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Treatment of The Cytokine Storm in COVID-19: Review of Clinical Pharmacology

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ABSTRACT: The cause of the COVID-19 pandemic can be attributed to the Acute Respiratory Syndrome Virus-2 (SARS-CoV-2). COVID-19 manifests with severe symptoms in the upper respiratory tract and can progress to a critical condition due to an acute hyperinflammatory response that triggers a cytokine storm. The cytokine storm refers to an excessive or impaired production of proinflammatory cytokines, resulting in immune dysregulation and uncontrolled inflammatory activity. To effectively address the hyperinflammatory state induced by SARS-CoV-2 infection, it is imperative to explore promising strategies aimed at overcoming the cytokine storm, such as the prompt initiation of anti-inflammatory therapy. Several classes of drugs can potentially prevent the deterioration of COVID-19 patients by mitigating immune system dysregulation and suppressing uncontrolled inflammatory responses. These drug classes encompass corticosteroids, chloroquine and hydroxychloroquine, inhibitors of interleukin-1 (IL-1), inhibitors of interleukin-6 (IL-6), inhibitors of tumor necrosis factor (TNF), and anti-inflammatory drugs. Additionally, tumor necrosis factor alpha (TNF-α) inhibitors, as well as inhibitors targeting the Janus kinase signaling pathway and activator of transcription (JAK/STAT), have exhibited efficacy in treating COVID-19. This efficacy is evident when considering the drug's mechanism of action and pharmacokinetics, while also taking into account the tolerable side effects associated with their usage.

Keywords: **clinical pharmacology; COVID-19; coronavirus; cytokine storm; cytokine storm therapy.**

ABSTRAK: Pandemi COVID-19 disebabkan oleh novel corona virus, yang kemudian berganti nama menjadi severe acute respiratory syndrome virus-2 (SARS-CoV-2) .karena tanda dan gejala saluran pernafasan atas yang disebabkan oleh virus ini. Pada pasien COVID-19 yang parah hingga kritis terjadi respons hiperinflamasi akut yang menyebabkan terjadinya badai sitokin yang juga merupakan salah satu komplikasi yang terjadi pada pasien kritis yang terinfeksi SARS-CoV-2. Badai sitokin adalah pelepasan sitokin proinflamasi yang berlebihan atau tidak terkendali yang menimbulkan kekacauan sistem kekebalan dan respons peradangan yang tidak terkendali. Untuk memerangi kondisi hiperinflamasi yang diciptakan oleh infeksi SARS-CoV-2, jelas memerlukan strategi yang menjanjikan dalam mengatasi badai sitokin seperti inisiasi pemberian terapi anti inflamasi dengan cepat. Golongan pengobatan yang dapat digunakan untuk mencegah terjadinya keparahan pada pasien COVID-19, dengan mencegah terjadinya kekacauan sistem kekebalan dan respons peradangan yang tidak terkendali ini dapat menggunakan kortikosteroid, klorokuin dan hidroksiklorokuin, interleukin-1 (IL-1) inhibitors, interleukin-6 (IL-6) inhibitors, TNF-α (Tumour necrosis factor alpha) serta, inhibition of the JAK/STAT (Janus kinase signal transducer and activator of transcription) pathway. Obat-obat ini menunjukkan potensinya kemanjurannya dalam menangani keterparahan COVID-19 jika dilihat dari mekanisme aksi obat, farmakokinetik, serta efek samping yang dapat ditoleransi.

Kata kunci: **COVID-19; corona virus; badai sitokin; terapi badai sitokin; farmakologi klinis.**

Introduction

Cortikosteroid (CS)

Corticosteroids are therapeutic agents employed for the treatment of diverse inflammatory and autoimmune disorders owing to their immunosuppressive and anti-inflammatory properties [13]. In the context of COVID-19, these agents are administered to patients with severe acute respiratory distress syndrome (ARDS) and those experiencing cytokine storm syndrome, aiming to attenuate the systemic inflammatory response and mitigate the onset of ARDS [15].

The World Health Organization (WHO) recommends the use of corticosteroids in specific scenarios among COVID-19 patients. These include individuals with respiratory failure, hypoxemia, those requiring mechanical ventilation, and patients with asthma or acute exacerbation of chronic obstructive pulmonary disease (COPD). Furthermore, corticosteroid administration is indicated for COVID-19 patients with severe and critical clinical conditions exhibiting persistent fever (>39°C), CT scan findings indicating more

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than 50% organ damage within 48 hours due to infection, elevated plasma concentrations of inflammatory cytokines such as IL-6 exceeding five times the normal limits, and patients who demonstrate an inadequate response to anti-IL-6 treatment [16].

Mechanism of Action

Corticosteroids are a class of steroid hormones produced by the adrenal cortex, encompassing glucocorticoids and mineralocorticoids. These hormones are synthesized through the metabolism of cholesterol. The term "corticosteroid" pertains to agents possessing glucocorticoid activity that exert regulatory effects on numerous cellular functions, such as development, homeostasis, metabolism, cognition, and inflammation [17].

The glucocorticoid effects of corticosteroids are mediated through both genomic and non-genomic mechanisms [18]. In the genomic mechanism, corticosteroids diffuse across the cell membrane and bind to glucocorticoid receptors in the cytoplasm, forming a glucocorticoid receptor complex. This complex translocates into the nucleus and binds to glucocorticoid response elements, leading to the modulation of gene expression. By transactivation, the activated glucocorticoid receptor complex enhances the release of anti-inflammatory genes, while by trans-repression, it reduces the release of pro-inflammatory genes. This results in the modulation of transcription and subsequent production of RNA and proteins, influencing cellular processes. Corticosteroids inhibit transcription factors involved in the synthesis of pro-inflammatory mediators, including macrophages, eosinophils, lymphocytes, mast cells, and dendritic cells. They also inhibit phospholipase A2, which is responsible for the production of various inflammatory mediators. Additionally, corticosteroids inhibit genes responsible for the secretion of cyclooxygenase-2, the induction of nitric oxide synthase, and pro-inflammatory cytokines such as tumor necrosis factor alpha and interleukins. It should be noted that corticosteroids can induce the upregulation of lipocortin and annexin A1 proteins, which reduce prostaglandin and leukotriene synthesis, inhibit cyclooxygenase-2 activity, and decrease neutrophil migration to inflammatory sites. Importantly, the intracellular nature of corticosteroid action allows these effects to persist even in the absence of detectable plasma levels[17,18].

The non-genomic effects of glucocorticoid action can occur through direct interactions with intracellular or membrane-bound glucocorticoid receptors, altering the physicochemical properties of cell membranes and subsequently inhibiting inflammatory cell functions [18].

Pharmacokinetic

Corticosteroids are steroid hormones that are synthesized and released by the adrenal glands in response to adrenocorticotropic hormone from the pituitary gland, which is regulated by corticotropin-releasing hormone from the hypothalamus. The adrenal cortex produces two primary corticosteroids: cortisol (a glucocorticoid) and aldosterone (a mineralocorticoid). Aldosterone plays a role in regulating sodium and water balance, while cortisol acts by inhibiting the release of inflammatory mediators [19].

In men, cortisol is secreted at a rate of approximately 15 to 20 mg per day, while women generally exhibit cortisol levels approximately 10% lower. Additionally, corticosterone, a corticosteroid hormone that serves as an essential intermediate in the synthesis of aldosterone from pregnenolone, is secreted at a rate of approximately 4 mg per day. Stimulation of adrenocorticotropic hormone (ACTH), which is produced by the anterior pituitary gland and regulated by the hypothalamic-pituitary axis to control cortisol and androgen production, can lead to an increase in corticosterone secretion of up to 40 mg per day [20–22].

Corticosteroids undergo enzymatic conversion to metabolites with reduced physiological activity and increased water solubility, facilitating their excretion in urine. The liver is the primary site for corticosteroid metabolism, and individuals with liver disease may exhibit elevated levels of free hormones due to impaired corticosteroid metabolism and altered serum steroid-binding proteins. While urinary excretion of cortisol is relatively low, approximately 100 μg/day, owing to significant reabsorption (80-90%) of filtered cortisol, this reabsorption predominantly occurs in the distal tubules of the kidneys. In contrast, conjugated metabolites of corticosteroids are filtered and excreted without significant reabsorption. Over 90% of secreted glucocorticoids are ultimately eliminated via urine, whereas less than 10% of secreted aldosterone is excreted in its free form in urine, with the majority excreted as glucuronide derivatives [21].

In plasma, cortisol is transported in three distinct forms: free cortisol, protein-bound cortisol, and cortisol metabolites. Approximately 80% of cortisol in circulation binds to cortisol binding globulin or albumin due to its lipophilic nature, while 5% circulates in an unbound form. In the presence of inflammation, the binding affinity of cortisol decreases, leading to an increase in the concentration of free cortisol to counteract the active inflammatory process. Conversely, during pregnancy,

there is a significant rise in the plasma level of cortisol binding globulin. Corticosteroid therapy or synthetic corticosteroids also bind to cortisol binding globulin, although their binding efficiency is lower compared to native cortisol [21,23].

