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Review

The Long Duration Consequence of Using Anti-inflammatory and Immunosuppressive Drugs in the COVID-19 Epidemic

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Abstract: The SARS-2 virus, responsible for the COVID-19 epidemic in early 2020, persists in posing a hazard to public health through the emergence of new mutations and surges in prevalence across several nations. Immunosuppressive medications treat both short-term and long-term inflammatory illnesses. The classification of these medications into various types is based on their action mechanisms. It is important to review the most recent data on the effectiveness and side effects of administering these drugs to patients because of the risk of severe inflammatory repercussions in COVID-19 patients, including acute respiratory failure and cytokine storm. This article presents accurate data on the advantages and disadvantages of using immunosuppressive medications in COVID-19 patients, while also providing a concise overview of the various types of these medications. Taken together, anti-inflammatory drugs and immune response inhibitors seem to be associated with better outcomes, such as shorter hospital stays and less need for mechanical ventilation, faster recovery from acute symptoms, and lower mortality rates, especially in the critically ill. However, one must consider the possibility of increasing treatment duration and vulnerability to fungal and bacterial infections. To minimize the negative effects of these medications, it is important to carefully balance their dosage and administration timing. Overall, the utilization of immunosuppressive medications, whether administered recently during illness or consistently for non-COVID-19 reasons, appears to have a beneficial impact on managing inflammation, expediting recovery, and decreasing mortality. However, it is crucial to exercise caution and avoid prescribing these drugs without proper consideration.

Keywords: Coronavirus; COVID-19; Immune System; Corticosteroid; Immunosuppression

1. Introduction

The SARS-2 virus, responsible for the COVID-19 epidemic in early 2020, persists in posing a hazard to public health through the emergence of new mutations and surges in prevalence across several nations [1]. Given the absence of a conclusive antiviral remedy for the SARS-2 virus and the ongoing debates on the efficacy of pharmaceuticals that hinder virus replication, especially in dealing with various strains, the focus of patient therapy has

transitioned towards maintenance techniques [2]. Countries located in the eastern and western regions of the world had minimal impact on the occurrence of diseases within communities. In contrast, the northern and southern areas have demonstrated their ability to accurately forecast disease epidemics. Preciously we reported that 2019-nCoV can remain viable for a maximum of 9 days when exposed to a temperature of 25°C. Nevertheless, if the temperature was above 30°C, its lifespan may decrease. Also, we found that the 2019-nCoV virus could be vulnerable to humidity, and it has a longer lifespan in conditions with 50% humidity compared to those with 30% humidity [3]. Temperature and humidity have a significant impact on determining COVID-19 mortality rates and may facilitate the transmission of the 2019-nCoV virus. According to current data, cold temperatures, together with dry and poorly ventilated air, seem to affect the stability and spread of 2019-nCoV [4]. Gathering comprehensive and precise medical records from individuals affected by COVID-19, and examining the Case Fatality Rate (CFR) in conjunction with the rate of recovery, could facilitate the pinpointing of regions with the greatest susceptibility, so enabling the provision of effective medical treatment. This could potentially result in the creation of point-of-care instruments that assist doctors in categorizing patients according to their specific care needs, hence enhancing the likelihood of survival from COVID-19 [5].

The primary problem lies in promptly identifying cases of COVID-19 infection in order to enhance illness management. Despite the high sensitivity of RT-PCR, studies have observed false-negative results in 20%–67% of infected patients. People commonly use Rapid Diagnostic Tests (RDTs) as a point-of-care assay to detect SARS-CoV-2 in pharyngeal and blood samples. The appeal of this option lies in its efficiency, affordability, and accessibility, but its key drawback is its limited sensitivity. Multiple studies have demonstrated that the quick testing of blood and pharyngeal samples has comparable sensitivity to RT-PCR. However, certain investigations have identified reduced sensitivity, particularly in asymptomatic individuals [6]. Individuals with weakened immune systems are more susceptible to severe illnesses, which in turn increases their risk of death. Some genes in the immune system, like human leukocyte antigen (HLA), inflammatory cytokines, and killer-cell immunoglobulin-like receptors, can change how the immune system responds to different pathogens. In COVID-19, a meta-analysis study demonstrates a significant association between HLA markers and both predictive biomarkers and mortality. However, a more formalized agreement is necessary to validate these findings. Planning new studies necessitates considering how to incorporate diseases with a poor prognosis, as they are associated with these immune genetic markers [7].

