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Review Article

Immunological Aspects of Cytokine Therapy, Signalling Pathway and its Molecular Mechanisms in the Fight Against SARS-CoV-2

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Abstract

The COVID-19 is a pandemic caused by SARS-CoV -2 virus has presented a striking challenge into the health care systems (HCSs) around the World and currently is the source of public health concern globally. The treatment of this disease has remained challenging as there are no proven effective vaccines or therapeutic agents against the virus. Cytokine Storm Syndrome (CSS) is an unregulated inflammatory process response arising from immune effector cells (IECs) releasing proinflammatory cytokines. That occurs as a result of the overproduction of pro-inflammatory cytokines. CSS is a frequently occurring feature of severe infections with COVID-19 pneumonia and violent inflammatory immune response (VIIR) is stimulated by cytokine storm syndrome (CSS) is misleading into the development of symptoms such as fever, throat infections, headaches, dizziness, fatigue, cardiomyopathy, lung injury, acute respiratory distress, multiple organ failure, and subsequent death of the majority of the patients. The new therapeutic strategies under investigation are targeting to the overactive cytokine response (OCR) within the anti-cytokine therapies and immunosuppressive agents. CSS helps to down-regulate and dampen the aberrant pro-inflammatory response of the host and may bring an understanding and insights into the treatment of the SARS-CoV-2 virus. In this review, we have outlined and discussed the different types of cytokines therapies and their mechanism of actions. Currently, being explored and evaluated those that are not yet evaluated for their efficacy and safety in the treatment of COVID-19 and associated with the cytokine storm syndrome (CSS). We suggested that the clinical trials should be initiated for those are new therapies that are not yet explored to evaluate their efficacy and safety in the management and treatment of COVID-19 pneumonia and the SARS-CoV-2.

Keywords: SARS-CoV-2; Cytokine Therapy; Therapeutic Targets; Cytokine Storm Syndrome

Introduction

SARS-CoV-2 was first identified in December 2019 in Wuhan city, China. It is an enveloped, positive-sense, single-stranded RNA virus with a nucleocapsid, being closely related to SARS-CoV-1 with which it shares around 79% of its genome [1,2]. Coronaviruses are named for their crown-like spikes on their surface and there are four main sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta [3]. SARS-CoV-2 belongs to the beta sub-grouping and is one of the seventh coronaviruses to date infecting humans [2]. Some coronaviruses such as OC43 β coronavirus [4], 229E α coronavirus [5], HKU1 β coronavirus [6], and NL63 α coronavirus [7], were associated with mild clinical symptoms, whereas SARS-CoV β coronavirus [8], Middle East respiratory syndrome coronavirus (MERS-CoV) β coronavirus [9], and SARS-CoV-2 caused severe diseases [3].

The pandemic of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome (SARS-CoV-2) has unveiled remarkable challenges to the healthcare systems in almost every country around the world. Currently, there are no proven effective vaccines or therapeutic agents (TAs) against the virus [10]. Since the outbreak of the novel coronavirus (COVID-19) disease has spread rapidly around the globe. Considering the potential threat of a pandemic, scientists and physicians have been racing to understand this new virus and the pathophysiology of this disease to uncover possible treatment regimens and discover effective therapeutic agents (ETAs) and vaccines [11].

Cytokines are small, non-structural proteins with low molecular weights (LMWs) which have a complex regulatory influence (CRI) on inflammation and immunity. They play a major role in many diverse functions including immune cell differentiation (ICD), inflammation, angiogenesis, tumorigenesis, neurobiology, and viral pathogenesis (VPs). In addition to inflammation, immunity, and infections, thus they may be useful biomarkers for health and disease and may act as important therapeutic agents (TAs) and as targets for specific antagonists in numerous immune and inflammatory diseases [12]. Acute respiratory distress syndrome (ARDS) is the leading cause of mortality in COVID-19 disease and tends to induce similar pathogenic features in SARS-CoV and MERS-CoV infections [13]. Cytokine storm (CS) also known as cytokine release syndrome, an unregulated systemic inflammatory reaction arising from the (CRS) regulation of inflammatory cytokines and chemokines by the immune effector cells (IECs), was identified as the leading cause of death in COVID-19 patients [14].

Treatment of cytokine storm involves the use of both antivirals to control the underlying infection and immunosuppressive agents to dampen the aberrant pro-inflammatory response of the host (ISAs). Several trials, evaluating the safety and effectiveness of immunosuppressant's commonly used in rheumatic diseases, are ongoing in patients with COVID-19 and cytokine storm, (CS) some of which are achieving promising results. However, such use should follow a multidisciplinary approach, be accompanied by close monitoring, be tailored to the patient's clinical and serological features, and be initiated at the right time to reach the best results [15].

The production of licensed medications would likely require a long lead time for novel medical therapies. Therefore, because of this need and urgency to establish the diagnosis and management of COVID-19, repurposing IFNs and other approved drugs is a possible alternative for the management of coronavirus infection in drug production. The potential drug options for SARS-CoV-2 infection include the use of nucleosides, enzyme inhibitors, host-targeted agents, convalescent plasma, and IFNs [16]. Interferons (IFN) stimulate the immune system in many ways, displaying numerous biological roles including anti-proliferative (AP), antiviral (AV), immunomodulatory (IM), and developmental processes [17]. In this paper, we will review, discuss the role and mechanism of action of cytokine inhibitors (Cis) or antagonists which have long been used as an anti-inflammatory and as immunosuppressive agents in the treatment of autoimmune diseases such as rheumatoid arthritis (RA) which can be employed and used as potential therapeutic agents in treatments of Cytokine storm syndrome (CSS) an unregulated systemic inflammatory reaction arising from the expression of proinflammatory cytokines (PICs) and chemokines by immune-acting cells (IACs) reported as the leading cause of death in COVID-19 patients.