The systemic corticosteroid drug class can be categorized into three classes based on their anti-inflammatory potency, mineralocorticoid potency, and duration of hypothalamic-pituitary axis suppression. These classes are referred to as short-acting (e.g., hydrocortisone), intermediate-acting (e.g., prednisone, prednisolone, methylprednisolone), and long-acting (e.g., dexamethasone) corticosteroids, as presented in Table 1 [17,19,23].

Adverse Drug Reaction

While corticosteroids are commonly utilized in the treatment of individuals with inflammatory and immune disorders, it is important to note that these drugs are not without potentially serious adverse effects. Particularly in patients with chronic diseases or those receiving high doses of corticosteroids, their impact extends to various organ systems and metabolic processes within the human body [17].

The gastrointestinal system is the most commonly affected by adverse drug reactions associated with corticosteroid use, accounting for 45.8% of reported cases. Examples of such reactions include stomatitis, nausea, vomiting, diarrhea, abdominal pain, and bloating. The cardiovascular system is affected in 18.6% of cases, leading to manifestations such as swelling and hypertension. Adverse reactions involving the psychiatric system account for 8.5% and may present as irritability, insomnia, anxiety, and psychosis. Dermatological reactions comprise 8.5% of cases, while metabolic, endocrine, musculoskeletal, and nervous system involvement accounts for 3.4%, 5.1%, 6.8%, and 3.4%, respectively [24].

In addition, the use of corticosteroids is associated with various side effects, including the following: (1) Glucocorticoid-induced osteoporosis, which occurs due to the activation of osteoclasts and a decrease in the function and number of osteoblasts and osteocytes [19,25,26] (2) Steroid-induced myopathy, characterized by reversible muscle damage that can affect the upper and lower extremities in individuals using high doses of glucocorticoids over an extended period [27] (3) Osteonecrosis of the femoral head, which may develop in conjunction with secondary hip osteoarthritis, trauma, or other nontraumatic factors unrelated to steroid treatment [28], (4) Metabolic side effects, such as hyperglycemia, hypertension, hyperlipidemia, and weight gain [29,30], (5) Growth retardation and delayed puberty in young children due to the chronic use of glucocorticoids for conditions like nephrotic syndrome and asthma [19], (6) Increased susceptibility to serious bacterial infections and opportunistic infections in individuals receiving corticosteroid treatment [31], (7) Dermatologic side effects, including ecchymosis, skin thinning and atrophy, acne, mild hirsutism, facial erythema, striae, impaired wound healing, hair thinning, and perioral dermatitis [19] (8) Major ocular side effects associated with corticosteroid use, such as steroid-induced glaucoma, cataract formation, delayed wound healing, and increased susceptibility to infections [32] (9) Gastrointestinal side effects, such as gastritis, peptic ulcer formation, and gastrointestinal bleeding [19] (10) Acute neuropsychiatric side effects,

Table 1. Corticosteroid groups and their pharmacokinetics [17,19,23]

Cortikosteroid	Equivalent glucocorticoid dose (mg)	Anti-inflammatory potential (relative)	Mineralcorticoid potency (relative)	Duration of effect
Short acting				
Hydrocortison	20	1	1	8-12
Cortisone acetate	25	0.8	0,8	
Intermediate acting				
Prednisone	5	4	0,8	12-36
Predinisolone	5	4	0,8	12-36
Methylprednisolone	4	5	0,5	12-36
Long acting				
Dexamethasone	0.75	25	0	36-54

including behavioral symptoms such as mania, agitation, depression, manic behavior, anxiety, delirium, mood lability, insomnia, dementia, and even overt psychosis, can occur as a result of glucocorticoid use [33].

Clinical Study in COVID-19

The administration of corticosteroid therapy in the context of COVID-19 is predicated on its ability to curb excessive inflammation or cytokine storms observed in affected patients. A clinical study conducted by Wu et al. provides support for the effectiveness of corticosteroids in the management of COVID-19 patients. The study involved 201 patients with a mean age of 51 years (interquartile range, 43-60 years), of whom 128 (63.7%) were male. Notably, the study revealed that the utilization of methylprednisolone significantly reduced the risk of mortality (hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.20-0.72), even among patients with a higher Pneumonia Severity Index grade as compared to those who did not receive methylprednisolone [34].

A meta-analysis encompassing 44 trials and a total of 20,197 COVID-19 patients was conducted to assess the effects of corticosteroid use. The findings of this study revealed several beneficial outcomes, including a 22.4% reduction in mortality among hospitalized COVID-19 patients compared to standard care (17.0%). Additionally, corticosteroid use exhibited favorable effects in terms of ventilator freedom and reduced time on mechanical ventilation. Nevertheless, it is important to note that the use of corticosteroids may potentially lead to delays in viral clearance and an increased risk of infectious complications [35].

The early administration of corticosteroids in patients with pneumonia caused by SARS-CoV-2 infection resulted in a 5% reduction in mortality. However, the use of corticosteroids did not have a significant impact on the risk of ICU admission, duration of hospitalization, placement of endotracheal tubes, or the need for mechanical ventilation [36]. These findings are further supported by a meta-analysis that examined the safety and efficacy of corticosteroids in SARS-CoV-2, SARS-CoV, and MERS-CoV infections, assessing parameters such as mortality, duration of hospitalization, ICU admission rate, and use of mechanical ventilation. The meta-analysis revealed that corticosteroid use led to a delay in viral clearance, with a mean difference of 3.78 days (95% confidence interval [CI] = 1.16, 6.41 days), but did not show a significant reduction in mortality, with a relative risk ratio of 1.07 (90% CI = 0.81; 1.42). Furthermore, corticosteroid administration was associated with prolonged hospital stay and an increased utilization of mechanical ventilation [37].

Therefore, while the use of corticosteroids can provide benefits in certain patients who exhibit an exaggerated inflammatory response, it is important to note that corticosteroid administration may also contribute to delayed viral clearance. Additionally, the evidence regarding the effectiveness of corticosteroids in improving survival, shortening hospital stays, reducing ICU admissions, and minimizing the need for mechanical ventilation remains inconclusive.

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine, known as antimalarial drugs, possess immunomodulatory properties that have been utilized in the treatment of COVID-19 infections. These drugs exert their effects through multiple mechanisms, including interference with the viral entry process. Specifically, they alter pH-dependent endosome-mediated viral endocytosis and inhibit SARS-CoV entry by modifying ACE2 receptor glycosylation and spike proteins. Furthermore, these drugs exhibit various other functions, such as: (1) modulation of the immune response by inhibiting cytokine production through TLR-7 and TLR-9 pathways, thereby reducing the secretion of pro-inflammatory cytokines including IL-6, TNF-α, IL-1, and IFN-γ; (2) impairment of lysosomal and autophagosomal functions; (3) inhibition of proteolytic processes and endosomal acidification; (4) interference with viral replication through post-translational modification of viral proteins and inhibition of viral particle binding to cellular receptors; and (5) blockade of viral-cell fusion and disruption of glycosylation of cellular receptors of SARS-CoV and ACE2 [15,38,39]

Mechanism of Action

Chloroquine was initially investigated during the SARS coronavirus epidemic in 2002-2003, where it demonstrated efficacy against the SARS-CoV virus. Notably, this virus shares a genetic sequence similarity of approximately 79% with SARS-CoV-2, commonly known as COVID-19 [40]. Hydroxychloroquine, a derivative of chloroquine, has shown improved inhibitory effects against SARS-CoV-2 [41,42] Moreover, hydroxychloroquine is more extensively utilized due to its higher water solubility, reduced toxicity, and improved long-term safety profile compared to chloroquine [43,44].

Chloroquine exerts its mechanism of action by impeding the binding of the virus to angiotensin-converting enzyme 2 (ACE-2) receptors, which are utilized by SARS-CoV-2 for cellular entry. This inhibition

occurs through the disruption of ACE2 receptor glycosylation [45]. Additionally, both chloroquine and hydroxychloroquine can hinder the function of sialic acid, particularly the 9-O-SIA variant [46]. Sialic acid serves as a receptor that facilitates the entry of SARS-CoV-2. Specifically, it binds to α2-6 linkage and α2-3 linkage sialic acid receptors expressed in the conjunctival and corneal epithelium, as well as in the nasolacrimal region where these receptors are present. This enables viral particles to enter host cells through the ocular route or respiratory tract via the nasolacrimal system [47].