At now, the primary approach to managing COVID-19 pneumonia is ensuring the provision of oxygen to both hospitalized and non-hospitalized individuals. It is crucial to manage inflammation, specifically by taking measures to prevent the occurrence of cytokine storms in individuals who are impacted [8]. A significant number of patients, especially young persons with strong immune systems, succumbed to lethal shock and circulatory collapse as a consequence of acute and unregulated inflammation [9]. In contrast, administering high dosages of anti-inflammatory medications, with the intention of preventing cytokine storm, increased the incidence of secondary infections and led to the development of mucormycosis (black fungus) in individuals with weakened immune systems and diabetic patients [10]. Additionally, a substantial portion of the patients consist of individuals who regularly consume immunosuppressive medications as a result of chronic autoimmune disorders or organ transplants [11]. Furthermore, these individuals have a reduced likelihood of experiencing severe or fatal inflammation, in addition to an increased risk of viral infections. Nevertheless, they encounter difficulties in effectively controlling pulmonary pneumonia and completely eliminating infections in this specific group of patients [12]. To address these concerns, it is imperative to make accurate selections regarding the specific kind and amount of drugs administered to manage inflammation in COVID-19 patients, considering the potential adverse effects of anti-inflammatory and immunosuppressive medications, as well as the high expenses associated with particular drug categories. The objective of this review paper is to examine several classifications of immunosuppressive medications and their application in the treatment of COVID-19.

2. Methods

2.1. Search Strategy

We systematically searched electronic bibliographic databases including PubMed, Scopus, EmBase, ISI web of Science and Google Scholar from 1980 t0 2024. The keywords used were “COVID-19” OR “COVID-19” OR “SARS-CoV-

2" OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "COVID-19 pandemic" OR "Pandemic" OR "COVID*" OR "Coronaviru*" OR "SARS Coronavirus*" OR "SARS-COV*" AND "anti-inflammatory" OR "immunosuppressive" OR "treatment". Using a variety of synonyms, each term was accurately defined and modified for each database. With the right boolean operators (AND, OR) and Medical Subject Headings (MeSH) phrases, the search technique ensured comprehensive coverage by include relevant terms. The use of any language was free from limitation. In July 2024, prior to the final analysis, we conducted the searches again, which led to the inclusion of further papers. The selected valid articles were studied and summarized and then were used in the compilation of the text according to the sequence of drug classification.

2.2. Study Inclusion

The selection of studies for review was based on the qualifying criteria established by two independent investigators, FR and KD. We thoroughly deliberated on any discrepancies to reach a consensus, and consulted a third reviewer (TK) if necessary.

2.3. Data Extraction

The retrieved data includes information on the author(s), publication year, study country, study period, anti-inflammatory medicine used, type of immunosuppressive, type of population (geographical region, cohort), and population baseline characteristics. We used EndNote version 9.0 to identify duplicate records.

3. Results

3.1. Immunosuppressive Medications

Different categories can classify immunosuppressive medications based on their general characteristics. We categorize the medications into seven main groups: corticosteroids, T-cell suppressors, B-cell suppressors, cytokine inhibitors, complement system inhibitors, adhesion molecule inhibitors, and antimetabolites. Indeed, there are instances where distinct categories overlap, leading to the simultaneous classification of certain medications under two categories. In this section, we will examine these seven classifications and their role in the management of coronavirus-affected individuals.

3.2. Children's COVID-19 Compared to Adults

Children have predominantly been exempt from the most severe consequences of COVID-19. While children are equally susceptible to contracting SARS-CoV-2 as adults, the majority of infected children often have moderate symptoms [13]. Occasionally, children who have contracted COVID-19 may not display any symptoms. Recent research has yielded more insights into the reasons why children exhibit greater resilience to COVID-19 compared to adults [14]. According to a preliminary study, children are less likely than adults to experience symptoms like fever, cough, or shortness of breath and require hospitalization. Nevertheless, children with COVID-19 (**Figure 1**), particularly those under the age of one, frequently experience severe illness [15].

An important concern is the robustness of innate immunity, which has been the subject of recent investigations revealing notable distinctions between the immune systems of infants and adults [16]. The primary role of the immune system is to recognize and eliminate minuscule entities that assault the body. This system comprises two primary components: intrinsic safety and adaptive safety. The innate immune system initiates the earliest defense against microorganisms. When the body's natural defense mechanisms are unable to completely remove the danger, the body's specialized defense mechanisms take over. While adaptive immunity exhibits more specificity and accuracy compared to innate immunity, its response time is relatively slower. An initial concern is the robustness of innate immunity, with recent studies highlighting notable distinctions in the immune systems of children and adults. These and other comparable studies indicate that the natural immune response in children is sufficiently robust to eliminate SARS-CoV-2 infection without requiring enhancement from the adaptive immune system. Children's innate immunity also offers the advantage of a significantly reduced occurrence of "cytokine storms" in comparison to adults. A cytokine storm refers to a potentially fatal excessive inflammatory response by the innate immune system, specifically targeting the lungs or other organs. Cytokine storms typically manifest in adults during the