Pathogenicity of SARS-CoV-2

The genome of coronavirus codes four primary proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E). The S protein is responsible for the activation of body cells via viral intrusion (VI) into target ACE-2 [18]. The SARS-CoV-2 virus uses the Angiotensin-converting enzyme 2 (ACE-2) receptor to attack endothelial and epithelial cells of the airway [19]. ACE-2 expression was high

in lung, heart, ileum, kidney, and bladder [20]. The entry of SARS-CoV into cells was initially by direct membrane fusion between the virus and the cell membrane. Besides the membrane fusion, the clathrin-dependent and independent endocytosis also mediate the entry of SARS-CoV into the cell (Figure 1). When the virus reaches the cells, the viral RNA is transmitted into the cytoplasm and converted into two polyproteins (PPs) and structural proteins (SPs) [21]. While the virus enters the cells, its antigen will be presented to the antigen presentation cell (APC), which is a central part of the body's antiviral immunity (AVI).

Figure 1: Entry of Corona Viruses into the host cells.

On Computerized tomography (CT) scan, the characteristic pulmonary ground-glass opacification can be seen even in asymptomatic patients. ACE-2 is highly expressed on the apical side of lung epithelial cells (LECs) in the alveolar space, the virus can likely enter and destroy them [22]. Epithelial cells (ECs), dendritic cells (DCs), and alveolar macrophages are three main components for innate immunity in the airway. About 80% of the infected patients display mild symptoms and mostly restricted to the upper and conducting airways while only about 20% of the infected patients will display severe infection and progress to stage 3 of the disease. The virus then reaches the gas exchange units of the lung and affects alveolar type II cells of the lungs [23].

Patients diagnosed with COVID-19 reported elevated numbers of leukocytes, irregular respiratory symptoms (IRSs), and decreased levels of pro-inflammatory cytokines (PICs) in plasma. The laboratory studies showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils. Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed [24]. The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, Anaemia, combined with the incidence of ground-glass opacities, an acute cardiac injury which results in difficulty breathing, chest pain, etc. Also Increase levels of cytokines and chemokines were found in patients with COVID-19 infection that included IL1-β, interleukin-1 receptor antagonist (IL-1RA), IL7, IL8, IL9, IL10, basic FGF2, Granulocyte colony-stimulating factor (G-CSF), Granulocyte-macrophage colony-stimulating factor (GM-CSF), IFNγ, inducible protein-10 (IP-10), Monocyte chemoattractant protein-1 (MCP-1), MIP1α, MIP1β, Platelet-derived growth factor subunit B (PDGFB), TNFα, and Vascular Endothelial Growth Factor A (VEGFA). Some of the severe cases that were admitted to ICU showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα That play a role in fostering the seriousness of the disease. Infection with the SARS-CoV-2 virus results in the display of symptoms ranging from minimal symptoms to mild and severe respiratory failure with multiple organ failure (MOF). Most COVID-19 patients will develop and display mild to moderate symptoms, while some may face hyper-inflammation induced by massive cytokines/chemokines production, which may lead to acute respiratory distress syndrome (ARDS). Although, there is no specific antiviral therapy for COVID-19, understanding the root causes and mechanism of hyper-inflammation induced by massive cytokines/chemokines production in the disease can help to presume possible therapeutic mediations [25].

Cytokine storm syndrome and severity of SARS-COV-2

Cytokine storm syndrome (CSS) is also known as Cytokine Release Syndrome (CRS) or "Hypercytokinemia" is a frequently occurring feature of severe infections with SARS, MERS, H5N1 influenza, and H7N9 influenza; it is associated with disease severity and is a major cause of death in the aforementioned diseases [26]. Cytokine storm syndrome is an unregulated systemic inflammatory response arising from immune effector cells releasing pro-inflammatory cytokines and chemokine which occur as a result of the overproduction of pro-inflammatory cytokines (PICs) such as tumor necrosis factor (TNF), interleukins (IL-1, IL-6, il-8) and interferons such as (IFN)-γ, etc. which lead to an increased risk of vascular hyperpermeability (VHP) which causes tissue vasogenic edema and often leads to multiple organs failure resulting in the death of the patient when the high cytokine concentrations are persistent over time (Figure 2). The development of a cytokine storm (CS) is a fatal immune condition characterized by rapid proliferation and hyperactivation of T cells, macrophages, natural killer cells (NKCs), and the overproduction of more than 150 inflammatory cytokines and chemical mediators (CMs) released by immune cells (ICs) [27].

Histological examination and biopsy samples obtained from a patient who died from severe COVID-19 show an increased concentration of highly proinflammatory $CCR4^+$, $CCR6^+$, $Th17^+$, CD4 T cells, suggesting that T cell hyperactivation contributed in part to the severe immune injury (SII) in this patient [28].

Figure 2: Cytokine Storm and Inflammatory Response.