Hydroxychloroquine exhibits the ability to mitigate cytokine storms through the inhibition of major histocompatibility complex (MHC) class II-mediated antigen processing and the release of autoantigens on T cells. Consequently, T cell activation is reduced, leading to decreased cytokine production by both T cells and B cells [48,49]. Furthermore, hydroxychloroquine can impact endosomal pH, influencing the function of toll-like receptors (TLRs). These receptors serve as mediators of inflammatory pathways within the intestine, playing a crucial role in linking innate and adaptive immunity in response to various ligands derived from pathogens [50]. The impact of hydroxychloroquine on TLRs results in the inhibition of TLR9 and TLR7 binding to their ligands and impedes DNA binding to cyclic GMP-AMP (cGAMP) synthase (cGAS). The latter is a stimulator of interferon 1 (IFN I) production via interferon regulatory transcription factor (IRF), thereby reducing the production of pro-inflammatory cytokines [51].

Pharmacokinetics

Hydroxychloroquine and chloroquine belong to the class of antimalarial drugs known as 4-aminoquinolines. These drugs possess weakly basic properties attributed to the presence of basic side chains in their chemical structures, enabling their accumulation within intracellular compartments. Hydroxychloroquine is administered in the sulfate form, whereas chloroquine is administered as its phosphate salt [51–54].

Hydroxychloroquine and chloroquine are absorbed in the upper gastrointestinal tract following oral administration of their respective dosage forms. The time required for oral absorption of hydroxychloroquine sulfate (200 mg) is approximately 0 to 0.85 hours (mean 0.43 hours) [55]. The oral absorption of both hydroxychloroquine (HCQ) and chloroquine (CQ) is generally considered to be good, with a bioavailability ranging from 0.7 to 0.8, except in cases of severe malnutrition, such as kwashiorkor [56].

Hydroxychloroquine and chloroquine exhibit a large volume of distribution, estimated to be around 800 L/kg, indicating their distribution in water-soluble compartments such as interstitial fluid and muscle [57]. These drugs have a half-life ranging from 40 to 50 days, and their blood clearance time is relatively low (e.g., hydroxychloroquine has a clearance time of 96 ml/min). Approximately 30% of these drugs bind to albumin, while around 40% bind to alpha1 glycoprotein. Moreover, there is differential binding based on stereoisomeric (R) and (S) metabolism, as well as strong binding to pigmented tissues and various cells, including mononuclear cells and muscle. Renal excretion plays a significant role, accounting for 40-50% of the elimination of these drugs [56].

Adverse Drug Reaction

Chloroquine and hydroxychloroquine are utilized in COVID-19 patients due to their immunomodulatory and antiviral properties; however, it is important to acknowledge the presence of several adverse effects associated with their use. Hydroxychloroquine generally exhibits better tolerability compared to chloroquine. Gastrointestinal (GI) disturbances such as nausea, vomiting, diarrhea, and abdominal discomfort are among the most commonly observed adverse effects of chloroquine and hydroxychloroquine [42,58]. Furthermore, long-term usage of these therapies can potentially lead to cardiomyopathy and retinal toxicity, whereas the risk of cardiomyopathy and retinopathy is significantly lower with short-term use [59].

According to a study conducted by Lane et al. in 2020, which investigated the safety of hydroxychloroquine alone and in combination with azithromycin during the widespread use in COVID-19 patients, it was found that short-term treatment with hydroxychloroquine was generally safe. However, when used in combination with azithromycin, it posed an increased risk of cardiovascular death within 30 days, as well as heart failure and chest pain/angina, possibly due to their synergistic effect on prolonging the QT interval. Furthermore, the use of hydroxychloroquine and/or chloroquine has been associated with the occurrence of cardiotoxic effects, including restrictive cardiomyopathy, dilated cardiomyopathy, cardiac rhythm disturbances related to QT interval prolongation, and cardiac conduction abnormalities such as bundle branch and atrioventricular block, as reported by other researchers [60–62].

Risk factors associated with the development of cardiotoxicity from chloroquine and hydroxychloroquine therapy include advanced age, female gender, prolonged duration of treatment (>10 years), high dosage, and

a history of pre-existing heart and kidney diseases. Consequently, additional diagnostic evaluations such as 2D echocardiography, cardiac magnetic resonance imaging (CMR), and endomyocardial biopsy are recommended to assess the occurrence of chloroquine and hydroxychloroquine-induced cardiotoxicity [61].

Prolonged use of chloroquine and hydroxychloroquine can lead to a serious side effect known as retinopathy. This retinopathy is attributed to the impact of these medications on lysosomal pH and function, phagocytosis of photoreceptor outer segments, disruption of lysosomal function within the retinal pigment epithelium (RPE), and impairment of autophagy in the RPE, ultimately affecting the stability and function of photoreceptor cell membranes. Unfortunately, there is currently no effective treatment available to restore vision in patients with retinopathy caused by chloroquine and hydroxychloroquine use. Therefore, management of this side effect primarily involves recognizing the occurrence of chloroquine and hydroxychloroquine retinopathy, discontinuing the medications, and seeking consultation with a rheumatologist for appropriate guidance and potential visual rehabilitation options as deemed necessary [63,64].

Special caution should be exercised in patients with established hepatic or renal impairment, as well as in those receiving medications that have the potential to harm these organs. Additionally, chloroquine and/or hydroxychloroquine use has been associated with the possibility of inducing severe hypoglycemia in individuals with diabetes who are concurrently taking hypoglycemic medications. Although infrequent, rare side effects such as bone marrow suppression or skeletal muscle weakness may also occur [65–67].

Clinical Study in COVID-19

To evaluate the antiviral effectiveness of chloroquine and hydroxychloroquine against SARS-CoV-2, several in vitro studies have been conducted using Vero E6 cells. These investigations have consistently demonstrated potent antiviral activity of both therapies [68–70]. In a study by Wang et al., Vero E6 cells infected with nCoV 2019 BetaCoV were treated with chloroquine, revealing its ability to effectively block SARS-CoV-2 infection at both the entry and post-infection stages. Thus, chloroquine exhibits antiviral properties suitable for prophylactic and therapeutic purposes [70]. While comparisons of in vitro antiviral potential between chloroquine and hydroxychloroquine have been conducted, differing findings have been reported. Some studies indicate that chloroquine possesses stronger antiviral activity against SARS-CoV-2 when compared to hydroxychloroquine, while others suggest the opposite, highlighting the stronger antiviral potential of hydroxychloroquine [68,69].

Chloroquine phosphate has demonstrated efficacy and safety in over 100 COVID-19 patients in China. It exhibited superior outcomes in terms of inhibiting pneumonia exacerbations, shortening disease duration, improving lung imaging findings, and promoting negative conversion of the COVID-19 virus. These findings have led to its recommendation in the Guidelines for the Prevention, Diagnosis, and Treatment of COVID-19-Induced Pneumonia issued by the National Health Commission of China [71]. Furthermore, a study by Gautret et al. in 2020 investigated the clinical and microbiological effects of hydroxychloroquine (HCQ) in combination with azithromycin in 80 relatively mild COVID-19 patients. The treatment involved HCQ 200 mg three times daily orally for 10 days, along with azithromycin 500 mg on the first day and 250 mg daily for four days. The results showed clinical improvement in all patients, except for one elderly patient who died and another who remained in intensive care. The treatment led to a rapid reduction in nasopharyngeal viral load, with 83% of patients testing negative on day 7 and 93% on day 8. Viral cultures from respiratory specimens were negative in 97.5% of patients by day 5. This therapeutic approach resulted in prompt patient discharge, with an average hospital stay of 5 days [72].

However, a study conducted by Group et al. in 2020 aimed to investigate the impact of hydroxychloroquine on hospitalized COVID-19 patients. The study revealed that among the group receiving hydroxychloroquine, 421 patients (27.0%) died within 28 days, while in the usual care group, 790 patients (25.0%) died (rate ratio, 1.09; 95% confidence interval [CI], 0.97 to 1.23; P=0.15). This suggests that patients treated with hydroxychloroquine were less likely to be discharged from the hospital alive within 28 days compared to the usual care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98). Moreover, the hydroxychloroquine group had a higher incidence of invasive mechanical ventilation or death (30.7% vs. 26.9%; hazard ratio, 1.14; 95% CI, 1.03 to 1.27) [73].

Interleukin-1 (IL-1) Inhibitors

In severe cases of COVID-19, acute respiratory distress syndrome (ARDS) can develop due to the excessive release of pro-inflammatory mediators. This process can lead to viral replication, lung injury, and potentially multi-organ failure [14]. Among the pro-inflammatory

cytokines involved, IL-1 plays a significant role. IL-1 consists of two distinct proteins, IL-1α and IL-1β, which contribute to the inflammatory response during infections and facilitate mechanisms such as fever and sepsis. IL-1 exerts its effects by binding to the IL-1 receptor (IL-1R), subsequently triggering transcription and activation of the NF-kB pathway, one of the key inflammatory pathways [74,75]. Several drugs targeting IL-1 have been approved, including anakinra, rilonacept, and canakinumab [76].

