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Inflammopharmacology

REVIEW

Pathogenic role of cytokines in COVID-19, its association with contributing co-morbidities and possible therapeutic regimens

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Abstract

The Covid-19, a threatening pandemic, was originated from China in December 2019 and spread quickly to all over the world. The pathogenesis of coronavirus is linked with the disproportionate response of the immune system. This involves the systemic inflammatory reaction which is characterized by marked pro-inflammatory cytokine release commonly known as cytokine release storm (CRS). The pro inflammatory cytokines are involved in cascade of pulmonary inflammation, hyper coagulation and thrombosis which may be lethal for the individual. That's why, it is very important to have understanding of pro inflammatory cytokines and their pathological role in SARS-CoV-2. The pathogenesis of Covid is not the same in every individual, it can vary due to the presence of pre-existing comorbidities like suffering from already an inflammatory disease such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), an immune-compromised patients suffering from Diabetes Mellitus (DM) and Tuberculosis (TB) are more vulnerable morbidity and complications following COVID-19. This review is particularly related to COVID-19 patients having comorbidity of other inflammatory diseases. We have discussed the brief pathogenesis of COVID-19 and cytokines release storm with reference to other co-morbidities including RA, IBD, COPD, DM and TB. The available therapeutic regimens for COVID-19 including cytokine inhibitors, anti-viral, anti-biotic, bronchodilators, JAK- inhibitors, immunomodulators and anti-fibrotic agents have also been discussed briefly. Moreover, newly emerging medicines in the clinical trials have also been discussed which are found to be effective in treating Covid-19.

Keywords COVID-19 · Cytokines release storm · Inflammatory diseases · Therapeutic interventions

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Introduction to COVID-19 and its epidemiology

The new variant of coronavirus appeared in December 2019 in Wuhan, a city of China. It belongs to the coronaviridae family comprising of a single stranded RNA (Li et al. 2020a). It is not the first time that this virus has affected the world but also in past two decades it twice alarmed the world such as Severe Acute Respiratory syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) (Yuki et al. 2020). In the mid-February 2020, the mortality and morbidity rate was the largest in the China, whereas in other Asian countries it remained low. Coronavirus not only infects humans but also animals (Koehorst et al. 2017). The coronavirus was first cultivated by the Tyrell and Bynoe from the patients with cold flu in 1966 (Tyrrell and Bynoe, 1966).

There are four sub-families of the coronavirus, namely alpha, beta, gamma, delta. The alpha and beta subfamilies

originate from mammals while other two originate from pigs and birds. The genomes size range is from 26 to 32 kb. The SARs-CoV virus is 96% similar to the genome of bat coronavirus (Zhang et al. 2020a). Recent studies confirmed that coronavirus cases doubled in every seven days and each patient spread infection indirectly to 2.2 individuals on an average (Bauch et al. 2005). Dense communities are at a greater risk to coronavirus than less populated areas (Zhao et al. 2020). The WHO identified thirteen countries at top risk of coronavirus for example Algeria, Angola, Ethiopia, Nigeria, south Africa, Mauritius, Ghana, Kenya, Tanzania, Zambia, Uganda, Congo (Bai et al. 2020). The common feature among these viruses is that they spread abruptly from person to person via respiratory droplets produced during cough and show symptoms in two weeks of incubation period. This time period is sufficient for the virus to replicate and form lesions in the respiratory system (Chan et al. 2020). The disease out comes varies between individuals due to different factors as few can recover without any treatment while others, depending on their health conditions, will require intervention. On this basis, the disease can be categorized in mild, moderate and severe illness (Li et al. 2020a).The common symptoms are fever, cough, dyspnea, myalgia, fatigue, diarrhea and sputum production (Chan et al. 2020). While the complications through which Covid patients can suffer from are pneumonia, secondary infections, multiple organ failure, acute cardiac injury and acute respiratory distress syndrome (ARDS). The ARDS is the significant complication of Covid-19 (Choudhary et al. 2021). About 15% of Covid-19 patients develop severe pneumonia and 5% eventually progress to acute respiratory distress syndrome (Xu et al. 2020). Recent studies indicate that patients with age greater than 60 years are at higher risk of getting infected than children (Chan et al. 2015).