High blood levels of cytokines and chemokines have been detected in patients with COVID-19 infection, including Interleukine-1 (IL1-β), Interleukine-1 receptor antagonists (IL-1RA), Interleukine-7 (IL-7), Interleukine-8 (IL-8), Interleukine-9 (IL-9), Interleukine-10 (IL-10), basic Fibroblast growth factor 2 (FGF-2), Granulocyte colony-stimulating factor-2 (G-CSF), Granulocyte-macrophage colony-stimulating factor-3 (GMCSF), Interferon-gamma (IFNγ), IP10, Monocyte chemoattractant Protein-1 (MCP-1), Macrophage inflammatory protein alpha (MIP1α), MIP1β, PDGFB, Tumor necrosis factor-alpha (TNF-α), and Vascular endothelial growth factor (VEGFA) [29]. The ensuing cytokine storm enhances a vicious inflammatory immune response which can cause clinical symptoms to evolve; such as high fever, chills, headaches, dizziness, general malaise, fatigue, vascular leakage, cardiomyopathy, lung injury, ARDS, multiple organ failure (MOF), and finally death in severe cases of COVID-19. The extent to accurately predict and intervene in the cytokine storm (CS) during COVID-19 pneumonia, as well as the ability to design effective specific strategies to impede excessive inflammation, is important and critical for patient's survival. Several different anti-cytokine strategies are effective in treating a variety of cytokine storm syndromes, including interleukin-1 (IL-1), IL-6, IL-18, and interferon-gamma medications. The therapeutics strategies under investigation are targeting the overactive cytokine response with anti-cytokine therapies or immunomodulatory, but this must be balanced with maintaining an adequate inflammatory response for pathogen clearance [30].

Cytokine therapy and fight against SARS-CoV-2 (COVID-19)

Clinical observations from different studies have signified Strong upregulation of cytokine production in patients severely infected with SARS-CoV-2 [31]. Unusual and uncontrolled production of cytokines has been observed in patients with severe cases of COVID-19. Concerning the above observations, therapeutic strategies to treat the cytokine storm (CS) in the pathogenesis of severe cases of SARS-CoV-2 are needed and deserve special attention. Following world health organization (WHO) guidelines and protocol in the treatment and management of COVID-19 pneumonia supportive therapy remains the most important management strategy for SARS-COV-2 Pneumonia. In patients infected with SARS-CoV related acute respiratory distress syndrome, cytokine-storm-targeted therapy (CSTT) was suggested and recommended for the treatment of severe pulmonary failure inferior (SPFI) to an excessive inflammatory response (EIR). The therapeutic use of cytokines as immunomodulatory that helps to regulate and normalize the immune system and boost the host defenses has been used traditionally to treat long-term chronic diseases, and several are already licensed for human use, including IL-2 and interferons (IFNs). One of the most extensively used cytokines as therapeutics agent is IFN-1, a type 1 interferon which inhibits viral replication [32].

Some studies showed that cytokine/chemokine clearance was achieved using artificial-liver blood-purification systems (ALBPSs). Positive results have been yielded in terms of remarkably downgrading the levels of 17 cytokines/chemokines: granulocyte/macrophage-colony-stimulating factor (GCSF), basic fibroblast growth factor (FGF), IFN-γ, IL-1 receptor antagonist, IL-12p70, IL-17A, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-9, platelet-derived growth factor-BB (PDGF-BB), regulated upon activation of normal T cell expressed and secreted (RANTES), TNF-α, and vascular endothelial growth factor (VEGF). These encouraging results were achieved after the first session of artificial-liver blood-purification therapy (ALBPT) and were maintained thereafter [33].

Interferons (IFN) works in many respects to strengthen the immune response by displaying various biological roles including antiviral, immunomodulatory, antiproliferative, and developmental behaviors. IFN therapeutic interferons are produced using recombinant DNA technology (RDT), and there are several clinically approved IFNs available: IFN α-2a (Roferon), IFN α-2b (Intron A), IFN α-n1 (Wellferon), IFN α-n3 (Alferon), IFN α -con 1 (Infergen), IFN β-1a (Rebif), IFN β-1b (Betaferon), IFN β -1a (Avonex), IFN β -1b (Betaseron), IFN α -2a (Pegasys), IFN α -2b (PegIntron), IFN α P-2b (Sylatron), and IFN γ-1b (Acimmune). Through the use of transgenic interferons IFNs (IFN -α, IFN -β, and exogenous interferons IFNs) in the treatment of SARS-CoV-1, SARS-CoV-2 and MERS-CoV have demonstrated that IFN response inhibits protein synthesis and virus replication [34] (Figure 3).

Figure 3: Transgenic interferons IFNs (IFN -α, IFN -β, and exogenous interferons IFNs) in the treatment of SARS-CoV-1, SARS-CoV-2 and MERS-CoV have demonstrated that IFN response inhibits protein synthesis and virus replication.

Assessment of cytokine profiles and immune cell subsets has important implications for selecting appropriate immunosuppressant's for example tocilizumab could be considered in patients with a high concentration of serum (IL-6). The fact that anti-viral immunity is required to recover from COVID-19, the benefits and detriments of using immunosuppressants on the patients should be carefully considered. To lessen the hyper inflammation caused by cytokine storm syndrome, interleukins (IL) inhibitors, tumor necrosis factor (TNFs), Janus kinase inhibitors (JKIs) and interferons are some of the few therapeutics drugs that are in clinical trials to evaluate their efficacy in treatment and management of COVID-19 [35].

