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Review Article

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Passive Immunotherapeutic Approaches for Treating Covid-19: A Comprehensive Review

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ABSTRACT

During the recent pandemic, COVID-19 (SARS-CoV-2) was the causative agent of the severe acute respiratory syndrome, which resulted in thousands of cases and high mortality rates in all the countries affected. This review focuses on immune-therapy techniques for treating COVID-19. The distinctive immunotherapeutic techniques are interferon administration, convalescent plasma, intravenous immunoglobulin, monoclonal antibodies, cellular treatments, and immunomodulatory drugs. Aside from antivirals, immunotherapy is recommended because of the immunity against the antigen in the infected patient and interferon activation is inhibited by the virus to avoid the immune response against it. In certain stages, interferons are used to cure the infection. Convalescent plasma therapy is used for patients with severe COVID-19 infection, all over the globe. A variety of antibodies fight against SARS-CoV-2 at different stages of its development and neutralize the virus. JAK inhibitors, corticosteroids, and others are used to modulate the immune response to control cytokine storms brought on by COVID-19 in its late phase. The changes in the cytokine storm and antibody reaction against SARS-CoV-2 require newly modified treatment for the patients to fight the infection. Researching about the manner of development, the immune response against the infectionandviral-mediated reactions help to find an efficient preventive and therapeutic medication.

Key words: *COVID-19, SARS-CoV-2, Immunotherapy, Monoclonal antibody, Interferon, Infection*

INTRODUCTION

Novel Coronavirus or COVID-19 triggered a critical health epidemic with significant socioeconomic implications. An announcement first took place in Wuhan, China, at the end of December 2019 [1]. On March 11, 2020, WHO declared a worldwide pandemic [2]. COVID-19 may stay non-indicative or may have light manifestations, advancing to a more extreme illness and can become fatal [3]. A critical component of the infection is its capacity to proliferate effectively through hosts using the respiratory tract, being incredibly infectious and causing Severe Acute Respiratory Syndrome (SARS) [4]. They are about 80–120 nm in diameter. The average size of their genome is 26 to 32 kb, making them the largest RNA infection is known to science [5]. COVID-19 and a bat origin coronavirus have shown 96%similarity in genome studies proving that the infection has originated from bats [6]. This virus falls under the Betacoronavirus (a positive-sense, single-stranded RNA enveloped virus) [7] genus of the Coronavirinae subfamily, which is in the Coronaviridae subfamily of the Nidovirales [8]. The genome encoding SARS-CoV-2 contains five structural proteins, including spike proteins (S), membrane proteins (M), envelop proteins (E), and nucleocapsid proteins (N) [6, 9]. In addition to genes encoding structural proteins, there are provisions for genes encoding viral proteins necessary for replication and nonstructural proteins, such as papain-like protease (PLpro) and coronavirus main protease (3CLpro) [10-12]. In

SARS CoV-2, infectivity is enhanced because it has a higher affinity to the Angiotensin-Converting Enzyme 2 (ACE-2) and neuropilin-1 (NLP1) host cell receptors via the S-spike protein [13-15]. The interaction of SARS-CoV-2 and its receptor-binding domain (RBD) with angiotensin-converting enzyme 2 (ACE2) on the host cell prevents it from being able to pass into the host cells [16]. In any case, the viral endurance decreases with higher temperatures, even at room temperature where it can survive up to nine days. By using 62–71% ethanol, 0.5% hydrogen peroxide, or 0.1% sodium hypochlorite on the surface of the water, it is likely to inactivate spontaneously [17].

Passive immunotherapeutic treatments against SARS-CoV-2

To ensure the patient's recovery, oxygen therapy, mechanical ventilation, antibiotics, and plasma therapies are the primary treatment methods and antibiotics to prevent secondary infections [18]. In an endeavor to manage immunodeficiency, immunotherapy hasbeen depicted as a supportive treatment. But, to limit the possibility of fatality, therapeutic medication has been restricted to extreme casesand in consolidated treatments [19]. For non-clinical and clinical trials, factors such as sex, age, pregnancy, diabetes, hypertension, autoimmune disorders, heart illnesses, malignancy, and heftiness would need to be examined to determine if an infected patient would benefit from the prior treatments [20]. Significantly, some potential immunotherapies are quite certain while focusing on immunity and pathways, and they are intended to stay away from unfortunate incidents, to be utilized solely to limit the infection actuated by the viral illness. Consequently, immunotherapy approaches are created to be helpful in any circumstance, paying little mind to comorbidity [21].