second week of severe and life-threatening COVID-19 cases [17]. Another concern is that children possess a more robust innate immune response, which enables them to effectively eliminate SARA-Cov-2 infection without significant reliance on the adaptive immune response. In 2024, researchers analysed blood samples from a cohort of COVID-19-diagnosed individuals, both adults and children. Researchers discovered that youngsters, who experienced less severe symptoms compared to adults, had reduced levels of compounds related to the adaptive immune response in their blood [18]. Additionally, their blood exhibited elevated amounts of molecules connected with the innate immune response [19]. In relation to COVID-19, one benefit of children's immune systems is their less mature adaptive immune system. Children, specifically, possess fewer complex T-cells. During a person's thirties, their T-cells, which were previously naïve, encounter certain infections and transform into memory T-cells. These memory T-cells are able to respond rapidly when the same pathogen or comparable structures enter the body. As individuals grow older, the process of converting naïve T-cells into memory T-cells becomes more prevalent, leading to a decrease in the body's generation of naïve T-cells. Consequently, adults possess a reduced number of inexperienced T-cells to identify and combat novel infections like SARS-Cov-2 [20]. Also, children are more susceptible to contracting COVID-19 than adults due to additional potential pathways of transmission. While the evidence is still equivocal, certain studies indicate that children have lower levels of angiotensin-converting enzyme receptor 2 (ACE2) in their nasal passages compared to adults. SARS-Cov-2 binds to ACE2, a protein that serves as a cellular receptor and entrance site for COV-19, allowing it to access the epithelial cells of the respiratory tract. Nevertheless, there is contradictory information concerning the variations in ACE2 expression in the nasal and pulmonary regions due to aging. Several investigations examining the viral particle concentration in the upper airways of individuals found no discernible distinction between children and adults. Another contributing factor to the lower prevalence of severe COVID-19 in children is their reduced susceptibility to underlying chronic conditions like obesity and diabetes. These pre-existing conditions increase the risk of more severe illness-related consequences [21].

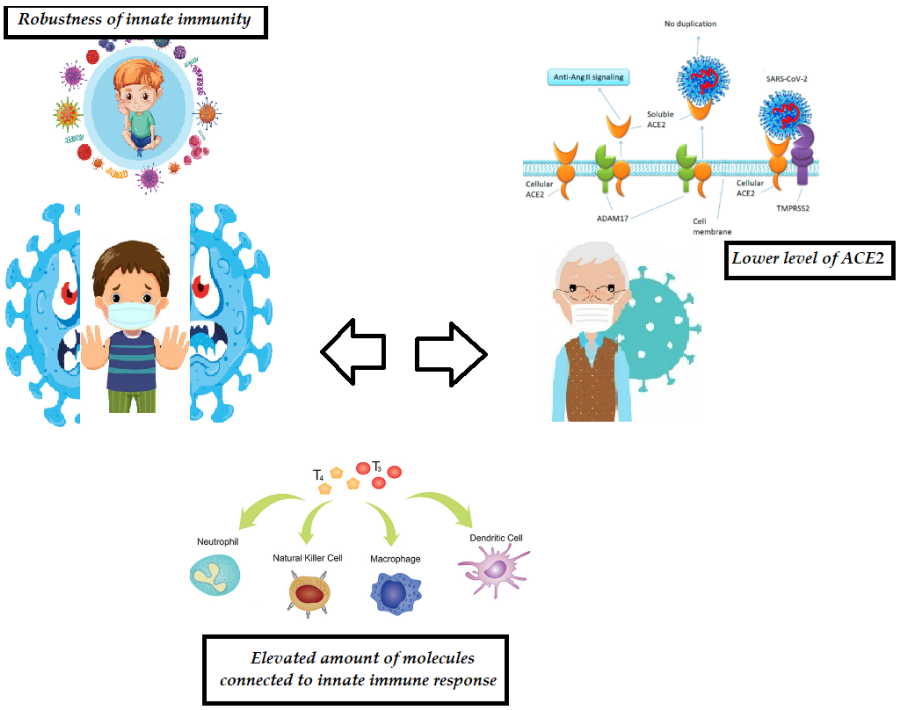

Figure 1. The possible reasons of different children's COVID-19 compared to adults.

This study specifically examines the impact of immuno-suppressive or immune-stimulating medications on the host's immune response to COVID-19. In this study, we provide a short sample and an overview of some medicines, followed by a synopsis of the findings from the identified studies for each respective drug (**Table 1**).

Table 1. Some types of immune-suppressing or immune-stimulating drugs are currently in use.

Study Reference	Study Design	Type of Drug	Target Disease	Findings
Tobinick 2004, USA [22]	Cohort	TNF-α inhibitor	SARS-CoV infection	has the potential to be a more targeted and efficient approach to repairing the severe damage to the alveoli
Atanasova et al. 2010, Netherlands [23]	Animal model	TNF-α inhibitor	Virus-endotoxin-induced respiratory disease	The disease could not be improved solely by inhibiting TNF-alpha
Fu et al. 2020, China [24]	Observational	low-dose steroids	SARS-CoV-2 infection	It could be a suitable choice for promptly treating inflammation in the lungs to avoid serious lung damage.
Fang et al. 2020, Greece [25]	Observational	low-dose steroids	SARS-CoV-2 infection	These treatments may serve as a viable alternative for these people.
Richardson et al. 2020, UK [26]	Observational	JAK inhibitors	SARS-CoV-2 infection	Diminish both the viral ingress and the inflammatory response in patients
Ma et al. 2018, China [27]	Observational	JAK inhibitors	TGEV	A unique approach to combat coronavirus infection.
Yang et al. 2017, Taiwan [28]	Experimental	JAK inhibitors	SARS-CoV infection	Represents a viable method for treating SARS-CoV or MERS-CoV.
Wathelet et al. 2007, USA [29]	Experimental	IFN inhibitors	SARS-CoV infection	Reduces viral replication and pulmonary damage
Chen et al. 2020, China [30]	Observational	IL-1 blockade	SARS-CoV-2 infection	Forecast the magnitude of the 2019-nCoV pneumonia
Guimarães et al, 2024, Multi-countries [31]	RCT	JAK inhibitors	SARS-CoV-2 infection	Result in clinical effect but no effect on liver enzymes