Mechanism of Action

Interleukin-1 (IL-1) is a proinflammatory cytokine that plays a crucial role in modulating pain sensitivity and reducing tissue damage. It is composed of two distinct genes, IL1A encoding IL-1α and IL1B encoding IL-1β. Both IL-1α and IL-1β bind to the same cell surface receptor known as IL-1 type 1 receptor (IL-1RI), which is widely expressed on various cell types. Binding of IL-1 to IL-1RI leads to the release of inflammatory mediators, chemokines, and other cytokines, contributing to the inflammatory response [77–80].

Anakinra functions by inhibiting the binding of IL-1α and IL-1β to the IL-1 receptor type 1 (IL-1RI), thereby preventing their interaction with the receptor [80–82]. Canakinumab, on the other hand, is a human monoclonal antibody that neutralizes IL-1β in the inflammatory cascade [80,81,83]. IL-1β is a key cytokine involved in the innate immune response, contributing to the production of cytokines, chemokines, and activation of macrophages [83]. It also promotes its own generation and plays a role in IL-6 production, leading to excessive inflammation, endothelial dysfunction, and potential myocardial injury [83,84]. Rilonacept, in contrast, is a soluble IL-1 receptor that binds to IL-1β, IL-1α, and IL-1Ra [80,81].

Pharmacokinetics

The IL-1 receptor signaling pathway plays a crucial role in the pathogenesis of various autoinflammatory and autoimmune diseases. Consequently, several therapeutic agents have been developed to specifically target the IL-1 receptor and modulate its signaling. Notable examples of these agents include anakinra, which is a recombinant IL-1 receptor antagonist, rilonacept, which is a soluble IL-1 receptor that has the ability to bind to IL-1β, IL-1α, and IL-1Ra, and canakinumab, which is a monoclonal antibody that effectively neutralizes IL-1β [85,86].

Anakinra is a protein with a relatively small molecular weight of 17,258 D, and it is produced through recombinant DNA technology using genetically modified Escherichia coli cultures. Being a non-glycosylated protein, anakinra exhibits limited distribution in the body due to its specific protein structure. Its molecular mass allows for easy filtration by the glomerulus and subsequent hydrolysis in the kidneys [87]. In patients with normal renal function, anakinra has a relatively short half-life of approximately 5 hours. However, in patients with end-stage renal disease, the half-life is approximately doubled compared to those with normal renal function, and the oral clearance (CL/F) is reduced by 75%. Therefore, a dose reduction is necessary for patients with significant renal impairment. Anakinra is typically administered once daily via subcutaneous injection at a dose of 100 mg. This dosing interval is much shorter compared to IL-1 inhibitors, reflecting the shorter half-life of anakinra. Notably, despite its relatively low molecular weight, anakinra cannot be effectively removed by dialysis [88].

In a study conducted by Chang et al., the pharmacokinetics of a single subcutaneous dose of 1 mg/kg anakinra were investigated in 15 Chinese patients with rheumatoid arthritis, of whom 12 were female. Following administration, the time to maximum plasma concentration (Tmax) ranged from 2.00 to 6.00 hours, with a mean value of 3.87 hours. The mean maximum plasma concentration (Cmax) was 687 ng/mL, with a standard deviation (SD) of 197 ng/mL. Subsequently, plasma concentrations declined, with a mean half-life (T1/2) of 3.76 hours (SD: 1.00 hours). The mean plasma clearance after dosing was 150 mL/min (SD: 52.1 mL/min) (Table 2). Furthermore, The pharmacokinetic values of Cmax, AUC0-∞, and CL/F were found to be comparable between Chinese and non-Chinese patients with rheumatoid arthritis [89].

Canakimumab, when administered via subcutaneous injection, exhibits a bioavailability of approximately 70% and a half-life of approximately 21-28 days. Being an antibody, its long half-life allows for dosing once a month or every two months. The typical subcutaneous dose of canakimumab is 150 mg [90]. In a study conducted by Wang et al., which employed a specific competitive ELISA method to analyze canakimumab, it was observed that a single subcutaneous dose of 150 mg in patients with cryopyrin-associated periodic syndromes (CAPS) resulted in a maximum serum concentration (Cmax) of 15.9 ± 3.52 μg/mL within approximately 7 days. The pharmacokinetic binding value of canakimumab was low, estimated to be 0.3 days−1. The absolute bioavailability of canakimumab derived from the NS0 cell line was calculated to be 63 ± 5%, while that from the Sp2/0 cell line was 70 ± 8%. The subcutaneous bioavailability of canakimumab is consistent with that of other IgG-type monoclonal antibodies, ranging from 63% to 70% [91]. Canakimumab has a

Table 2. Pharmacokinetics of anakinra [89]

Parameter	Mean (15 patient)	S.D.	CV(%)	Median	Range
Tmax (h)	3.87	1.60	41.3	3.00	2.00-6.00
Cmac (ng/ml)	687	197	28.6	719	372-968
T1/2 (h)	3.76	1.00	26.6	3.65	2.22-5.70
AUC0–last (ng h/ml)	7190	2440	33.9	7610	4050-13,700
AUC0–∞ (ng h/ml)	7250	2450	33.7	7650	4070-13.800
CL/F (ml/min)	150	52.1	34.8	147	60.3-226

Tmax: time at which Cmax was observed; Cmax: maximum observed concentration; T1/2: half-life associated with the terminal phase; AUC0–last: area under the concentration–time curve of time 0 to the last detectable concentration; AUC0–∞: area under the concentration–time curve of time 0 to infinity; CL/F: plasma clearance after s.c. administration.

molecular weight of approximately 150 kDa and exhibits a very small volume of distribution in adult CAPS patients after subcutaneous administration, with an average of 8.33 ± 2.62 L and a total Vss of approximately 6.0 L. Renal elimination of canakimumab is minimal due to its large molecular size, resulting in limited excretion through the kidneys. The majority of canakimumab elimination occurs through intracellular catabolism. Additional pharmacokinetic data for canakimumab in CAPS patients, based on non-compartmental analysis, include (1) average serum clearance after subcutaneous administration (CL/F) of 0.228 L/day, (2) average long elimination half-life (t1/2) of 26.1 days after a single subcutaneous dose, (3) serum clearance of 0.174 L/day, (4) 70% bioavailability, and (5) CL/F of 0.249 L/day [92].

Rilonacept exhibits slow absorption, with peak plasma concentrations achieved approximately 3 days after subcutaneous administration. The recommended dosing regimen for rilonacept is once weekly (160 mg via subcutaneous injection) due to its half-life of approximately 7.5 days. Rilonacept is eliminated by mononuclear phagocytes in the reticuloendothelial system, facilitated by its large molecular weight. The substantial size of rilonacept renders it non-dialyzable, obviating the need for dose adjustments in patients with end-stage renal disease undergoing dialysis [93]. In a study conducted by Radin et al., which examined the safety and pharmacokinetics of subcutaneous rilonacept in well-controlled patients with end-stage renal disease, the mean values for key pharmacokinetic parameters were as follows: Cmax, 17.2 mg/L; tmax, 2.80 days; t1/2, 7.63 days; and AUC0-∞, 199.3 d·mg/L [93].

Adverse Drug Reaction

Controlled studies of anakinra, canakinumab, and rilonacept have revealed a higher incidence of viral upper respiratory tract infections in patients compared to those receiving placebo. While upper respiratory tract infections are generally not life-threatening, it is crucial to closely monitor patients receiving biologic therapy, especially if there is concern about bacterial infections involving organisms like Streptococcus pneumoniae and Streptococcus aureus. It is worth noting that infection is a common adverse effect of biologic therapy [80,94]. Nevertheless, when compared to other biologic drugs, the use of these three IL-1 inhibitors has demonstrated a high level of safety in terms of susceptibility to potential infections. Additionally, local reactions at the injection site have been reported as a common side effect of these IL-1 inhibitors [95].

Anakinra, being a therapy that has been used and studied for a longer duration compared to rilonacept or canakinumab, has provided clearer insights into its limitations regarding infections. Based on the findings from anakinra studies, it is recommended not to initiate anakinra therapy in patients with active infections. Moreover, anakinra treatment should be discontinued if a serious infection or sepsis occurs during its use. Patients with a history of severe infection should exercise caution when using anakinra, and its use in individuals with a history of tuberculosis should be approached with caution as well. Similar considerations should be given to the use of rilonacept and canakinumab in relation to infections [95].

Clinical Study in COVID-19

During the COVID-19 pandemic, a subset of severe to critical COVID-19 patients exhibited circulatory disturbances, severe lung damage, multiple organ dysfunction, and heightened immune activity characterized

by elevated levels of interleukin (IL)-1, IL-6, granulocyte monocyte colony-stimulating factor (GM-CSF), interferon-γ-inducible protein 10 (IP-10), tumor necrosis factor-α (TNF-α), and other inflammatory cytokines. These immune responses were associated with unfavorable clinical outcomes [96–99]. Therefore, one potential therapeutic approach for COVID-19 patients, particularly those in severe to critical condition, could involve the use of IL-1 inhibitors such as anakinra, rilonacept, and canakinumab to suppress pro-inflammatory cytokines.