Few medications have shown effectiveness against COVID-19. Many scientists have begun to study the different drugs that inhibit SARS-CoV-2 and performed many clinical trials, after the announcement of the pandemic by WHO [22, 23]. The first analyzed drugs were inhibitors that targeted the viral infection. Remdisivir is the drug that blocks viral RNA synthesis, and it falls into the category of adenosine-analogs. The clinical trials with Remdesivir for COVID-19 patients have shown promising results as well. COVID-19 is not currently being studied to see whether nucleoside analogs like ribavirin and favipiravir are effective in treating it [24]. The immune response is triggered by the invasion of a virus on antigen-presenting cells (APCs) through the major histocompatibility complex (MHC). Interferons are produced from the diseased cell to signal and alert the neighboring cells to defend against the infection, this response is induced byinnate immunity [25]. Type I interferons (interferon-alpha and - beta) are inhibited by the coronavirus and escape the innate immune response. Also, SARS-CoV-2 inhibits the cytokine pattern and affects the immune response between humoral (Th1) and cellular(Th2) responses. The research was published based on 20 recovered patientsthat cellular response suppressed the virus [26-29]. The T cell-mediated immunity was blocked by the ability of the virus to hinder the APCvia inhibition of MHC class I and II molecules [30]. The unstoppable secretion of provocativecytokines is known as a cytokine storm. It is initiated by the drop in lymphocyte count during the second stage of infection. IFN-α, IFN-γ, GM-CSF, G-CSF, IL-1s, IL-6, IL-12, IL-18, IL-33, TNF-α, and TGF-s are among the inflammatory cytokines. Chemokines, which can include CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10, are also inflammatory cytokines. While the patient is recovering from the infection, the cytokine levels are also restored. Lung injury and various organ failures are caused due toARDS (acute respiratory distress syndrome) which is stimulated by the cytokine storm. Considering all these impacts, immunityis compromised in severely infected patients. To cure SARS-CoV-2, immune modulation is a necessary treatment, knowing the role of immunity and the condition of the immune system at different stages of infection in the infected patient [31]. Numerous methodologies can be directed as immunotherapeutic medicines for COVID-19.

Interferon-based immunotherapy

Type I IFNs

A host's immune response relies on the defense mechanism of interferons to several infections. The IFN-signaling pathways are compromised by COVID-19 to inhibit the secretion of IFN-1. Since the virus inhibits IRF-3 (Interferon Regulatory Factor 3), STAT-1 (Signal Transducer and Activator of Transcription 1) and STAT-2 (Signal Transducer and Activator of Transcription 2) are essential intracellular pathways for releasing IFNs [32]. The amount of generation IFN differs from person to person according to their age, still, the IFN-based immune responses are induced against SARS-CoV-2. Kids have a low IFN-secretion range, which is the reason for early initiation of IFN and suppresses the infection, causing low mortality, whereas elders, have an insufficientimmune reaction due tothe high limit of IFN secretion, causing the

slowdown in the generation of IFN. Some of the vital difficulties against SARS-CoV-2 for immunity are insufficient IFN secretion and the hindrance of the IFN-secreting pathway [25]. IFN-α and β aretreated against COVID-19 proved to be more effective since the virus is more susceptible to these interferons [33]. IFN-β1b, lopinavir, and ritonavir combination are more efficiently suppressing SARS-CoV-2 than lopinavir-ritonavir combination. The early triple treatment is also proven to decrease the development of infection leading to serious conditions [34]. IFN-based immunotherapy is acceptedin clinical testing of infected patients due to the positive outcome that type I IFNsare efficient against SARS-CoV-2, in in-vitroconditions [35]. For knowing how effectively the treatment works, several clinical trials were performed in various countries that included IFN-α1β, IFN-β, recombinant human IFN-α, IFN-β1a, and IFN-β1b. The recent studies on Covid 19 reported that, there is a single cell transcriptomic investigation of the Peripheral immune responses and no expression of cytokines been observed in Monocytes and Lymphocytes. But the immune cells have capable of expressing the interferon stimulated genes in few Covid 19 affected patients. This genes will provide the pathway for entry of virus and further metabolism of the proteins.