TNF-α, Tumor Necrosis Factor Alpha; JAK inhibitor, Janus kinase inhibitor; TGEV, Transmissible gastroenteritis virus; IFN inhibitors, inhibitor of Type Iinterferons; RCT, Randomized controlled trial.

3.3. Corticosteroid Drugs

Recommended to treat a range of inflammatory illnesses, these medications have widespread effects on all types of immune system cells. Corticosteroids connect to glucocorticoid receptors inside cells and manage many cellular functions by connecting to glucocorticoid-responsive areas in the nucleus. The medicines affect the immune system in a number of ways, but their main effect is to stop the production of cytokines by controlling transcription factors like NF-κβ and AP-1 [32]. When IL-2 is blocked, the number of T cells drops, Th1 cells stop differentiating, apoptosis begins, eosinophils directly die or IL-5 is blocked, and macrophages stop working because IL-1 and TNF-α are blocked [33]. The impact of these medications on neutrophil function is minimal. Nevertheless, these medications hinder the movement of neutrophils towards areas of inflammation, intensify their release from the bone marrow, diminish their programmed cell death, and increase the number of white blood cells. Corticosteroids do not effectively block B cells, and they only cause a slight decrease in immunoglobulin synthesis in these cells [34]. Since the onset of the SARS-CoV-2 outbreak, clinical settings have employed this category of drugs due to their established anti-inflammatory properties [35]. A preliminary clinical study showed that the administration of dexamethasone decreased the mortality rate of patients within the initial four weeks of infection and diminished the requirement for mechanical breathing [36]. Following this study, researchers conducted multiple trials in various nations and centers. Out of these, six studies corroborated the findings of the initial study; two trials reported adverse effects of steroid usage; and one trial did not observe any distinction between individuals using this medication and other patients [37–42]. Three investigations reported the harmful effects of these medications, specifically when they administered high doses for an extended period [43]. These trials vary in the type, dosage, and duration of corticosteroid administration, targeting distinct patient groups with varying ages and immunological profiles. Therefore, the heterogeneity of the studied patients and the variations in the application method are responsible for the divergent and occasionally conflicting outcomes. However, it appears that the short-term and logical use of these medications could be beneficial, particularly in younger individuals who may experience uncontrolled inflammatory reactions to infection. However, administering large amounts of steroids to those with weakened immune systems might hinder the successful elimination of viral infections and could lead to further infections, including severe fungal infections such as mucormycosis. Five cohort studies show that this category of medications does not eliminate the virus from patients. Furthermore, two studies suggest that these medications have extended the duration, a discrepancy that may be due to methodological variations [44,45].

3.4. ACE Inhibitors

Previous studies have not observed an association between the use of ARBs/ACEIs and negative/positive clinical outcomes of COVID-19 [46–48]. This finding is also found in the largest meta-analysis conducted on the effect of ARBs/ACEIs use on short-term outcomes of COVID-19 [49]. The most recent meta-analysis also showed that the use of ARBs/ACEIs in patients with COVID-19 does not increase the risk of COVID-19 infection, disease severity, or mortality [50]. Recent studies and analyses suggest that ACE2 may be a host receptor for 2019-CoV-SARS/nCoV, which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels [51]. The level and pattern of human ACE2 expression in different tissues may be important for the susceptibility, symptoms, and clinical outcomes of 2019-CoV-SARS/nCoV infection. It has also been reported that East Asian populations, which have higher ACE2 levels in tissues than other populations, may have different susceptibility or response to 2019-CoV-SARS/nCoV under similar conditions [3]. Therefore, the detection and control in this population requires greater sensitivity and precision.