Interleukins (IL) inhibitors

Interleukin (IL) inhibitors may help to remediate the severe damage to lung caused by cytokine storm syndrome (CSS) in patients with severe COVID-19 infections (Table 1). This include:

Sr. No.	Therapeutic Agents	Target Cytokine	Mechanisms of Action	References
1.	Tocilizumab	IL-6 Receptor	Bind To Both Soluble and Membrane Bound IL-6 Receptor and Inhibit IL-6 and Trans Signaling.	[36]
2.	Sarilumab	IL-6 Receptor	Bind and Inhibit IL-6 Pathway	[38]
3.	Siltuximab	IL-6 Receptor	Bind To IL-6 and Prevent Its Binding To Both Soluble and Membrane Bound IL-6 Receptor.	[41]
4.	Anakinra	IL-1 α, IL-1 β	It Bind To and Block IL-1 Alpha and IL-1 Beta.	[43]
5.	Canakinumab	IL-1 β	Neutralizes IL-1 Beta and Prevents Its Interaction With IL-1 Receptor.	[47]
6.	Etanercept	TNF-α	Bind To TNF Alpha And Prevent It From Binding To Cell Bound TNF Receptors, Thus Inhibiting Signaling of The Target Cell.	[49]
7.	Adalimumab	TNF-α	Bind To TNF Alpha and Prevent It From Binding To Its Receptors.	[53]
8.	Infliximab	TNF-α	Bind To TNF Alpha And Form Complexes With The TNF Alpha There By Ceasing The Biological Activity And Signal Of TNF Alpha.	[54]
9.	Golimumab	TNF-α	Inhibit The Activity of TNF Alpha In Areas Such As Joint.	[55]
10.	Certolizumab	TNF-α	Bind To Both The Soluble and Membrane Bound TNF Alpha There by Inhabiting Its Inflammatory Action.	[57]
11.	Baricitinib	JAK 1, JAK 2, JAK 3 And TYK 2	Bind To and Inhibits The Activity of JAK 1, JAK 2, JAK 3 And TYK 2.	[59]
12.	Tofacitinib	JAK 1, JAK 2, JAK 3	Binds To and Inhibits The Activity of JAK 1, 2, and 3.	[61]
13.	Upadacinib	JAK 1	Binds To and Inhibits The Activity Of JAK 1.	[62]
14.	Ruxolitinib	JAK 1 and JAK 2	Inhibits Dysregulated JAK Signaling Required For Recruitment of Signal Transducers and Activators of Transcription (STATs) to Cytokine Receptors.	[63]
15.	Fedratinib	jAK 2	Bind To JAK 2 and Inhibit JAK 2 Activation And JAK-STATS Signaling Pathways.	[64]

Table 1: Different Therapies, Their Target Cytokine and Mechanisms of Action in fighting against SARS-CoV-2.

Interleukins (IL-6) inhibitor

Interleukin 6 (IL-6) is a cytokine that is produced by many types of cells. It is a pleiotropic cytokine with diverse immunological activities. It plays a pivotal role in the differentiation of mature B cells into plasma cells, and combined with TGF-β, it promotes the differentiation of naive $CD4^+$ T cells into Th17-cells and prompts the production of acute-phase proteins (APPs) such as CRP, fibrinogen, serum amyloid A, and hepcidin. IL-6 promotes the transformation of megakaryocytes into platelets and the activation of hematopoietic stem cells in bone marrow [36]. The explicitness of IL-6 in SARS-CoV-2 comes from the fact that an elevated level of IL-6 is complemented with inflammatory cytokine storm severity. Therefore targeting IL-6 and its receptor by sarilumab, Siltuximab, and tocilizumab monoclonal antibodies and other interleukins 6 (IL-6) antagonists could alleviate cytokine storm-related symptoms in severe cases of COVID-19 [37].