Type III IFNs

Type III IFNs or IFN-λ (lambda)is a part of the antiviral response against SARS-CoV-2. The IFN-λ signaling pathway is activated by the activation of Janus kinase (JAK)-STAT, which causes the expression of IFN-related genes [36]. A powerful immune reaction against COVID-19 is induced by the treatment with IFN-λ. Researchers in a clinical trialistesting Peginterferon IFN-λto cure an infection using type III IFN. Creating a satisfactory immune response against the infection is critical for the IFNs in the beginning phase of COVID-19 [37]. Granulocytes, lymphocytes, monocytes, and macrophages induce the immune defense against SARS-CoV-2 in the extreme stages of the infection. More quantity of proinflammatory cytokines is secreted due to the excess initiation of the monocytes and macrophages. To determine the appropriate IFN-based treatment, it must be known which phase of infection is present. With the use of IFN in the early stages of infection, a powerful immune response can be initiated against the SARS-CoV-2. Hyper activated immune reactions are caused by injecting IFN but in serious phases, it intensifies the cytokine storm. Therefore, the immunomodulatory method for suppressing the uncontrollable immune reaction and immunotherapy is not considered for patients with extreme infections [25].

Convalescent plasma therapy

An old method of treating disease is known as convalescent plasma therapy, which involves injecting serum from an infected patient after they have recovered from the disease. After injection, the antigens are killed by the antibodies present in the convalescent plasma. Patients affected by SARS-CoV-2 havea favorable impact on utilizing convalescent plasma therapy; it was featured in the latest research. Fiveextremely infected SARS-CoV-2 were administered with convalescent plasma, three patients were completely cured of the infection and werereleased, and two patients were monitored for 37 days for side effects [38]. There are some risks related to this therapy. There is a greater risk of serum-associated illness and immune-related infections with convalescent plasma therapy. Moreover, there is a higher risk of spreading infection in convalescent plasma therapy because of the antibodies produced by other viral strainsagainst an established COVID strain. Among the dangers related to the therapy is the possibility of spreading an infection from other viral strains [39]. There was no negative control group in all trials with convalescent plasma used in evaluating the effectiveness of the therapy. Furthermore, human monoclonal antibodies for an antigenic determinant or epitope of SARS CoV-2 must be recognized before COVID-19 can be prevented.

The virus present in the blood can be restrained via binding to the virus and hindering its entrance into the host cells by neutralizing antibodies in the convalescent plasma (CP) [40, 41]. Depending on the kind of microbe, pathogenesis, and treatment conventions the efficacy of CPT changes [42]. The recovery pace can be improved by early transfer of CP and presumably efficient for extremely infected patients, like the other coronaviruses, SARS-CoV, and MERS which are already studied against plasma therapy. The virus present in the blood increases during the first week of the infection like in other viral diseases [41, 43]. It may not be effective in the final phase of patients. To be sure, CPT can't fundamentally decrease the death rate among end-stage patients due to their infection seriousness. However, CPT is not needed for patients with less infection because they can naturally recover [44]. The efficiency of CPT is raised due to the concentration of COVID-19 neutralizing antibodies in the CP. Before the transfer of plasma, the antibody levels are not

determined, a few investigations showed that the IgG increase around three weeks after the side effect begins and tops at week 12. Thus, the effective CP is obtained from the donors 12 weeks after the activation of the symptom [45, 46].