3.5. T-cell Suppressive Drugs

T-cells serve as commanders of the immune system, overseeing immunological responses and regulating their intensity and duration. Thus, by blocking this specific cell line, one may effectively regulate a substantial portion of the immune cell population and their respective functions. Patients undergoing organ transplants administer T-suppressive medications to induce long-lasting and efficient tolerance towards the transplanted organ, thereby suppressing the immune response. This category encompasses a range of drugs, including antibodies that target surface markers (CD3) and inhibitors of molecules that stimulate cell activity. However, calcineurin-inhibiting drugs are the most significant and commonly used type of T-suppressor drug. These medicines work by attaching to cyclophilin and stopping calcineurin phosphatase from doing its job. This stops T-cell functions that depend on it from happening. It interferes with the enzyme's phosphatase activity. Cyclosporine and tacrolimus are the most renowned medications in this pharmacological group [52]. Patients with coronavirus do not receive calcineurin inhibitors, despite their strong anti-inflammatory properties, due to the crucial role of T cells in combating intracellular microorganisms and eliminating viral infections. The available research in this field solely pertains to the SARS-coronavirus and the MERS-coronavirus. In vitro studies have demonstrated that cyclosporine and tacrolimus effectively hinder the replication of these viruses [53]. The next category of drugs that inhibit T-cells are mTOR (mechanistic target of rapamycin) inhibitors. Rapamycin combines with FK506-binding protein (FKBP12) to form a complex. This complex blocks mTOR in a variety of ways, mainly by stopping T cells from working. The primary pharmaceuticals in this classification include rapamycin, sirolimus, and everolimus. Laboratory investigations demonstrate that these medicines have the ability to suppress the growth of MERS-coronavirus [54]. A study has demonstrated that SARS-coronavirus-2 enhances the activity of mTOR signaling in a controlled laboratory setting. This discovery suggests that there may be potential benefits to administering medications from this category to patients with coronavirus. Furthermore, mTOR inhibitors not only decrease the activity of effector T cells, but they also promote the function of regulatory lymphocytes, thereby improving their anti-inflammatory capabilities. As a result of this problem, numerous clinical trials are currently underway to investigate the impact of sirolimus and other medications in the same category. However, the public has not yet received the findings of these trials.

3.6. B-cell Suppressive Drugs

Monoclonal antibodies are the main type of drug in this group. They selectively target surface markers on B lymphocytes and kill them by damaging mechanisms such as complement activation and antibody-mediated cell lysis. Alternatively, they can hinder cell differentiation by preventing the transmission of evolutionary signals. It is indisputable that the presence of antibodies, particularly those with neutralizing properties, is crucial in preventing the virus from accessing target cells. Additionally, the mechanisms by which antibodies destroy viral particles play a vital role in eliminating coronavirus infection [55]. However, real-life evidence may show no logical justification for inhibiting B cells. Additionally, real-life evidence shows that people who use rituximab for other reasons, like rheumatologically conditions and autoimmune disorders, have a better outlook than people who are being treated with corticosteroids. Rituximab is a monoclonal antibody that specifically targets the CD20 marker found on B cells. People commonly use Rituximab to treat disorders resulting from the immune system producing harmful

antibodies against the body's own tissues. On the other hand, certain individuals receiving this medication have reported unusually severe cases of COVID-19. This raises doubts about the beneficial effects of the drug in reducing inflammation induced by the Corona virus infection [56]. Hence, further trials involving larger populations are required to assess the efficacy of this medication class in treating Corona.

3.7. Cytokine Inhibitor Drugs

These drugs can either directly bind to the target cytokine, inhibiting its activity and subsequent degradation and elimination, or bind to the target cytokine receptor, preventing the cytokine from binding and transmitting its message. Alternatively, they can bind to crucial cytokine signaling molecules, leading to significant disruptions in the signaling pathway [57]. It is important to note that the third category has the ability to hinder the function of a broader range of cytokines compared to the previous two categories, thanks to the presence of shared message routes within cells. As a result, there has been a growing interest in utilizing these medications. Examples of cytokine inhibitory medicines and their applications in the management of coronavirus infection are listed below.

3.8. IL-6 Inhibitor Drugs

One of the most potent inflammatory cytokines is known to be interleukin-6. Its elevation during infection and inflammation leads to fever and a substantial rise in inflammatory markers like CRP in the bloodstream. Monoclonal antibodies, tocilizumab and sarilumab, specifically target interleukin-6 and effectively block inflammatory reactions [58]. Given this aspect, we administered both of these medications to individuals with COVID-19 for therapeutic purposes, resulting in diverse outcomes. While the majority of the research focused on the beneficial impacts of utilizing these medications to treat patients, other studies found no notable distinction between two groups Consequently, this inhibition helps to mitigate tissue damage and inflammation of patients: those receiving these pharmaceuticals and those receiving other treatments. Furthermore, a retrospective investigation revealed a higher mortality rate among those who received tocilizumab [59]. This medicine improved hospital patients' 21-day survival rate, decreased the need for mechanical breathing, and lowered the rate of ICU admission. Two of these studies, done on patients with more severe illnesses, demonstrated more substantial advantages from the use of these medications compared to the control group of patients who had a better overall health status [60,61].

3.9. Tumor Necrosis Factor (TNF) Inhibitor Drugs

TNF-α is an inflammatory cytokine that usually rises when someone has a serious lung injury. It starts a cytokine storm and makes it easier for SARS-CoV-2 to bind to its receptor, angiotensin-converting enzyme 2 (ACE2) [62]. Hence, TNF-α inhibitors could be implemented as a potent therapeutic approach to mitigate the advancement of COVID-19. Currently, researchers are conducting numerous ongoing clinical trials in this domain. However, two concluded investigations have demonstrated the positive outcomes of employing TNF-α inhibitors in coronavirus patients. One study demonstrated that the medicine infliximab had a substantial positive impact on the respiratory health of patients. Another study found that the administration of the drug CERC-002 resulted in a reduction in mortality among COVID-19 patients [63].