- **Tocilizumab**: Tocilizumab is an immunosuppressive drug (ISD), mainly for the treatment of rheumatoid arthritis (RAs) and systemic juvenile idiopathic arthritis (SJIAs), a severe form of arthritis in children. It is a humanized monoclonal antibody against the IL-6 receptor. It binds to both soluble and membrane-bound IL-6 receptor and inhibits IL-6-mediated cis and trans-signaling (Figure 4) [38]. A patient was diagnosed with COVID-19 upon his return from Iceland a few days after, he was admitted to hospital as he developed respiratory failure and was transferred to the intensive care unit where he received further treatment, including tocilizumab (IL-6 receptor inhibitor) where he subsequently showed clinical improvement. A recent study shows that In the treatment of 21 patients with severe COVID-19, tocilizumab was used and the clinical data showed that the symptoms such as hypoxygenmia, and CT opacity changes were improved after the treatment in most of the patients [39]. In another study patients with mild to severe COVID-19 infection received one or two doses of tocilizumab (400 mg/dose) in addition to standard therapies used including lopinavir and methylprednisolone as reported in the Diagnosis and Treatment Protocol for Novel Coronavirus (6th interim edition). Most patients experienced clinical improvement including low oxygen requirement (LOR) (15/21, 75%), a decrease of CRP, an increase in lymphocyte levels, decreased fever, and improved chest tightness. Based on this data, on March 3rd, 2020, The National Health Commission of China included tocilizumab in its 7th edition of COVID-19 therapy recommendations. Tocilizumab has been approved by the U.S. Food and Drug Administration for the treatment of severe CAR T cell-induced CRS. Another study conducted in New Jersey showed an improved survival rate among patients who received Tocilizumab among 547 ICU patients [39].
- **Sarilumab:** Sarilumab is a humanized monoclonal antibody that binds and inhibits IL-6 and promotes signaling, resulting in decreased in [40]. It has a direct effect on IL-6, which plays a pivotal role in inflammation and joint damage but also affects CYP3A4. Sarilumab inhibits the interleukin-6 (IL-6) pathway by binding which results in the blockage of the IL-6 receptor. IL-6 may play a role in promoting the hyperactive inflammatory response in the lungs of patients who are severely affected by COVID-19. The scientific reasons that support the use of (interleukin-6 (IL-6) Signalling is that sarilumab may potentially prevent cytokine-mediated pulmonary injury drive-by or accelerated by infection with SARS-CoV-2 and thereby alleviating the severity and/or decrease the mortality among patients with Covid-19 pneumonia when administered in confluence with antiviral therapy (Figure 4). sarilumab an inhibitor of soluble and membrane IL-6Rα may help to lower the severity of respiratory difficulty of SARS-COV2 infection, but there is no evidence that it has anti-viral potential. Clinical trials are on progress intending to examine the efficacy of the drug in the acute form of SARS-CoV-2 infection [41].
- **Siltuximab:** Siltuximab is a humanized recombinant chimeric monoclonal antibody (MAb) distinctive and specific for the interleukin-6 (IL-6) receptor and may potentially hammer cytokine release syndromes (CRSs) symptoms such as fever, difficulty in respiration, fatigue, organ failure, and death) in patients severely infected of COVID-19. Siltuximab binds human interleukin-6 (IL-6) and prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors (Figure 4). In recent research findings from an observational case-control study of COVID-19 Patient response to treatment with Siltuximab, the serum CRP levels reduced to within the normal range by Day 5 and remained stable in all 16 patients and 33% (7/21) of the patients experienced an improvement in their condition with a reduced need for ventilation [42].

Interleukin 1 (IL-1) inhibitors

Interleukin 1 (IL-1) is a member of the pro-inflammatory protein family called cytokines and plays a crucial role during inflammation [43]. It also plays a vital role in cytokine storm syndrome (CSS) which results in multi-organ failure and subsequent death of the patients. In SARS-CoV-2 the multifarious synthesis and release of inflammatory IL-1 occur after the COVID-19 virus bind to the Toll-like Receptor (TLR). Activation of this receptor causes a biochemical cascade that begins with the formation of pro-IL-1 cleaved by caspase-1 and then followed by activation of inflammasome. Binding the SARS-COV 2 virus to the Toll-Like Receptor (TLR) causes the discharge of pro-IL-1β which is cleaved by caspase-1, followed by inflammatory activation and the creation of active mature IL-1β which is a lung inflammation conciliator (LIC). Subdual of pro-inflammatory IL-1 and IL-6 family members has been shown to have a therapeutic effect in several inflammatory diseases (SIDs), including viral diseases (VDs) [42].

Figure 4: IL-6 Signaling Pathway.

- **Anakinra:** Anakinra is a humanized recombinant interleukin 1 (IL-1) receptor antagonist which was accepted and approved in 2001 in the USA and 2002 in EUROPE for use in the treatment of rheumatoid arthritis patients (RAsPs). It is 17 kDa recombinant, non-glycosylated human IL-1Ra that binds to and blocks IL-1α and IL-1β. It was approved for the treatment of rheumatoid arthritis, cryopyrin-associated periodic syndromes (CAPSs), and Still's disease. Interleukin 1 family of receptors triggers an innate immune response and was associated with damaging inflammation. Anakinra behaves closely to the natural interleukin-1 receptor antagonist by inhibiting combatively the binding of IL-1α and IL-1β to the type 1 receptor IL-1. **C**linical trials are currently on progress to examine the effectiveness of Anakinra in the treatment of COVID-19 infections [44].
- **Canakinumab:** Canakinumab is a human monoclonal antibody that specifically targets and neutralizes IL-1 beta; thereby preventing its interaction with IL-1 receptors. Canakinumab, prevent the binding of IL-1 (a pro-inflammatory cytokine that mediates various inflammatory and immunological responses. A retrospective analysis of ten patients with confirmed cases of COVID-19 infection was treated with Canakinumab which was administered subcutaneously in a single 300mg dose, in April 2020, at the Infectious Disease Clinic of SS. Annunziata Hospital in Chieti, Italy in combination with hydroxychloroquine (200 mg twice daily) and lopinavir-ritonavir (400 mg twice daily of lopinavir and 100 mg twice daily of ritonavir). It was found out that Canakinumab was well tolerated with no recorded adverse side effect or reaction and was associated with a rapid and significant decrease in serum C-reactive protein at day 1 and day 3 and an improvement in oxygenation, with the PaO2:FiO2 ratio increasing between baseline and day 3 and day 7 after treatment. At 45 days under treatment, all ten patients were alive and discharged from the hospital without physical obstructions caused by COVID-19 or the need for oxygen therapy [45].
- **Tumour necrosis factors inhibitors (TNF):** Tumor necrosis factor (TNF) is predominantly a type II transmembrane protein with a sequence of 212 amino acids and is found in stable homotrimers. TNF alpha conversion enzyme (TACE) is a metalloprotease capable of cleaving membrane-integrated TNF and releasing TNF in a soluble homotrimeric form [46]. Monoclonal antibodies have established the TNF blocking strategy as an important treatment for immune diseases including inflammatory intestinal disease and rheumatoid arthritis. Tumour necrosis factor (TNF) inhibitors have been used for many years in severe cases of autoimmune inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, etc. TNF are found in blood and disease tissues of patients with COVID-19 and are important in nearly all acute inflammatory reactions, acting as an amplifier of inflammation and might reduce some of the processes that occur during COVID-19 lung inflammation [47].