Monoclonal antibody therapy

A particular variety of B-cells that generate a set of antibodies against a particular epitope is called monoclonal antibodies (mAbs). Many infections and cancer are treated with the help of mAbs [47]. Several monoclonal antibodies created specifically against the S1 region of SARS-CoV have shown that they can kill virulent diseases by inhibiting the ACE receptors to bind to the respective host cell. These antibodies include m396 80 R and S230.15 [48]. SARS-CoV was entirely eradicated by the monoclonal antibody CR3014, which inhibited replication of the genome and transmitted the virus. SARS-CoV is inhibited by this immune response by decreasing SARS-CoV's affinity towards the binding of ACE receptor and the host cells, similar to the way the immune response itself works [49]. SARS-CoV-2's receptor-binding domain and SARS-CoV are different, so the S1 domain targets monoclonal antibodies (like CR3014, m396) against this domain region of SARS-CoV are not efficient. In a new study, it was found that the human monoclonal antibody-like CR3022 kills the SARS virus and its variant. Taking everything into account, research published that CR3022alone, or combined with different medications is strongly effective in suppressing COVID-19 [50]. The human monoclonal antibody 47D11 also inhibits SARS-CoV-2 by inhibiting the conserved sequences on the S1B protein's receptor-binding domain. In uninfected people, these antibodies can prevent the spread of viral diseases. To create monoclonal antibodies capable of controlling or stopping SARS-CoV-2, it is best to focus on the receptor-binding domain. In addition, further research will reveal that in severely infected patients, COVID-19-specific monoclonal neutralizing antibodies can be used to suppress the virus.

Inhibition of cytokine pathways

Inter-leukin 1 inhibition

In various viral diseases, a pro-inflammatory cytokineknown asIL-1β plays a vital function in the development of respiratory infection. Fever and respiratory fibrosis are caused due to release of IL-1β by the macrophages because of alveolar inflammation. Extremely infected patients have more elevated levels of IL-1β. Hence, ARDS and cytokine discharge disorder can be controlled by the hindrance of the IL-1β in extreme phases of the SARS-CoV-2 and a viable way to deal with diminished development. SARS-CoV-2 clinical trials have approved Anakinra(NCT04341584), a recombinant IL-1 receptor antagonist. Canakinumab has been suggested as a possible mAb against IL-1β in clinical testing of SARS-CoV-2 [37].

Inter-leukin 6 inhibition

The hemorrhage in the lung is due to the damage to the air sac present in the lung, because of the ARDS caused by the exorbitant secretion of IL-6. At last, pneumonic fibrosis is induced due to these impacts. Serious infection of SARS-CoV-2 causes higher serum IL-6 levels. Consequently, the seriousness of SARS-CoV-2 is decreased by inhibiting IL-6 which inverts the inflammatory reactions. IL-6 initiated proinflammatory pathway can be blocked by the anti-IL-6 mAb, Tocilizumab (ACTEMRA). In some infected patients, treatment with tocilizumab has shown a positive effect. Tocilizumabhasan indirect antiviral impact against COVID-19. The damaging effect on the lungs by COVID-19 is suppressed Tocilizumab. The rise in hepatic compounds, hypercholesterolemia, skin allergy, and fungal infection are some of the unfavorable impacts involved in the needless use of tocilizumab. An antibody that inhibits IL-6 receptor signaling by inhibiting the interleukin-6 (IL-6) signaling is Sarilumab (KEVZARA). FDA has authorized a stage III clinical trial to examine the infected patients with two IL-6 mAbs, Tocilizumab, and Sarilumab.

TNF inhibition

By inhibiting NF-κB, thalidomide (*-N-[phthalimido] glutarimide) inhibits proinflammatorycytokines such as TNF-α and IL-8. In reaction to COVID-19 innate immunity secretes TNF-α. The initiation of immune defense against SARS-CoV-2 has appeared to be a major function of TNF-α and is one of the primary cytokines secreted by innate immunity. In serious infection of SARS-CoV-2, hyper inflammation can be controlled by blocking the TNF-α, based on the function of the TNF-α in the development of the cytokine storm. The connection between soluble TNF-α and its receptor is suppressed by XPro1595, a soluble

TNF-α-neutralizing protein. A clinical trial of XPro1595 is carried out against SARS-CoV-2(NCT04370236) [37]. Within eight days of thalidomide treatment with methylprednisolone (glucocorticoid) in a mixture with low-portion methylprednisolone (glucocorticoids), a COVID-19 pneumonia patient's clinical condition improved, including an improvement in oxygen levels lessening nausea, easing tension to decrease oxygen utilization, and lung exudation. After 5 days of treatment, cytokine levels, such as IL-6, IL-10, and IFN-γ, returned to their regular state. Concurrently, lymphocyte counts, D4+ T cells, CD8+ T cells, NK cells, and B cells additionally rose notably.