3.10. IL-1 Inhibitor Drugs

Anakinera is a medication that functions as an antagonist of the interleukin-1 receptor. We use it to treat autoinflammatory conditions such as familial Mediterranean fever and Stills disease. Researchers think that this medicine works by stopping macrophages from becoming too active. Overactive macrophages make more inflammatory cytokines and chemokines in response to inflammatory cytokines in the environment, especially IL-1α and IL-1β. Consequently, this inhibition helps to mitigate tissue damage and inflammation. In addition to intravenous administration, physicians can also prescribe this medication subcutaneously, which enhances control over its concentration in the patient's bloodstream [64]. Researchers found that administering anakinra to COVID-19 patients with a CRP level exceeding 100 units and a ferritin level exceeding 900 ng/ml led to a reduction in mortality within 21 days. However, the duration of treatment for patients who survived was longer compared to the control group. Other studies recommend not taking dexamethasone with this treatment. When administered together, there is a likelihood of increased secondary infections, but this does not result in a substantial improvement

in patient survival [65].

3.11. JAK inhibitor Drugs

Janus kinase enzymes, specifically JAK1, JAK2, JAK3, and TYK2, play a crucial role in the signaling cascade of several inflammatory cytokines. As a result, medications that block these enzymes reduce the activity of many cytokines at the same time. The ability to suppress inflammatory reactions has proven to be more advantageous than earlier medications. Recently, researchers have devised a novel method to utilize these medications for the treatment of various immunological illnesses. Various cohort studies and clinical trials have administered baricitinib and ruxolitinib, the two primary medications in this category, to over 2000 COVID-19 patients. These studies demonstrated that the use of JAK inhibitors resulted in a decrease in the need for invasive mechanical ventilation, a reduction in hospitalization rates in the intensive care unit, and a decrease in the occurrence of acute respiratory failure to some degree. However, the duration of hospitalization for patients did not significantly decrease. Furthermore, the early usage of these medications appears to closely link their favorable benefits [66]. As a result of their ability to stop the signaling pathway of inflammatory cytokines and also block adapter-dependent kinase-1 (AAK1), which helps viral particles enter cells, Janus kinase inhibitors, especially baricitinib, have shown good results in the treatment of very sick patients. Nevertheless, it is important to acknowledge that these medicines have the ability to suppress several cytokines, including type 1 interferons, hence diminishing the antiviral properties of these interferons [26]. Researchers reported promising results using latest JAK inhibitors such as upadacitinib [67], ruxolitinib [68], and tofacitinib [31]compared to placebo in patients with COVID-19 infections.

3.12. Immunosuppressive Medicines

During inflammation, complement components break apart, and their chemotactic properties help bring more immune cells to the site and turn these cells on, especially neutrophils and macrophages. On the other hand, the C5a molecule, which is made when enzymes break down complement fragment 5, has strong pro-inflammatory properties. Partially suppressing its activity can effectively regulate inflammatory reactions, particularly in cases involving antibody-mediated responses [69]. Some COVID-19 individuals with moderate to severe symptoms have received administration of eculizumab, a C5-specific antibody. Administration of this medication typically decreases the concentration of inflammatory markers in patients' blood, leading to a quicker improvement in clinical symptoms. Another pharmaceutical compound belonging to this classification is Vololimb, which specifically targets the C5a fragment of the complement system. The findings of a clinical trial demonstrated that this medication effectively decreases the death rate among critically ill patients with cardiovascular conditions [70].

3.13. Drugs that Interfere with Cell Adhesion Processes

These medicines usually bind to molecules on the surface of immune cells, especially T lymphocytes. This stops them from attaching to antigen-presenting cells or the vessel wall to cause diastasis. Thus, these medications disrupt the normal functioning of these cells, leading to the suppression of immunological responses. Most people use this pharmacological class to manage chronic autoimmune illnesses that specifically target specific tissues, like multiple sclerosis. Fingolimod is a medication that belongs to the category of drugs that attach to the sphingosine-1 phosphate receptor and hinder the departure of T-cells from secondary lymphatic organs [71]. Studies conducted retrospectively on multiple sclerosis (MS) patients treated with fingolimod revealed that the incidence of severe COVID-19 cases and acute symptoms in these patients was comparable to the general population. It appears that administering this medication does not improve or deteriorate coronavirus infection in individuals [72]. Currently, it is important to mention that clinical trials have not administered medications from this category to COVID-19 individuals without underlying conditions. However, researchers have only studied the impact of these drugs on the intensity of symptoms in patients who consistently take them for any reason.