In the initial retrospective cohort study conducted in Italy, high-dose intravenous (IV) anakinra (5 mg/kg twice daily) was administered to patients with COVID-19, acute respiratory distress syndrome (ARDS), and hyperinflammation. The study showed that high-dose anakinra treatment resulted in a reduction in serum C-reactive protein levels and improved respiratory function in 21 out of 29 patients (72%). Moreover, the survival rate in the high-dose anakinra group was 90%, significantly higher than the standard of care group with a survival rate of 56% (p=0.009). Mechanical ventilation-free survival was also better in the anakinra group (72%) compared to the standard of care group (50%) (p=0.15). Notably, discontinuation of anakinra did not lead to a recurrence of inflammation. These findings indicate that high-dose anakinra treatment is safe and associated with comparable survival benefits and positive clinical outcomes in patients with COVID-19 [100]. Furthermore, the use of anakinra has been shown to significantly decrease the need for invasive mechanical ventilation in the intensive care unit and reduce mortality in severe COVID-19 patients, without causing serious side effects [101,102]. These observations suggest that anakinra may represent a safe and effective therapeutic option for the management of severe forms of COVID-19.

The initial retrospective analysis examined the use of canakinumab in ten patients (nine white males and one white female) with confirmed COVID-19, bilateral pneumonia, hyperinflammation (serum C-reactive protein ≥50 mg/L), and respiratory failure (requiring supplemental oxygen without invasive ventilation). The administration of canakinumab (single dose of 300 mg subcutaneously) was well tolerated, with no reported injection site reactions or systemic adverse events. Notably, canakinumab treatment resulted in rapid and significant reductions in serum C-reactive protein levels on days 1 and 3. Improvement in oxygenation was observed, as evidenced by an increase in the PaO2:FiO2 ratio from baseline to day 3 and day 7 post-treatment. Importantly, all patients were discharged alive without physical limitations due to COVID-19 or the need for oxygen therapy. Furthermore, none of the patients experienced neutropenia or sepsis, in contrast to patients who did not receive canakinumab but instead received hydroxychloroquine and lopinavir-ritonavir [103]. In addition, the efficacy of canakinumab was demonstrated even in elderly patients with severe cases of COVID-19, as it helped mitigate the high risk of multiorgan damage by restoring diuresis, improving the overall condition of the patients, and significantly reducing interleukin-6 (IL-6) and natural killer (NK) cell levels [104].

Rilonacept, an IL-1 inhibitor, has been widely utilized in the treatment of various inflammatory disorders, owing to its well-documented anti-inflammatory properties [105–107]. However, it is important to note that as of September 2021, the manufacturer of rilonacept has chosen to voluntarily withdraw the drug from the market due to commercial considerations [108].

Interleukin-6 (IL-6) Inhibitors

Tocilizumab, an antagonist of the interleukin-6 (IL-6) receptor, is commonly employed in the treatment of rheumatoid arthritis [39]. Its mechanism of action involves blocking IL-6 signaling to immune effector cells, leading to reduced immune activation and attenuation of the inflammatory response [109]. Given that COVID-19 patients often exhibit elevated serum IL-6 levels, tocilizumab has been incorporated into the management guidelines for COVID-19, particularly in cases of severe illness [15].

The recommended dose of tocilizumab is 4-8 mg per kilogram of body weight or a fixed dose of 400 mg diluted in 100 ml of 0.9% saline solution. In cases where the initial dose does not yield a satisfactory response, an additional dose may be administered at the same dose after 12 hours, but no more than two doses should be given. The maximum allowable single dose of tocilizumab is 800 mg [109].

In addition to tocilizumab, sarilumab is another interleukin-6 (IL-6) inhibitor. Sarilumab is an IgG1 monoclonal antibody that targets the IL-6 receptor (IL-6R) and disrupts the signaling pathway mediated by IL-6. Sarilumab has received approval from the U.S. Food and Drug Administration (FDA) for the treatment of patients diagnosed with rheumatoid arthritis [110].

Mechanism of Action

IL-6 plays a crucial role in the pathogenesis of cytokine storm syndrome observed in patients with COVID-19. Multiple studies have demonstrated elevated plasma concentrations of IL-6 in severe cases

of COVID-19, highlighting its significance [2,100-103]. Moreover, IL-6 has been implicated in the development of respiratory failure, acute respiratory distress syndrome, secondary infections, and mortality in individuals with COVID-19 [111].

IL-6 is produced by various cell types including monocytes, macrophages, T cells, B cells, epithelial cells, endothelial cells, and fibroblasts, in response to various stimuli [112]. IL-6 receptors exist in two forms: membrane-bound IL-6 receptors (mIL-6R) present on immune cells, and soluble IL-6 receptors (sIL-6R) generated through cleavage of mIL-6R [112–114]. IL-6 binds to these receptors, leading to the dimerization of glycoprotein 130 (gp130), a transmembrane protein, and subsequent activation of Janus kinases (JAKs) that initiate intracellular signaling, including mitogen-activated protein kinase (MAPK) signaling and signal transducer and activator of transcription (STAT) pathways [115]. The release of IL-6 is often accompanied by tumor necrosis factor α (TNFα), disrupting physiological homeostasis by promoting a shift toward proinflammatory conditions [116].

IL-6 inhibitors, such as toclizumab and sarilumab, are therapeutic agents that competitively block the binding of IL-6 to its receptor. Tocilizumab is a recombinant human monoclonal antibody, while sarilumab is a recombinant human IgG1 antibody. Both therapies function through the same mechanism of action, which involves targeting the IL-6 receptor protein responsible for immune system-induced inflammation and inhibiting the IL-6 signaling pathway [117].

Pharmacokinetics

Tocilizumab received FDA approval in 2010 for the treatment of rheumatoid arthritis (RA) and has subsequently been approved for RA and related conditions in over 75 countries. The approved administration route for toclizumab is intravenous (IV), with a recommended dosage of 4 mg/kg every 4 weeks. The dosage may be adjusted to 8 mg/kg based on the individual's clinical response [118].

Tocilizumab is a monoclonal antibody that acts by inhibiting interleukin-6 (IL-6) signaling. Monoclonal antibodies, characterized by their high molecular weight, are not metabolized by cytochrome P450 enzymes in the liver or eliminated by the kidneys [119]. Instead, these antibodies undergo proteolytic degradation at a site in rapid equilibrium with plasma, contributing to their clearance [120]. Due to their size and hydrophilicity, monoclonal antibodies have limited membrane transfer and are widely distributed throughout the body [121]. Clearance of monoclonal antibodies involves two main pathways. The first is linear clearance (CL), which occurs through proteolytic degradation. The second pathway involves target engagement, such as the binding of tocilizumab to IL-6R, followed by internalization and intracellular degradation [122].

According to the pharmacokinetic analysis conducted by Frey et al., a two-compartment structural model with parallel and nonlinear elimination (Michaelis-Menten) was identified in a cohort of 1793 patients with moderate to severe rheumatoid arthritis (RA). These patients received intravenous infusions of tocilizumab at doses of 4 or 8 mg/kg every 4 weeks as part of four phase III clinical trials. The analysis generated simulated steady-state mean and accumulation values for the area under the concentration-time curve (AUC), maximum serum concentration (Cmax), and minimum serum concentration (Cmin) of tocilizumab over a period of 48 weeks as shown in Table 3 [123].

The pharmacokinetics of toclizumab are not affected by age and race, and therefore, no dose adjustments are required based on these factors. However, a correlation has been observed between body surface area (BSA) and toclizumab clearance (CL), which also impacts linear CL [123]. This suggests that the main clearance mechanism of toclizumab occurs in tissues and involves catabolism by the reticuloendothelial system [124]. Furthermore, it has been observed that the clearance of tocilizumab is lower in women compared to men, which can be attributed to differences in body size. Consequently, there are variations in the values of AUC, Cmax, and Cmin between men and women. Additionally, the maximum elimination rate of tocilizumab is influenced by factors such as serum albumin levels, creatinine clearance, and smoking status. The maximum elimination rate decreases with lower serum albumin levels, increases with higher creatinine clearance, and is higher in smokers [123].

The pharmacokinetic parameters of sarilumab have been described in a study conducted by Christine et al., as shown in Table 4. The study investigated the pharmacokinetics of sarilumab after repeated dosing of 150 mg every 2 weeks and 200 mg every 2 weeks in two phase III studies. The findings showed that sarilumab pharmacokinetics are influenced by body weight, which in turn affects sarilumab clearance, the minimum steady state concentration following repeated doses, and the maximum concentration of sarilumab [125].