Complement system inhibition

The inert proteins present in the serum and part of innate immunity are known as complements. Itcauses the initiation of neutrophils and helps the antiviral property of the immunity, afterthe activation. Some elements of the system have identical roles like cytokines, but they are not cytokines. In the development of the infection, thecomplement system induces a significant function with these processes. The fact that COVID-19 displays some pathophysiological characteristics, such asthromboticmicroangiopathy (TMA), and acute kidney injury, might be due to complement activation. The complement system is made up of two components: C3 and C5. Avdoralimab, zilucoplan, and ravulizumab are approved as C5 blockers and AMY-101 is an approved C3 blocker used in clinical trials to prevent SARS-CoV-2 transmission [37]. There was evidence of complement actuation in the kidney of six COVID-19 patients by the availability of C5b-9 complement in their renal tubules. As a monoclonal antibody, eculizumab prevents complement activation and disrupts C5b development. The complement-mediated AKI-related COVID-19 is decreased using eculizumab, in which the research involves a 14-year-old female. Several findings from the research indicate that lab tests, clinical indications, and chest X-rays have improved.

Cell Therapy

Mesenchymal stem cell therapy

Severe immunomodulatory impacts are caused by a set of stem cells known asmesenchymal stem cells (MSCs). For treating various long-term inflammatory disorders MSCs are used because of the immunomodulatory impacts. MSC secretes growth factors such as keratinocyte growth factor (KGF), glial cell line-derived neurotrophic factor, hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), that induce reviving effects on target tissues. The immunomodulatory effects of MSCs trigger a response in T lymphocytes and M2 macrophages, inhibit T lymphocyte overexpression, as well as restrict proinflammatory cytokines secretion. Cytokine storm and its damaging impact on the lungs are suppressed by hindering proinflammatory cytokines and immune cells. Suppression of alveolar fibrosis and secretion of growth factors and IL-10 can lung quality. Various in vivo and clinical testing have appeared to decrease influenza-related respiratory damage by using MSC treatment. MSC is recommended to treat acute respiratory damage in serious SARS-CoV-2 infected patients due to the immunomodulatory impacts and recently released information on the efficiency and safety of MSC treatment. Transfer of ACE2-negative MSC was performed in 7SARS-CoV-2-pneumonia patients knowing the destructive impacts of the cytokine storm and excessive immune response. After the transplant, the patients were under 14 days of observation. After 2 days of the transfer, the manifestations and aspiratory capacity of the patients were fully enhanced. Amajor improvement was observed in one of the patients who had an extreme SARS-CoV-2 infection and was discharged after 10 days of infusion. Additionally, a rise in the number of peripheral lymphocytes, a decrease in the amount of inflammatory cytokine-producing cells, and a serum level of inflammatory markers were observed after transplantation. The transplantation of MSCs with ACE2-negative status appears to be a safe and effective treatment for SARS-CoV-2. MSC-derived secretome is used as another MSC therapeutic approach. Using vesicles and exosomes present outside of the cell, MSC secretes extracellular components (Secretome) to the media of cell culture. These components of the secretome are derived from MSCs. Similar to MSCs from other origins, the MSC-derived secretome has positive immunomodulatory, reproductive, and anti-inflammatory outcomes. A possible treatment technique against SARS-CoV-2 is MSC-derived secretome and is recommended as the other MSC approaches. Inhaler and intravenous solutions are the 2 methods to regulate the secretome. Clinical trials are conducted for the secretome approach to evaluate its reliability and effectiveness against COVID-19.