3.14. Platform Include Multiple Medications Alters Cytokine Storm

If a bacterial infection is causing the cytokine storm, it can be treated with antibiotics. The easiest way to treat a cytokine storm is with infectious diseases such as COVID-19. In general, the treatment in this case is based on weakening the immune system and strengthening another part of the body. Among the treatments currently approved

by the World Health Organization (WHO) to combat this disease [73], can named the use of corticosteroids in people with underlying diseases, aspirin (in mild cases), oxygen therapy, medications that affect the body's immune system, such as cyclosporine, biological therapies that block certain cytokines, plasma exchange (plasmapheresis), and statin drugs [74]. Several well-organized trials have been conducted to combat COVID-19 and reported promising results. One of these trials id I-SPY, including include I-SPY 1 and 2, which introduced a platform of multiple medications that could alter cytokine storm [75,76]. These trials showed beneficial effects and advantages in different diseases such as breast cancer, and introduced this platform as a useful approach to rapidly screen multiple drugs against COVID-19 as well [77,78].

3.15. Comparing Treatment Modalities

In the final review of the studies, the results showed that the drug Remdesivir has a role in treating and improving the symptoms of patients with COVID-19, but definitive results require larger and more comprehensive studies [79]. Favipiravir is one of the drugs that has effective therapeutic effects and fewer side effects, but its therapeutic effects are weaker than Arbidol [80]. The effective therapeutic role of Arbidol against COVID-19 has been reported in all the studies reviewed, but more detailed studies are needed to investigate the presence of side effects following this drug [81]. Also, among the drugs under review, Kaletra and Ritonavir/Lopinavir had the weakest results, which could be an important factor in changing the attitude of therapists in using these drugs alone or in combination [82]. In addition, the results of studies conducted to compare the therapeutic effects of chloroquine and hydroxychloroquine confirm the preference for using hydroxychloroquine in the treatment of patients with COVID-19 [83]. Other studies examining the drugs Adalimumab, Intravenous Immunoglobulins (IVIG), Imatinib, and Sivelestat have suggested that although these drugs may be effective in improving ARDS and inflammatory responses, their use requires larger clinical trials to confirm their use [84]. Meanwhile, IFNs (Interferons) and Tocilizumab, when used with an initial antiviral drug, could be considered as part of the treatment of patients with COVID-19 [85]. Given the global crisis caused by the COVID-19 pandemic and the need to achieve effective and definitive treatment, the need for more clinical trials and large randomized controlled studies to confirm the effective role, safety profile, and side effects of all tested drugs is increasingly felt [86–88].

3.16. Drugs Classified as Antimetabolites

These medications disrupt the process of creating DNA, which leads to a notable decrease in the body's ability to produce lymphocytes and thereby weakens the acquired immune responses. The primary medications in this category are methotrexate, mycophenolate mofetil, and azathioprine [89]. A comparative study between patients on long-term methotrexate treatment and a control group revealed that the case group exhibited milder symptoms of COVID-19, such as fever, cough, and shortness of breath. Additionally, indicators of disease severity, including pulmonary involvement, ferritin level, white blood cell count, and CRP levels, were lower in the case group compared to the control group. This study concluded that methotrexate usage does not increase the risk of developing COVID-19. Patients who take methotrexate may also have less severe disease. This could be because it stops acute inflammatory reactions by blocking TNF-α and IL-6 and increasing regulatory T-cells [90]. Transplant patients should take mycophenolate mofetil, an antimetabolite of mycophenolic acid, as a medication. This medicine stops the enzyme inosine-5'-monophosphate dehydrogenase from working. This makes the amounts of guanosine and deoxyguanosine nucleotides inside cells drop by a lot. As a result, this hinders the production of new DNA and prevents the growth of T and B lymphocytes. A cohort study has demonstrated a correlation between the use of mycophenolate mofetil and a decrease in mortality among people with coronary conditions [91]. Additionally, studies have documented that this medication inhibits the reproduction of SARS-coronavirus-2 in a controlled laboratory environment, but it does not affect the reproduction of SARS-coronavirus-1 or MERS-coronavirus [92]. There is a lack of specific clinical trials on the impact of azathioprine. However, previous studies have shown that 6-mercaptopurine, a byproduct of azathioprine metabolism in the body, inhibits the replication of SARS-corona and MERS-corona viruses in laboratory settings [93].

4. Discussion

Every second, countless foreign agents, many of which are pathogens, enter our bodies. Our immune and defense systems are an army of cells and proteins that are organized and used to defend against disease and infection.

Pathogenic foreign agents also include some viruses, bacteria, and mutated cells that are ready to harm our bodies [94]. The immune system protects us against foreign agents such as bacteria, viruses, fungi, and toxic substances. During the outbreak of infectious diseases such as the coronavirus, it is necessary to strengthen it more than ever. All living things are equipped with an immune system [95]. Even a single-celled organism like a bacterium has a rudimentary immune system that is used to protect the bacteria from bacteriophages. Immune system inside human body is an effective and powerful biological machine that protects us from foreign invaders such as bacteria, viruses, fungi, and toxins (chemicals produced by microbes) [96]. In some cases, this response can be so strong that it can lead to fever, pain, swelling, and even bleeding.

