of Anakinra in patient with secondary haemophagocytic lymphohistiocytosis (sHLH). Several trials are underway for evaluating the efficacy of Anakinra.

However, Anakinra may be associated with an increased risk of infections.

**LEFLUNOMIDE**

Leflunomide is one of the Disease-Modifying Anti-Rheumatic Drugs (DMARD) which is commonly used in the treatment of rheumatic arthritis. It is a pro-drug and is rapidly and completely converted to its active metabolite, the malononitriloamide A77 1726, known as teriflunomide. It reversibly inhibits enzyme dihydroorotate dehydrogenase (DHODH) which results in inhibition of pyrimidine synthesis. It also inhibits tyrosine kinases interfering with cell signal transduction, inhibition of nuclear factor kappa beta and anti-tumor effects. Due to its anti-inflammatory action, it may be used in the management of COVID-19. One study by Wang *et al*., compared the safety and efficacy of Leflunomide for the treatment of refractory COVID-19 in adult patients to standard care. 27 hospitalized adult patients (≥18 years of age) with radiologically confirmed pneumonia and SARS-CoV-2 positive for more than 28 days despite standard care, were assigned to receive standard of care (SOC, grp I) or Leflunomide + SOC (grp 2). After 2 weeks, grp 2 patients who continued to be SARS-CoV-2-positive received Leflunomide for 14 days while continuing SOC. It was found that Leflunomide is effective in enhancing SARS-CoV-2 clearance and hospital discharge in refractory COVID-19 patients. Several other trials are being done to look for Leflunomide efficacy. One phase I/II trial is investigating the best dose and side effects of Leflunomide in treating a patient with COVID-19 with past or present cancer. Other uses of leflunomide were seen in the treatment of various virus infections like Cytomegalo Virus (CMV), polyoma virus and Human Papilloma Virus (HPV). Toxicity of Leflunomide was associated with GI disturbances, liver toxicity, hypertension, skin rashes, weight loss and teratotoxic.

**THALIDOMIDE**

It is another DMARD that can be used in COVID-19 due to its anti-inflammatory and anti-proliferative action. Thalidomide has been found effective in viral infections associated with lung injury. Some studies had shown that thalidomide has an immune remodeling effect by inhibiting Tumor Necrosis Factor which is associated with COVID-associated lung injury. In a study by Amra *et al*., with 30 patients were assigned to receive thalidomide to other 30 as usual treatment. It was found that patient with thalidomide was associated with a decrease in ICU admission. In another nonrandomized comparative study, it was found that thalidomide with a short-term glucocorticoid is an effective and safe regimen in severely ill COVID-19 patients. A case report on the use of oral thalidomide (100 mg once daily) with methylprednisolone (40 mg iv BD for 3 days than 40 mg IV OD for 5 days) in severe ill COVID-19 infections showed significant improvement in clinical conditions including oxygen index and improve in inflammatory markers. These studies are done only on a small group of population and a large interventional study is required to prove its better efficacy and results. However, these drugs are associated with severe toxicities like birth defects, sensorimotor peripheral neuropathies, edema, somnolence, rash, fatigue, hypotension, hypercoagulability and constipation.

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