Adverse Drug Reaction

When considering the use of tocilizumab and sarilumab in COVID-19 patients, caution should be

Table 3. Simulated mean and accumulation ratios for AUC, Cmax, and Cmin following 48 weeks of tocilizumab treatment [123]

Parameter	Tocilizumab	
	4 mg/kg	8 mg/kg
Steady state, mean (SD)		
AUC ×103 , h·µg/mL	13 (5.8)	35 (16)
Cmax, µg/mL	88 (41)	183 (86)
Cmin, µg/mL	1.5 (2.1)	9.7 (11)
Accumulation ratios		
AUC	1.1	1.2
Cmax	1.0	1.1
Cmin	2.0	2.4

AUC: area under the serum concentration-time curve; Cmax: maximum concentration; Cmin: minimum concentration; SD: standard deviation

exercised, especially in patients who are immunosuppressed. This includes individuals who have recently received other biologic immunomodulating agents, as well as patients meeting any of the following criteria: (1) alanine transaminase levels exceeding 5 times the upper limit of normal, (2) high risk of gastrointestinal perforation, (3) presence of serious uncontrolled non-SARS-CoV-2 bacterial, fungal, or viral infections, (4) absolute neutrophil count less than 500 cells/µL, (5) absolute lymphocyte count less than 500 cells/µL, (6) platelet count less than 50,000 cells/µL, and (7) known hypersensitivity to tocilizumab or sarilumab [126].

Toclizumab, as an IL-6 inhibitor therapy, generally exhibits a favorable safety profile; however, there have been reports of certain adverse reactions associated with its use. Among a study population of 295 patients, the most commonly reported adverse reactions occurred in 77.3% of cases and included infections, hypersensitivity reactions, abnormal liver function tests, myocardial infarction, and bleeding [127]. Furthermore, a study conducted by Soin et al. comparing the tocilizumab group to the standard care group in terms of COVID-19 development on day 14 revealed additional adverse reactions associated with tocilizumab. These adverse reactions encompassed anaphylactic reactions, anaphylactic shock, renal failure, pulmonary fibrosis, drug-induced liver injury, pancreatitis, pancytopenia, serious infections, and hypersensitivity reactions [117,128].

The safety profile of sarilumab usage has raised concerns regarding the occurrence of secondary bacterial respiratory infections, respiratory failure, and neutropenia in patients treated with this therapy [129]. Other randomized controlled trials (RCTs) assessing the safety of sarilumab in COVID-19 patients have also reported an elevated incidence of liver function test abnormalities, serious bacterial and fungal infections, as well as common adverse events such as neutropenia, elevated alanine aminotransferase, injection site erythema, upper respiratory tract infection, urinary tract infection, and bronchitis when compared to placebo [130–132].

To mitigate the potential side effects of toclizumab, it is crucial to assess liver enzyme levels prior to initiating treatment, monitor neutrophil and platelet counts, evaluate cardiac and renal function, and exercise caution in patients with a risk of gastrointestinal perforation. Similarly, sarilumab should not be administered during active infection, and certain laboratory parameters, including neutrophil count, platelet count, liver enzymes, and lipid profile, should be regularly monitored. It is important to note that patients with absolute neutrophil counts below 2,000/mm3, platelet counts below 150,000/mm3, or liver enzymes exceeding 1.5 times the upper limit of normal should not initiate sarilumab treatment [117].

Clinical Study in COVID-19

On December 21, 2012, the Food and Drug Administration (FDA) granted approval for intravenous (IV) tocilizumab as a treatment for COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, such as non-invasive ventilation (NIV), mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [133,134].

In the absence of tocilizumab availability, sarilumab may serve as an alternative treatment option. According to the findings of the REMAP-CAP trial, both tocilizumab and sarilumab exhibit similar clinical benefits in terms of improving survival rates and reducing the duration of organ support [135,136]. Nevertheless, it is important to note that sarilumab should only be utilized when tocilizumab is unavailable or impractical, as the evidence supporting the use of tocilizumab is more substantial than that for sarilumab. Furthermore, it is worth mentioning that the currently approved dosage form for sarilumab in the United States is subcutaneous injectio [126].

TNF-α (Tumour Necrosis Factor Alpha) Inhibitors

TNF (tumor necrosis factor) is a pro-inflammatory cytokine that is produced by activated macrophages and plays a significant role in the inflammatory response, thereby contributing to the hyperinflammatory state observed in COVID-19. Furthermore, TNF induces the release of neutrophil extracellular traps (NETs), which in turn activate the thrombosis and coagulation cascade, ultimately leading to the formation of blood clots. Additionally, NETs induce cell death in the lung epithelium, resulting in alveolar damage and fibrosis in COVID-19 patients. It is important to note that the combined action of TNF and interferon (IFN)-γ leads to cell death characterized by pyroptosis, apoptosis, and necroptosis [137].

TNF inhibitor therapy encompasses adalimumab, infliximab, etanercept, and golimumab. These medications effectively inhibit the progression of a hyperinflammatory state in COVID-19 patients by suppressing the formation of neutrophil extracellular traps (NETs). Furthermore, TNF inhibitor therapy mitigates COVID-19-induced thrombosis, decreases the production of other proinflammatory cytokines such as IL-1 and IL-6, and attenuates pulmonary capillary leakage associated with COVID-19 [137,138].

Mechanism of Action

Macrophages play a crucial role in maintaining tissue homeostasis and serve as the frontline defense against various pathogens. They recognize pathogen- and damage-associated molecular patterns (PAMPs/DAMPs) through pattern recognition receptors (PRRs), which are present on their plasma membrane and within their intracellular compartments. Four major sub-families of PRRs include Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-leucine-rich repeat (LRR)-containing receptors (NLRs), retinoic acid-inducible gene 1 (RIG-1)-like receptors (RLRs; also known as RIG-1-like helicases-RLH), and C-type lectin receptors (CLRs). Upon activation of these PRRs, macrophages produce the pleiotropic cytokine tumor necrosis factor-alpha (TNF). TNF exerts its effects on various cell types, including macrophages themselves. It induces macrophage inflammatory activity while also regulating macrophage survival and death. TNF binds to two different types of receptors expressed by macrophages, namely TNF receptor-1 (TNFR1) and TNF receptor-2 (TNFR2). Activation of these receptors triggers multiple signaling pathways, including the activation of transcription factors (such as nuclear factor-κB), proteases (caspases), and protein kinases (such as c-Jun N-terminal kinase and MAP kinase). Consequently, these signaling events lead to the activation of target cells, eliciting inflammatory and immune responses characterized by the release of various cytokines and the initiation of apoptotic pathways. The biological effects of TNF encompass the activation of other cells, such as macrophages, T cells, and B cells, as well as the production of proinflammatory cytokines (e.g., IL-1, IL-6) and chemokines (e.g., IL-8, RANTES). TNF also promotes the expression of adhesion molecules (e.g., ICAM-1, E-selectin), inhibits regulatory T cells, upregulates RANK ligand, facilitates the production of matrix metalloproteinases, and induces apoptosis [139–141].

Table 4. Model-estimated sarilumab steady-state exposure [125]

Parameter, mean ± SD	Sarilumab 150 mg	Sarilumab 200 mg
AUC0–14d (day·mg/L)	202±120	395±207
Ctrough (mg/L)	6.35±7.54	16.5±14.1
Cmax (mg/L)	20.0±9.20	35.6±15.2

AUC0–14d : area under the serum concentration-time curve of 0-14 days; Cmax: maximum concentration; Ctrough: plasma trough concentrations

Tumor necrosis factor (TNF) is a key player in inflammatory conditions and its excessive production contributes to pathogenesis. The administration of TNF antagonists aims to reduce the levels of TNF in circulation and at the site of inflammation. TNF is predominantly generated by activated macrophages.

Pharmacokinetics

The absorption of TNF inhibitors is dependent on the route of administration. Infliximab is administered intravenously, allowing for complete drug entry into the systemic circulation and minimizing interpatient variability. Intravenous infusion preparations may sometimes trigger reactions, and pretreatment with antihistamines, acetaminophen, and corticosteroids can be employed to prevent these reactions. On the other hand, adalimumab, golimumab, and certolizumab pegol are administered via subcutaneous injection. As a result, the quantity of drug that can be delivered through these preparations is limited, and the extent of absorption may vary among individuals [141,142].

Adalimumab is a TNF inhibitor therapy that is administered subcutaneously. It follows a multiple-dose regimen, with evenly spaced doses administered once or twice per week. Etanercept, another TNF inhibitor, is also administered subcutaneously, either twice-weekly or once-weekly. Infliximab, on the other hand, is administered via short intravenous infusion lasting 2 hours. It requires a loading dose regimen during weeks 0, 2, and 6, followed by a single maintenance dose with dosing intervals of 4 or 8 weeks [143,144].

TNF inhibitors are distributed in extracellular fluids prior to entering cells, and this distribution is influenced by the specific characteristics of each drug, such as molecular weight and water solubility. In the case of infliximab, which is administered intravenously in high doses, the blood concentration reaches a peak and then rapidly decreases until the next dose is administered. Conversely, when adalimumab, golimumab, or certolizumab pegol are injected subcutaneously, the drug concentration remains relatively consistent over time. This is due to the slower absorption and elimination of the drug following subcutaneous injection, resulting in a more uniform concentration profile [145].