The body's defense system is an interconnected structure made up of white blood cells, antibodies, complex proteins, networks, and various organs that work together in harmony. Some immune system elements act like a barrier to prevent bacteria and viruses from entering various organs of the body, such as the brain [97]. While others hunt and destroy them, this process requires that the body first recognizes foreign agents from its own cells and molecules and then destroys or renders them harmless. For the immune system to function properly, it must be able to identify and remove pathogens, including bacteria, viruses, and parasites, from the body's tissues. Although the immune system is effective in combating many diseases caused by bacteria and viruses, it takes time to adapt. First, pathogens must be identified, and this happens when specific antibodies are produced in the body. When an antibody recognizes an antigen of a pathogen, it attaches itself to it, which allows the rest of the immune system to recognize the invader and attack it. On the other hand, pathogens can also change rapidly and adapt to the body's conditions, making it impossible for the immune system to recognize and neutralize them. However, our multiple defense mechanisms have also evolved to identify and neutralize pathogens.

The most common immune system disorders are immunodeficiency, autoimmune diseases, and over-activity of the immune system [98]. Autoimmune diseases, which the body's immune system considers its own cells as foreign and destroys them. This reaction may be due to the inappropriate production of antibodies that are secreted against molecules on the surface of the body's cells [99]. This disorder is sometimes due to the similarity of the antigens of self-cells to non-self-cells and sometimes due to errors in the functioning of the immune system in old age or for hereditary reasons. Consequences of an overactive immune system autoimmune diseases can affect organs and tissues including red blood cells, blood vessels, thyroid gland, pancreas, muscles, joints, and skin, and can also lead to inflammatory diseases and cancer. Autoimmune diseases include chronic anemia, type 1 diabetes, rheumatoid arthritis, and multiple sclerosis. Immune Deficiency Disease that 0ccurs when the body's immune system is less active than normal, which can lead to deadly infections. In humans, immunodeficiency can be congenital or caused by acquired factors such as HIV/AIDS or the use of immunosuppressive drugs. Immune over-activity disorders, of which some people are born with certain genes that cause their immune system to be sensitive to harmless environmental substances and to overreact when exposed to these substances, called allergens [100]. Having an allergic reaction is the most common example of an overactive immune system. Allergy to dust, microscopic organisms around us such as mites and fungi, pollen and plants, and food allergies are examples of allergens. In a very severe case of anaphylactic shock, the immune system reaction can be so strong that it can even be dangerous and fatal. Asthma, allergic asthma, allergies, eczema, allergic rhinitis are examples of diseases caused by an overactive immune system.

It is not clear what role the coronavirus plays in cases where it affects organs other than the lungs. In fact, either the virus itself can cause organ damage or the body's immune response plays a larger role. Overall, understanding what parts of the body can be affected by the virus is crucial for caring for patients with COVID-19 [101]. Both in prevention and during the COVID-19 pandemic, to reduce the symptoms and complications caused by disease, even in long-term type, managing the human immune system and strengthening it is of great importance [102]. Therefore, we suggest you use the supplement boosting immune system. This product is specifically formulated for the COVID-19 pandemic caused by SARS-CoV-2 and plays a significant role in modulating antiviral, antibacterial immunity and regulating the inflammatory response [103]. Such supplementation increases the function and resistance of the host immune system against infectious agents, which reduces the risk, severity and duration of infectious diseases.

5. Clinical and Health Policy Implications

According to the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), several types of coronavirus vaccines have been produced and used in several countries around the world, and they are considered the only vaccines for treating this disease. Of course, some drugs have also been effective in increasing the speed of treatment for the coronavirus so far. Generally, anticoagulant drugs, dexamethasone, are prescribed during the treatment of coronavirus. Dexamethasone is only prescribed as a coronavirus treatment drug when people are in the acute stage of the disease, and in the early stages, rest and quarantine will be the best treatment. Countries and the world should learn from such tragedy and harmful experience to be prepared, well-equipped and have experts and well trained human resources alongside medications to combat such diseases.

6. Conclusions

Overall, the utilization of immunosuppressive medications, whether administered recently during illness or consistently for non-COVID-19 reasons, appears to have a beneficial impact on managing inflammation, expediting recovery, and decreasing mortality. However, it is crucial to exercise caution and avoid prescribing these drugs without proper consideration. Avoid excessive and prolonged use to ensure a proper balance between suppressing inflammation and maintaining antibacterial defense. Presently, the corticosteroid group of immunosuppressive medicines has the most extensive data regarding their efficiency and side effects. This, coupled with their cheaper cost and widespread availability, makes them a recommended therapy option for managing critically ill patients. Administering more potent medications like tocilizumab or baricitinib may potentially have positive results. Furthermore, extensive research has determined that the ongoing administration of immunosuppressive medications to individuals with chronic autoimmune illnesses does not heighten their susceptibility to coronavirus infections. Furthermore, if infection occurs, it actually improves the prognosis for these patients. In general, according to research, the use of nutritional supplements strengthens the immune system. However, given that the immune system suffers the most damage in COVID-19, the use of these supplements helps a lot in the recovery process of the disease.

Author Contributions

Developed the concept, conducted the data analysis, wrote, and revised the first draft of the manuscript, F.R. and I.I.; Developed the concept, contributed to the draft review, editing, and validation, M.S.H. and A.S.M.; Developed the concept participated in language editing, and data analysis, A.S.B. and A.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declared no conflict of interest.

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