Anti-TNF therapies previously revealed protective effects in lethal SARS-CoV infection. Several TNF-blocking antibodies (e.g. adalimumab, etanercept, and golimumab) are successfully used to treat inflammatory diseases, and these therapies have been urgently recommended for the treatment of COVID-19 patients. TNF-α is among the members of tumor necrosis factors superfamily and It is produced mainly by activated macrophages, B cells and NK, T, and exerts its action through two receptors called TNFR1 and TNFR2. After binding to its receptors, TNF-α leads to multifarious and often incompatible effects. TNF-α is a strong antiviral cytokine that acts directly by killing the virus-infected cells before maximum virus replication. Nevertheless, it is understood that the SARS-CoV-2 viral spike protein is capable of activating the ACE2 ectodomain TNF-α-converting enzyme (TACE)-dependent shedding, which is coupled to TNF-α production and is vital for the entrance and invasion of the virus into the cell. Tumour necrosis factor (TNF) family of receptors and cytokines are often targets for drugs. Inhibition of TNF--α can be achieved with a monoclonal antibody such as adalimumab, infliximab, Certolizumab pegol, golimumab or with etanercept. Established anti-tumour necrosis factor (TNF) therapies such as adalimumab, infliximab, Certolizumab pegol, golimumab or with the etanercept have demonstrated a good record of reduced inflammation in inflammatory disease such as inflammatory bowel disease, rheumatoid arthritis and could potentially treat patients who develop acute respiratory distress (ARDS), due to inflammatory plethora that occurs in patient with COVID-19 [48].

In a recent study that assess the efficacy and safety of anti-tumour necrosis factor in treatment of covid-19 shows a positive result where a group of patients suffering from inflammatory bowel disease (IBD) and COVID-19 simultaneously treated with anti-TNF-α and steroid, the results shows that the prevalence of severe and complicated cases of COVID-19 is lower in patients in treatment with anti-TNF-α than that reported for patients taking steroids as only 15% of IBD patients with COVID-19 in treatment with anti-TNF-α needed hospitalization, and very few of them required intensive care unit or died (3%) compared with patients taking steroids where about 67% needed hospitalization and about 25% required intensive care unit or died [49].

- **Etanercept:** Etanercept is a 150 kDa molecular weight genetically engineered tumor necrosis factor TNF-α antagonist used for the treatment of rheumatoid arthritis, psoriasis, psoriatic arthritis. It consists of two identical chains of recombinant human TNF-receptor p75 monomer fused with the Fc domain of human immunoglobulin (IgG) G1. Etanercept is a competitive inhibitor of the binding of TNF-α to the cell surface TNF receptors thus inhibiting the proinflammatory activity of TNF. Etanercept binds to soluble TNF-α, hindering its ability to bind to cell-bound TNF receptors thus inhibiting signalling of the target cell and thereby preventing the biological effects of TNF production. A recent study reported a case of recovery from COVID-19 of 60 year old man treated with etanercept 50 mg, subcutaneous, weekly and methotrexate 20mg subcutaneous, weekly for spondyloarthritis [50].
- **Adalimumab:** Adalimumab is absolutely human recombinant IgG1 monoclonal antibody, it is an antagonist of TNF-α, which is able to hinder the binding of TNF-α to its receptors. It is 148 kDa molecular weight protein, heterodimeric and consists of 1330 amino acids sequences. Adalimumab works by binding to TNF-α and hampered it from binding to both types of its receptors and thereby leveraging downstream processes that are regulated by TNF-α. It binds to TNF-α with relatively high affinity, with dissociation constant (KD) values between 7.05x10-11M to 10x-10. Currently a trial title "A Randomized, Open-Label, Controlled Trial For The Efficacy And Safety Of Adalimumab Injection In The Treatment Of Patients With Severe Novel COVID-19" (ChiCTR2000030089) is on progress to evaluate the efficacy and safety of adalimumab in treatment of patients with severe cases of COVID-19 pneumonia in china [51].
- **Infliximab:** Infliximab (IFX) is the first monoclonal TNF antibody approved for human treatment, it is a purified, recombinant DNA-derived chimeric human-mouse IgG monoclonal antibody and contains approximately 30% murine variable region of amino acid sequence, which contribute to antigen-binding specificity to human TNFα and The remaining 70% correspond to a human IgG1 heavy chain constant region and a human kappa light chain constant region. Infliximab can quickly form stable complexes with the human soluble or the membrane form of TNF and cease the biological activity and signals of TNF. Infliximab is administered by intravenous infusion and it is indicated for the induction and maintenance of remission of moderate-severe IBD. It is a TNF alpha inhibitor and full IgG1-antibody which is approved for severe cases of rheumatoid arthritis, methotrexate, and psoriasis arthritis as well as for inflammatory bowel disease. As of the time of writing this paper there is no any clinical trials is initiated to evaluate the efficacy of infliximab in management and treatment of COVID-19 pneumonia [52].