The volume of distribution at steady state is an important pharmacokinetic parameter that characterizes the distribution of a drug within the body, and it is closely related to the total amount of drug present in the body in relation to the plasma concentration at a given time [146]. Among TNF inhibitors, infliximab has the lowest volume of distribution, ranging from 3 to 5 liters. This indicates that infliximab is primarily distributed within the blood circulation and shows limited distribution to extravascular tissues. Consequently, a lower dose of infliximab is required to achieve a desired plasma concentration due to its tendency to remain in the plasma. Golimumab also has a volume of distribution of less than 5 liters. On the other hand, other TNF inhibitors such as adalimumab have slightly higher volumes of distribution, ranging from 4.7 to 6 liters, while etanercept exhibits the highest volume of distribution, ranging from 7 to 12 liters, with a 60% bioavailability. The higher volume of distribution for adalimumab and etanercept suggests that these drugs have a greater tendency to distribute beyond the plasma into tissues and extravascular fluid. Consequently, a higher dose is required to achieve a desired plasma concentration [144,146].

The primary mechanism of clearance for monoclonal IgG, including anti-TNF agents, is intracellular degradation [147]. Due to their high molecular weight, TNF inhibitors and antibody derivatives are not cleared through the kidneys as they have limited glomerular filtration [119]. Table 5 provides a summary of the pharmacokinetic properties of TNF inhibitors [148].

Adverse Drug Reaction

The adverse effects of TNF inhibitors are typically mild and do not necessitate discontinuation of the medication. However, serious infections are known to occur and require careful monitoring. Common adverse effects of TNF inhibitors, observed in more than 10% of patients, encompass headache, injection site reactions following subcutaneous administration, infusion reactions following intravenous administration, rash, anemia, mild transaminitis, upper respiratory tract infection, sinusitis, cough, pharyngitis, diarrhea, nausea, and abdominal pain [141].

Due to the potential side effects associated with TNF inhibitors, it is crucial to conduct laboratory monitoring to detect signs of infection before, during, and after treatment. Complete blood count should be performed at the initiation of treatment, followed by regular monitoring at intervals of at least every 3 to 6 months [149,150]. It is important to note that TNF inhibitors should not be administered to patients receiving live immunizations due to the risk of serious infectious complications associated with these medications. Furthermore, the use of TNF inhibitors poses an increased risk for patients undergoing major surgeries such as hip or knee replacement. In such cases, the administration of TNF inhibitors should be

Table 5. Pharmacokinetic properties of TNF inhibitors [148]

Sampel Sampel	Pharmacokinetics			Dosing	
	Half-life (days)	Clearance (ml/h)	Volume of distribution (l)	Administration	Frequency
Adalimumab	14 (10-20)	12	4.7-6	subcutaneous	2 weeks
Certolizumab pegol	14	17	6.4	subcutaneous	2 or 4 weeks
Etanercept	4.25	6.7	6–18	subcutaneous	Once a week or two
Golimumab	14	4.9–6.7	~5	subcutaneous	1 month
Infliximab	7.7-9.5	5.4	~5	subcutaneous	6-8 weeks

temporarily discontinued one week before the surgery, including one full dosing cycle, and resumed two weeks after the surgery, provided that there is no ongoing infection and the surgical incision is healing properly [151].

Anti-tumor necrosis factor (anti-TNF) agents should not be administered to patients with a history of hypersensitivity reactions to these agents. Furthermore, caution should be exercised when using this therapy in patients receiving ongoing treatment for New York Heart Association (NYHA) Class III or IV congestive heart failure, as it may not be recommended. While conventional nonbiologic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine can be used in combination with anti-TNF agents, concurrent use of anti-TNF agents with other biologic immunosuppressive agents is contraindicated [141].

Clinical Study in COVID-19

COVID-19 patients experience a heightened inflammatory response and cytokine storm, which can lead to extensive tissue damage and mortality. The TNF-α pathway plays a significant role in tissue necrosis and cytokine storms associated with COVID-19 [152]. The intervention of blocking this TNF-α-mediated inflammatory cell death pathway aims to mitigate the extent of tissue damage inflicted.

A case-control study conducted by Salesi et al. examined COVID-19 patients, a small subset of whom received treatment with TNF-α blockers (5.22%, 6/115), while the majority did not receive such treatment (27.34%, 38/139). The study revealed that the use of adalimumab, infliximab, and etanercept therapy significantly reduced the risk of developing COVID-19 by 96.8%, 95%, and 80.3% respectively ($p < 0.05$). This study indicates that TNF-α inhibitors have the potential to reduce the incidence or improve the course of COVID-19 disease [153]. Furthermore, the use of TNF-α inhibitors has been associated with a lower likelihood of hospitalization in severe COVID-19 patients, as demonstrated in a systematic review with meta-analysis conducted by Kokkotis et al., which compared TNF-α inhibitors with other treatments for underlying inflammatory conditions [154].

While TNF inhibitors have shown beneficial effects in COVID-19 patients and are generally considered safe, caution is warranted regarding the safety implications of these drugs due to their immunosuppressive properties.

Inhibition of The JAK/STAT (Janus Kinase Signal Transducer and Activator of Transcription) Pathway

The binding of COVID-19 to angiotensin II (Ang II) activates the JAK/STAT pathway in various cells and tissues, including the cardiovascular system, renal proximal tubule cells, mesangial cells, brainstem astrocytes, and hepatocytes. This signaling cascade leads to enhanced immune cell infiltration and upregulation of proinflammatory cytokines such as TNF-α, IL-1, IL-6, and interferon (IFN)-γ in the affected tissues [155].

JAK/STAT pathway inhibitors such as tofacitinib, ruxolitinib, and baricitinib have been shown to exert multiple effects in the context of COVID-19. Apart from non-selectively suppressing the activation of numerous cytokines, these inhibitors also inhibit the early entry of SARS-CoV-2 during infection. Additionally, they target AP2-associated protein kinase-1 (AAK1), which is involved in mediating the endocytosis and intracellular transport of SARS-CoV-2 through ACE-2 receptors, thus impeding viral entry into the body [155].

Mechanism of Action

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway plays a critical role in cellular functions, serving as a central communication node. This pathway encompasses a wide

array of cytokines, growth factors, hormones, interferons (IFNs), interleukins (ILs), and colony-stimulating factors, totaling over 50 signaling molecules [156].

The activity of cytokines within the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway is initiated through their binding to specific receptors located on the cell membrane. Signal transduction within this pathway is mediated by two main subgroups of cytokine receptor interactions: the type I receptor group, which encompasses various interleukins, colony-stimulating factors, and hormones like erythropoietin, prolactin, and growth hormone, and the type II receptor group, which includes interferons and interleukin-10-related cytokines [157].

Janus kinases (JAKs) are a family of tyrosine kinase enzymes comprising four members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), as shown in Table 6. These JAK members selectively interact with the intracellular domain of cytokine receptors. JAK1 and JAK2 are involved in various processes, including host defense, hematopoiesis, neural development, and growth. In contrast, JAK3 and TYK2 have limited roles in immune responses [158].

The signaling cascade of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway begins with the binding of JAK to its respective receptor, leading to receptor activation and subsequent transphosphorylation on specific tyrosine residues, a process referred to as transactivation. This transphosphorylation creates a docking site for the recruitment of a latent cytoplasmic transcription factor called STAT [159]. Once phosphorylated and dimerized following JAK activation [160], the phosphorylated STAT dissociates from the receptor docking site and translocates into the nucleus. Inside the nucleus, it binds to specific DNA sequences to either activate or repress gene transcription, thereby regulating various cellular processes [159,161]. Mammals have multiple identified STAT proteins, including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6, each exerting distinct effects (see Table 6).