Natural killing cell therapy

A type of lymphocytes and element of innate immunity that has a function in primary immune reaction against virus or cancer called NK cells. A cancer cell's immune response to NK cells can be independent of an antigen. NK cell-based immunotherapy has shown promising results in treating tumors in an increasing number of clinical studies. NK cells fight against the infected cells by the stimulation of macrophage-associated cytokines and type I IFNs. The speed and MHC-independency are some important properties of the NK inferred immunity. It has been suggested by clinicians after the outbreak that NK cells can be used as an effective therapy for SARS-CoV-2. The NK cell-based therapy has subsequently gained acceptance in China for the antiviral defense and improving immunity toCOVID-19 infection [37]. A synthetic molecule called an antibody recruiting molecule (ARM^{TM}) contains a total of three binding groups: a linker, a spike protein, and an antibody binding region, a linker. ARM binds to the virus as well as lymphocytes through FC*R, causing the NK cells and macrophages to destroy the virus. By attaching the spike protein to the surface of COVID, ARM keeps the virus from interacting with ACE2 receptors on the hostcells. It provides viral proteins *to cells that introduce antigens, which* in turn can actuate chronic immunity. The studies has also proven that, immunization will be the effective way to prevent the spread of COVID-19 [50].

Immunomodulators

JAK inhibitors

JAK-STAT pathway is an intracellular cytokine signaling mechanism that contains JAK as a component. Theinterference in the phosphorylation of STAT is due to the secretion of proinflammatory cytokine by the induction of JAK. Manyproinflammatory cytokines are secreted due to the phosphorylation of the STAT. SARS-CoV-2 sufferers usually experience a cytokine storm after infection due to a decrease in proinflammatory cytokines secreted by the inhibiting of JAK by this agent. Several JAK-inhibitors, including Baricitinib, Fedratinib, and Ruxolitinib, are effective in reducing SARS-CoV-2 infection with anti-inflammatory effects in many diseases namely rheumatoid arthritis and myelofibrosis. Effective therapy for acute pneumonia in SARS-CoV-2 can be treated with a JAK blocker known as Baricitinib has been shown in the latest study. Adapter-linked protein kinase 1 receptor is hindered by Baricitinib which results in the restriction of the virus to enter the host cells and decreases the infection by repressing JAK. Four factors have led to the increased interest in Baricitinib over other drugs:

- Anti-incendiary properties
- The higher level of fondness for NAKs
- Ability to enhance related ongoing aggravation in interferonopathies
- The compound has great potential as a blend treatment since they have a low limiting effect on plasma protein and a low relationship with cytochrome P drugs.

To decrease the infection of the host and the chance of the virus reemergence, Baricitinib is recommended along with antiviral medications, including Lopinavir, Ritonavir, and Ramsudavir in cases of COVID-19. Cytokine storms and the pathology of Coronaviruses are largely determined by Th17 cells, including the cytokines that they produce. Fedratinib (JAK2 inhibitor) could be used to decrease COVID-19 death because this cell depends on the JAK signaling pathway for separation and to work as an effector system [48].

Antimetabolites

An enzyme known as papain-like protease (PLpro) deubiquitinates and replicates SARS-CoV-2's genome. The viral class inhibitors drugs mostly target PLpro. Still, PLpro is proved to be vulnerable to antimetabolites due to the therapeutic activity. Some of the important SARS-CoVPLpro blockers are 6-mercaptopurine (6MP) and 6-thioguanine (6TG). In in-vivo and in-vitro conditions PLpro of SARS-CoV and MERS-CoV is inhibited by an immunosuppressant, Mycophenolatemofetil has proved to be effective. To know the efficiency more therapeutic research is required. The effectiveness of the antimetabolites has no authoritative proof.

Calcineurin inhibitors

T-cell initiation is suppressed due to the hindrance of calcineurin which makes tacrolimus (Calcineurin inhibitor) efficient against COVID-19. It is usually used in organ transplantation procedures. It was found to be efficient against MERS in renal transfer patients who were contrasted with a patient who was not administered tacrolimus during the operation. Cell line research showed that tacrolimus is powerful against SARS-CoV. To know the efficiency against COVID-19 more research assuredly is required. The efficiency of calcineurin inhibitors and cyclosporine has no conclusive proof.