- **Golimumab:** Golimumab is a human IgG1κ monoclonal antibody which is used as an immunosuppressive drugs. It is derived from immunizing genetically engineered mice with human TNFα. Golimumab targets tumour necrosis factor alpha (TNF-alpha), a pro-inflammatory molecule and hence is a TNF inhibitor, Golimumab inhibits the activity of the cytokine, tumor necrosis factor alpha (TNFα) in areas such as the joints and blood, increased TNFα is associated with chronic inflammation seen in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis and help to decreases the inflammation in these conditions [53].
- As a human monoclonal antibody, golimumab binds and inhibits soluble and transmembrane human TNFα. Inhibition of TNFα prevents it binding to its receptors, which prevents both leukocyte infiltration through prevention of cell adhesion proteins such as E-selectin, ICAM-1 and VCAM-1, and pro-inflammatory cytokine secretion such as IL-6, IL-8, G-CSF and GM-CSF *in vitro.* Consequently, in patients with chronic inflammatory conditions, decreases in ICAM-1 and IL-6 as well as C-reactive protein (CRP), matrix metalloproteinase 3 (MMP-3), and vascular endothelial growth factor (VEGF) were observed. As of the time of writing this paper no any clinical trial has been initiated to evaluate the efficacy and safety of golimumab in patients with COVID-19 pneumonia [54].
- **Certolizumab:** Certolizumab pegol is a PEGylated monoclonal antibody against the tumor necrosis factor-α (TNF-α). It is humanized antigen-binding fragment (Fab') of a monoclonal antibody that has been conjugated to polyethylene glycol. It is formed with a humanized Fab fragment of 50kDa, integrated to a 40 kDa polyethylene glycol moiety replacing the Fc antibody region. A clinical trial using Certolizumab pegol (a TNF-alpha blocker) along with other anti-virus therapies may have beneficial effects in COVID-19 patients. In view of this anti-TNF therapy using Certolizumab pegol should be evaluated in patients with COVID-19 to evaluate its efficacy in treatment of COVID-19 pneumonia [54].

Janus kinase (JAK) inhibitors

Janus kinases family composed of JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). They are intracellular enzymes that transfer signals arising from the interaction of cytokines and growth factors with receptors found in the cellular membrane. These enzymes phosphorylate and activate the transcription protein transducers and activators (STATs), which switch intracellular activity including gene expression. The JAK-mediated signaling pathway is pivotal in influencing immune system activation, as cytokine receptors are expressed on most immune cells. JAK inhibitors modulate the signaling pathway by hindering the phosphorylation and activation of STATs [55].

Janus kinase inhibitors are a class of selective synthetic immune suppressants administered orally that operate by inhibiting the function of one or more members of the JAK family (JAK1, JAK2, JAK3, TYK2), interrupting the JAK-STAT signaling pathway. Most of the JAK inhibitors are particularly effective in inhibition of JAK 1 and JAK2 and less in JAK 3 and TYK 2 and therefore are particularly effective at inhibition of IL-6 and interferon (IFN- γ but also inhabit IL-2 and the IFN- α/β signalling cascade. JAK inhibitors can treat cytokine storm by inhibiting multiple inflammatory cytokines. Due to the large immunosuppressive effect of JAK inhibitors. The National institute of health (NIH) has commended to be used for treatment of COVID-19 patients. The JAK inhibitors recommended are baricitinib, tofacitinib, upadacinib, ruxocitinib and fedracitinb [56].

Baricitinib

Baricitinib, is an oral Janus kinase (JAK) 1/JAK2 inhibitor approved for the treatment of rheumatoid arthritis (RA) that was independently predicted, using artificial intelligence (AI) algorithms, to be useful for COVID-19 infection as it reported to have anti-cytokine effects and as an inhibitor of host cell viral propagatio. Richardson *et al* suggested Baricitinib as a possible therapy for COVID-19 because it is believed to have anti-viral effects due to its similarity to the AP2-associated protein AAK1, decreased endocytosis of SARS-CoV-2 and diminished the virus' capacity to infect lung cell. Baricitinib inhibits JAK1 and JAK2, with an average activity against TYK2 and significantly lesser against JAK3 [57].

Baricitinib have yielded a positive results in treatment of COVID-19 pneumonia. In a pilot study of clinical trial carried out in Italy. Four patients with covid-19 who presented varying degrees of disease severity were admitted to ward, plasma level of IL-6 was detected in all of the patients as would be expected of patients with COVID-19. All four patients shows an improvement in signs and symptoms and decrease in plasma IL-6 level as well as reduction in SARS-COV2 RNA viral load as identified by real-time reverse transcriptase polymerase chain reaction (RT-PCR). In another large number of clinical trials for testing drugs for covid-19. the potential CNS penetration of the six most common drugs (hydroxychloro-

quine, Baricitinib, Ruxolitinib, Remdesivir Tocilizumab, Lopinavir/ritonavir JAK inhibitor baricitinib is the second most likely drug to enter the brain after hydroxychloroquine and is currently being studied in randomized controlled trials including a major US NIAID review [58].

In another pilot study to assess the effectiveness of Baricitinib in treatment of covid-19, Baricitinib was used in combination with lopinavir-ritonavir in a patients showing moderate symptoms were treated for two weeks and another group with a combination of lopinavir/ritonavir tablets 250 mg/bid and hydroxychloroquine 400 mg/day/orally for 2 weeks as a control. In the Baricitinib-treated group, compared with the baseline, all clinical characteristics and respiratory function parameters improved significantly at both week 1 and week 2. In week 2 no significant changes were recorded in the control group [59].