The JAK/STAT signaling pathway plays a crucial role in regulating a wide range of immunoregulatory

Table 6. Cytokines associated with Janus kinases and the Associated diseases [158,163]

JAK/STAT	Influenced signaling	Associated diseases
Janus kinase 1	IFNα/β, IFNγ, IL-2, IL-4, IL-7, IL-9, IL-21, sitokin famili IL-6, sitokin famili IL-10	• T and B cell acute lymphoblastic leukaemia • acute myeloid leukaemia • acute myeloid leukaemia with severe congenital neutropenia • activated B cell-like diffuse large B ce • lymphoma
Janus kinase 2	IFNγ, IL-3, IL-5, GM-CSF, EPO, TPO, G-CSF, GH, leptin	• polycythaemia vera • essential thrombocytosis • myelofibrosis • Hodgkin lymphoma • Down syndrome-associated B cell acute lymphoblastic leukaemia • primary mediastinal B cell lymphoma
Janus kinase 3	IL-2, IL-4, IL-7, IL-15, IL-21	• megakaryoblastic leukaemias
Tyrosine kinase 2	IFNα/β, IFNγ, IL-12, IL-23	• imunodefisiensi primer • Susceptibility to mycobacterial and viral infections • chronic mucocutaneous candidiasis
STAT1	Semua IFN	• Susceptibility to mycobacterial and viral infections • chronic mucocutaneous candidiasis
STAT2	IFN Tipe I	• Increased susceptibility to viral mutations due to deficiency
STAT3	Il-6 dan sitokin gp130 lainnya	• AD-HIES (Autosomal dominant hyper-IgE syndrome)
STAT4	IL-12, IL-23, interferon tipe I	• Rheumatoid atritis • Systemic lupus erythematosus (SLE)
STAT5a/STAT5b	IL-2, EPO, TPO, GM-CSF, GH, IL-7	• Deficiency causes autoimmunity, bleeding diathesis, immunodeficiency, and stunting
STAT6	IL-4, IL-13	• Asthma Symptoms • Atopy • Elevated IgE levels

processes, including hematopoiesis, immune function, tissue repair, inflammation, apoptosis, and adipogenesis [162]. Inhibition of this pathway has been achieved through various therapeutic approaches, such as the use of tofacitinib, ruxolitinib, and baricitinib. Tofacitinib selectively inhibits Janus kinases 1 and 3, with some inhibitory effect on Janus kinase 2, while having minimal impact on tyrosine kinase 2 [158,163]. On the other hand, both baricitinib and ruxolitinib target and inhibit Janus kinases 1 and 2 [163]. By blocking the activity of Janus kinases, these medications interfere with signaling pathways activated by various cytokines and hematopoietic growth factor receptors, thereby modulating the immune response [164].

Pharmacokinetics

Tofacitinib is a novel Janus kinase inhibitor administered orally. After oral administration, tofacitinib is rapidly absorbed, reaching peak plasma concentrations approximately 1 hour later, with a mean terminal half-life of approximately 3.2 hours. The majority (69.4%) of the drug remains in its parent form in the plasma, while each metabolite represents less than 10% of the total concentration. Hepatic clearance accounts for approximately 70% of the total clearance, while renal clearance contributes to the remaining 30%. Tofacitinib undergoes several metabolic pathways, including oxidation of the pyrrolopyrimidine and piperidine rings, side-chain oxidation of the piperidine ring, N-demethylation, and glucuronidation. The primary metabolic enzymes involved in tofacitinib metabolism are CYP3A4, with a minor contribution from CYP2C19, as determined by the cytochrome P450 (P450) profile [165]. The mean pharmacokinetic parameters (standard deviation) of tofacitinib are presented in Table 7.

Ruxolitinib demonstrates favorable absorption with a high bioavailability of 95%, and approximately 97% of the drug binds to albumin. The mean maximum concentration (Cmax) of ruxolitinib (immediate release tablets) is achieved within 1 to 6 hours, with an absorption rate constant (Ka) of 3.43 hours -1. The volume of distribution of ruxolitinib differs between men and women, possibly attributed to differences in body weight. The liver, primarily through the action of CYP3A4, is responsible for the main metabolism of ruxolitinib. Consequently, alterations in CYP3A4 activity due to inducers or inhibitors may impact ruxolitinib metabolism. Ruxolitinib is primarily eliminated through the kidneys. Therefore, patients with hepatic or renal impairment may experience changes in various pharmacokinetic parameters of ruxolitinib and may require dosage adjustments [166,167].

Adverse Drug Reaction

Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways play a crucial role in modulating the immune response. However, the alteration of immune response through these pathways can lead to an increased susceptibility to severe bacterial, fungal, mycobacterial, and viral infections, including opportunistic infections such as tuberculosis and non-spreading herpes zoster. The elevated infection risk is associated with a reduction in natural killer (NK) cell function resulting from the inhibition of Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3) [157]. Furthermore, the use of JAK/STAT inhibitors may also elevate the risk of developing cancer due to the blocking effect on interferon and natural killer cell activity. Activation of Janus kinase occurs through erythropoietin and colony-stimulating factor signaling pathways. Inhibition of Janus kinase 2 (JAK2) leads to anemia, neutropenia, and thrombocytopenia as a consequence of its inhibition [163].

Clinical Study in COVID-19

The inhibition of the JAK/STAT pathway represents a promising approach to mitigate the progression of COVID-19. However, caution must be exercised when using these inhibitors for prolonged durations, as they may disrupt the immune response and potentially facilitate the proliferation of SARS-CoV-2. The effectiveness of JAK/STAT pathway inhibition in reducing hyperinflammatory states, rather than promoting viral clearance, has been demonstrated in a study conducted by Rojas and Sarmiento. Their findings revealed that the administration of ruxolitinib to patients with severe hyperinflammatory COVID-19 and hematologic disorders resulted in rapid improvement and subsequent discharge of the patients [168].

In a randomized controlled phase II trial conducted by Cao et al., the efficacy and safety of ruxolitinib, a JAK 1 and JAK 2 inhibitor, were evaluated in patients with severe coronavirus disease. Although treatment with ruxolitinib in combination with standard care did not lead to significantly accelerated clinical improvement, patients who received ruxolitinib exhibited a trend towards faster clinical improvement. Furthermore, the ruxolitinib group showed significant reductions in the levels of seven cytokines, including interleukin-6 (IL-6), nerve growth factor β (NGF-β), interleukin-12 (IL-12) (p40), macrophage migration inhibitory factor (MIF), MIP-1α, macrophage inflammatory protein 1β (MIP-1β),

Table 7. Pharmacokinetics of tofacitinib [165]

	T max	Cmax	AUC 0-last	AUC 0-∞	t1/2
Tofacitinib	1.1 (0.5) h	397 (62) ng/ml	1,670 (381) ng*h/ml	1,680 (380) ng*h/ml	3.2 (0.6) h

and vascular endothelial growth factor (VEGF), when compared to the control group [169].

Result and Discussion

Cytokine storm, characterized by an excessive and uncontrolled inflammatory response, is a major contributor to the development of acute respiratory distress syndrome (ARDS), multiple organ failure, and mortality in COVID-19 patients. This systemic inflammatory response is triggered by the overactivation of immune cells and the excessive production of pro-inflammatory cytokines, leading to immune system dysregulation and uncontrolled inflammation [170,171]. Several laboratory biomarkers, including interleukin-6, ferritin, leukocytes, neutrophils, lymphocytes, platelets, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase, aspartate aminotransferase, creatinine, and D-dimer, serve as important indicators of cytokine storm in COVID-19 cases [172]. In a study by Cappanera et al., a rapid scoring system was proposed to identify COVID-19 patients in the early stages of cytokine storm. This scoring system utilizes the presence of lymphopenia accompanied by elevated levels of D-dimer (>1000 ng/mL), lactate dehydrogenase (>300 IU/L), ferritin (>600 ng/mL), and/or CRP (>10 mg/dL) as criteria. By identifying these patients promptly, appropriate interventions such as immunomodulators, corticosteroids, and cytokine antagonists can be administered in a timely, safe, and effective manner to prevent disease progression and reduce mortality [173].

However, there is significant concern regarding the use of anti-inflammatory drugs, such as corticosteroids, as they may potentially prolong viral clearance and increase the risk of secondary infections, particularly in patients with pre-existing immune disorders. Moreover, the efficacy of biological agents targeting specific pro-inflammatory cytokines is limited, as they only inhibit specific inflammatory factors and may not effectively control the overall cytokine storm in COVID-19, where multiple cytokines are involved. Additionally, certain anti-inflammatory drugs like JAK inhibitors also suppress the production of important antiviral cytokines such as INF-α, which may reduce their effectiveness in treating viral-induced inflammatory cytokine storms, such as those seen in COVID-19 [13]. Therefore, careful consideration of the selection and timing of anti-inflammatory therapies is crucial in COVID-19 patients. While this article has provided an overview of potential drug classes for cytokine storm management in COVID-19 patients, along with their mechanisms and side effects, it is important to note that this study is a qualitative analysis based on previous research. Future investigations should critically evaluate the existing literature addressing well-defined research questions in order to provide the most accurate and evidence-based recommendations for the management of cytokine storms in COVID-19 patients

Conclusion

Excessive inflammation and an exaggerated immune response can lead to a phenomenon known as a cytokine storm. This cytokine storm results in systemic inflammation, multi-organ damage, prolonged hospitalization, and even death if not properly managed. Therefore, in addition to antiviral therapy, the use of drugs to mitigate the cytokine storm plays a crucial role in the treatment of COVID-19 patients. There is substantial evidence supporting the efficacy of therapies aimed at reducing cytokine storms in the treatment of severe COVID-19 cases. This evidence demonstrates that inhibitors of interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), and the Janus kinase (JAK) pathway, as well as anti-inflammatory drugs including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and chloroquine/hydroxychloroquine, can effectively attenuate the damaging effects of cytokine storms, particularly in severe COVID-19 patients.

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