Metal-based agents

Gold, ruthenium, and bismuth are some metal-based agents that are considered in treating SARS-CoV-2 patients. The FDA accepted gold compound primarily recommended for treating rheumatoid arthritis is known as auranofin (Ridaura®). The precise process of this substance is still unclear, but it is categorized as an immune-modulating and anti-inflammatory agent. In treating viral diseases as well as HIV auranofin has earned more concentration. In restricting the viral rendering, inertness, and viral renascence, hydroxychloroquinewas found to be less effective than auranofin on account of HIV. JAK1 and STAT3 pathways are suppressed due to the inhibition of IL-6 signaling by auranofin were speculated. Restriction of COVID-19 viral reproduction and cytokine expression due to the viral stimulation in the human cells are reduced by the micromolar concentration of the auranofin was observed.

Corticosteroids

Due to their immunomodulatory effects, dexamethasone and other oral/IV corticosteroids were the first recommended medication for cytokine storm in a serious SARS-CoV-2 infection. In nuclei, themanifestation of pro-inflammatory transcription factors is suppressed by the anti-viral property ofcorticosteroids [47]. The infusion of corticosteroids can reduce the infection and ARDS in serious patients with SARS-CoV-2 hyper-inflammation, while for mediocre patients it is not necessary. For the assessment of the effectiveness of the drug-induced treatment against serious SARS-CoV-2 infection, many clinical trials are carried out. Vascular necrosis and diabetes are some of the aftereffects of corticosteroids (immunosuppressant medicine). Based on these immunological therapies, the strategy can be highly compassionate and stress implied. The statistical analysis reports states that, only by changes in the public environment the prevention and the measures can be reduce the spread of Covid-19 [46].

CONCLUSION

There is no potential treatment for COVID-19, despite the race for development at the scientific level. Immunotherapies referred to here were governed by integrated therapies. The benefits of monoclonal antibodies over serum treatment and intravenous immunoglobulins as immunotherapy to inhibit viral transmission or passage include their purity, selectivity decreases the cause of blood-borne infection and greater protection. The use of monoclonal antibody combinations increases the efficiency of suppressing the virus by identifying various epitopes that present on the viral surface. Though there are some recentadvances in the development of monoclonal antibodies like passive immunotherapy, there is no advertised monoclonal antibody for COVID-19. Using monoclonal antibodies in clinical applications is limited by the difficulty, cost, and tedious nature of large-scale manufacturing. Production of advanced protein should be developed so that the antibodies can be provided for an affordable price. To help the patient's immunity and recoup for the inhibition of COVID-19 is done by triggering the immunity via a passive immunotherapeutic approach during the beginning phases of the infection. In various countries, the efficiency of CPT is tested with potential outcomes. Cytokine storm maybe stimulated by the dysfunction of the immunity during the final phase of SARS-CoV-2in extremely infected patients. The most effective therapeutic approaches for patients in these situations are immunosuppressive drugs, such as JAK inhibitors, TNF-α blockers, corticosteroids, and various immunosuppressive, antiviral medications. To prevent the undesirable immune inhibition in benefit the viral replication in the host, various drugs in these classes are being studied for their advantages, disadvantages, effectiveness, and damaging impacts. The patients administered with a low portion of dexamethasone have better survival benefits were discovered. In extreme cases, the inflammatory reaction is administered to develop ARDS which is an essential factor. An illustration of suppressing the coronavirus is hindering the regulation of the type-1-IFN-associated pathway by aiming at the virus. The immunomodulatory technique established for the inflammatory reaction administration is used to attenuate the extreme antiviralreaction. Patients with extreme COVID-19 infection are treated utilizing Tocilizumab successfully improved clinical indications and research discoveries like white

blood cell (WBC) count, CRP, and amount of lymphocytes got back to ordinary levels. Moreover, Thalidomide is known for its effects onreducing lung injury and aspiratory fibrosis, including producing T cells, inhibiting inflammation, and impeding cell proliferation. The patients suffering from SARS-CoV-2 are treated with Tocilizumab, sarilumab, tocilizumab, IL-6 inhibitors, and Baricitinib, a JAK inhibitor, which may be more effective than the usual anti-inflammatory drugs. From this review, we conclude that immunotherapy is an effective treatment against COVID-19.

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