Tofacitinif

Tofacitinif is an oral Janus kinase (JAK) inhibitor used for the management and treatment of rheumatoid arthritis. Tofacitinif is a specific inhibitor of JAK3 and to a minor extent JAK1 and JAK2 and can effectively block inhibitors of the JAK1/3-dependent cytokines (IL-2, IL-4, IL-15, and IL-21). A clinical trials Title "A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study Assessing The safety and efficacy of tofacitinif in hospitalized participant with covid-19 pneumonia who are receiving standard of care therapy" (NCT04412252) have started on 4th June, 2020 to examine and evaluate the effectiveness of tofacitinib in management and treatment of SAR-CoV-2 virus. The trial comprise of 240 participants and the estimated date of completion of the study is October 18, 2020 [60].

Updacinib

Upadacinib is an oral Janus kinase (JAK) 1-selective inhibitor and a disease-modifying ant rheumatic drug (DMARD) used in the treatment of rheumatoid arthritis to slow down disease progression and development. The FDA approved Upadacinib in August 2019 for the treatment of patients with mild to severely active rheumatoid arthritis and was also approve in December 2019 by the European Commission for the same indication. It is currently being investigated in several clinical trials to assess its therapeutic effectiveness in other inflammatory diseases [61].

Upadacinib works by inhibiting the Janus Kinases (JAKs), which are essential downstream cell signalling mediators of pro-inflammatory cytokines. It is believed that these pro-inflammatory cytokines play a vital role in many autoimmune inflammatory conditions. As of the time of writing this paper there are no any clinical trial going on to evaluate the efficacy of Upadacinib or any data to support its effectiveness in fighting COVID-19 pneumonia but it can be used as a potential therapeutics in the treatment of COVID-19 [62].

Ruxolitinib

Ruxolitinib is a JAK kinase inhibitor which specifically inhibits Janus Associated Kinases (JAKs), JAK1 and JAK2. It regulate the cytokine-stimulated signalling through the inhibition of JAK1 and JAK2. It inhibits dysregulated JAK signalling required for recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus, leading to modulation of gene expression [63].

Currently two trials are ongoing in USA to evaluate the efficacy of Ruxolitinib in the treatment of patients with COVID-19 associated with Acute Respiratory Distress Syndrome (ARDS). The First Trial Title "A Phase 3, Randomized, Double Blind, Placebo Controlled. Multicentre Study to Assess The Efficacy And Safety Of Ruxolitinib In Participants With COVID-19 Associated Ards Who Require Mechanical Ventilation (Ruxcovid-Devent)."(NCT04377620). The study have commenced on May 24, 2020 and the estimated date of completion is on July 29, 2020 and is comprised of 500 participants. The second study title "A Phase 3, Randomized, Double Blind, and Placebo Controlled. Multicentre Study To Assess The Efficacy And Safety Of Ruxolitinib In Patient With COVID-19 Associated With Cytokine Storm Syndrome (Ruxcovid)" NCT0436137 was also on progress to evaluate the efficacy (as measured by a composite endpoint of proportion of patients who die, develop respiratory failure [require mechanical ventilation], or require intensive care unit care) of Ruxolitinib + standard-of-care (SoC) therapy compared with placebo + SoC therapy, for the treatment of COVID-19 by Day 29. The study has commenced on May 1, 2020, and the estimated date of completion is on October 13, 2020, and comprised of 402 participants [64].

Fedratinib

Fedratinib is an eclectic inhibitor of JAK2 kinase recently approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with myelofibrosis. It is an effective Ja-

nus kinase (JAK2) inhibitor that has been approved for use in myelofibrosis, both as a first-line agent and in second-line due to the Ruxolitinib failure or intolerance. Fedratinib contends with natural type JAK2 as well as the mutant form of JAK2 V617F for ATP binding, which results in inhibition of JAK2 activation and inhibition of the JAK-STAT signalling pathway. As of the time of writing this paper, there is no clinical trial going on to evaluate the efficacy of Fedratinib or any data to support its effectiveness in fighting COVID-19 pneumonia but it can be used as a potential therapeutics in the treatment of COVID-19 [65].

Conclusion

In conclusion, the challenges to date facing the world are to identify a specific treatment of the novel coronavirus (COVID-19) as there are no proven effective vaccines or therapeutic agents against the virus. Several clinical trials have been explored some are on progress while some are not yet explored to evaluate the efficacy and safety of different cytokine therapies in the management and treatment of COVID-19 and associated cytokine storm syndrome, some of which have yielded positive results. Cytokine inhibitor or antagonists tocilizumab, Siltuximab, Canakinumab, etanercept, and Baricitinib have being administered either alone or in combinations with other anti-viral drugs and they have yielded positive results in management and treatment of COVID-19, while sarilumab, Anakinra, adalimumab, Tofacitinif, and Ruxolitinib currently clinical trials are on progress to evaluate their effectiveness in management and treatment of COVID-19 pneumonia while in the case of infliximab, golimumab, Certolizumab, Upadacinib, and Fedratinib are not yet explored and therefore, clinical trials should be initiated to evaluate their efficacy and safety in the management of the novel coronavirus.

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Conflict of Interest

Nil.

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