Structure of COVID-19 virus and its pathogenesis

The structure of coronavirus species is much similar to each other with minor differences. The basic structure of coronavirus includes a membrane that encloses the virus. All the viruses contain single stranded and non-segmented RNA which is 30 kilo base pair long (Fehr and Perlman 2015). The shape of coronavirus is spherical and has club like protein projections known as spikes. The four basic functional structures of viruses are spikes, envelope, membrane and proteins (Hulswit et al. 2016). The spike protein facilitates the binding of virus to the host receptor, i.e. Angiotensin Converting Enzyme 2 (ACE-2). Pathogenesis of COVID-19 has been shown in Fig. 1. The envelope and membrane determine the shape of virus while the nucleocapsid protein is bound to the genetic material to form the nucleocapsid. The hemagglutinin esterase protein increases the virus ability to attack the host cell surfaces (Klausegger et al. 1999).

The coronavirus enters into the host cell by binding through the ACE2 receptors which are widely expressed on lungs basically in type 2 alveolar cells while few on kidney, liver, heart, intestine and testis (Li et al. 2020b). Epithelial cells, alveolar macrophages, and dendritic cell basically triggers the innate immunity in the lungs. The dendritic cells along with macrophages will phagocytize the infected apoptotic cell enabling the antigen presentation to T cells (Yoshikawa et al. 2009). The spike (S) proteins are cleaved by the cellular proteases, transmembrane protease serine 2 (TMPRSS2), into two subunits S1 and S2. The S1 unit facilitates the binding to the host cell receptor and the S2 subunit allows the fusion of viral and cellular membrane (Zhang et al. 2020b). These spike proteins are specifically recognized by the T cells initiating an immune response consisting of T cells or plasma cells that will produce antibodies against the viral spike proteins. The virus entry initiates the immune response of human. This immune response includes several protective pathways (Belouzard et al. 2009; Channappanavar et al. 2014). As the body fails to combat the coronavirus, this deregulation of immune response leads to the hyper inflammation of covid'19 known as cytokine storm (Ye et al. 2020) As a first step on entry of viral RNA the immune cells sense it through viral derived pattern associated molecular pattern (PAMPs). This viral RNA muddles to and stimulates pattern recognition receptors (PRR's), located on immune cells which triggers the immune response. The most commonly involved RNA-PRR's are Toll like receptors (TLR) 7 and 3, cytoplasmin RNA sensors namely retinoic acid inducible gene I (RIG-I) and melanoma differentiation associated protein-5 (MDA5). This in turn, translocate the transcription factor NFkB and IRF3 which in turn triggers the T1IFN and other innate pro inflammatory cytokines, e.g., TNF-α, IL-6 and IL-1. The auto amplification promotes their own expression (Prompetchara et al. 2020; Bosch et al. 2003). The elevated expression of these pro-inflammatory mediators are the indicators of the severity of disease causing multi-organ failure which may lead to death. In chronic conditions, however, there are also the chances of developing ground glass infiltrate, lymphopenia, hyper-ferritinemia, increased lactate dehydrogenase, IL-6 and erythrocyte sedimentation rate (ESR) (Tay et al. 2020).The virus inside the lungs not only replicate in alveolar cells bust also damage it. The injured alveolar cell activates the alveolar macrophages that not only phagocytize the injured cells but also release IL-1, IL-6, IL-8, cytokines, other chemokine's and TNFα. This pro-inflammatory mediator stimulates the nerve endings responsible for the cough reflex (Jia et al. 2005). The TNFα and IL-1 cause the increase in vascular permeability which increases the number of adhesion molecules allowing the recruitment of more circulating monocytes and neutrophils to the injured site. The increased vascular permeability causes the outflow of fluid into interstitial spaces and alveoli

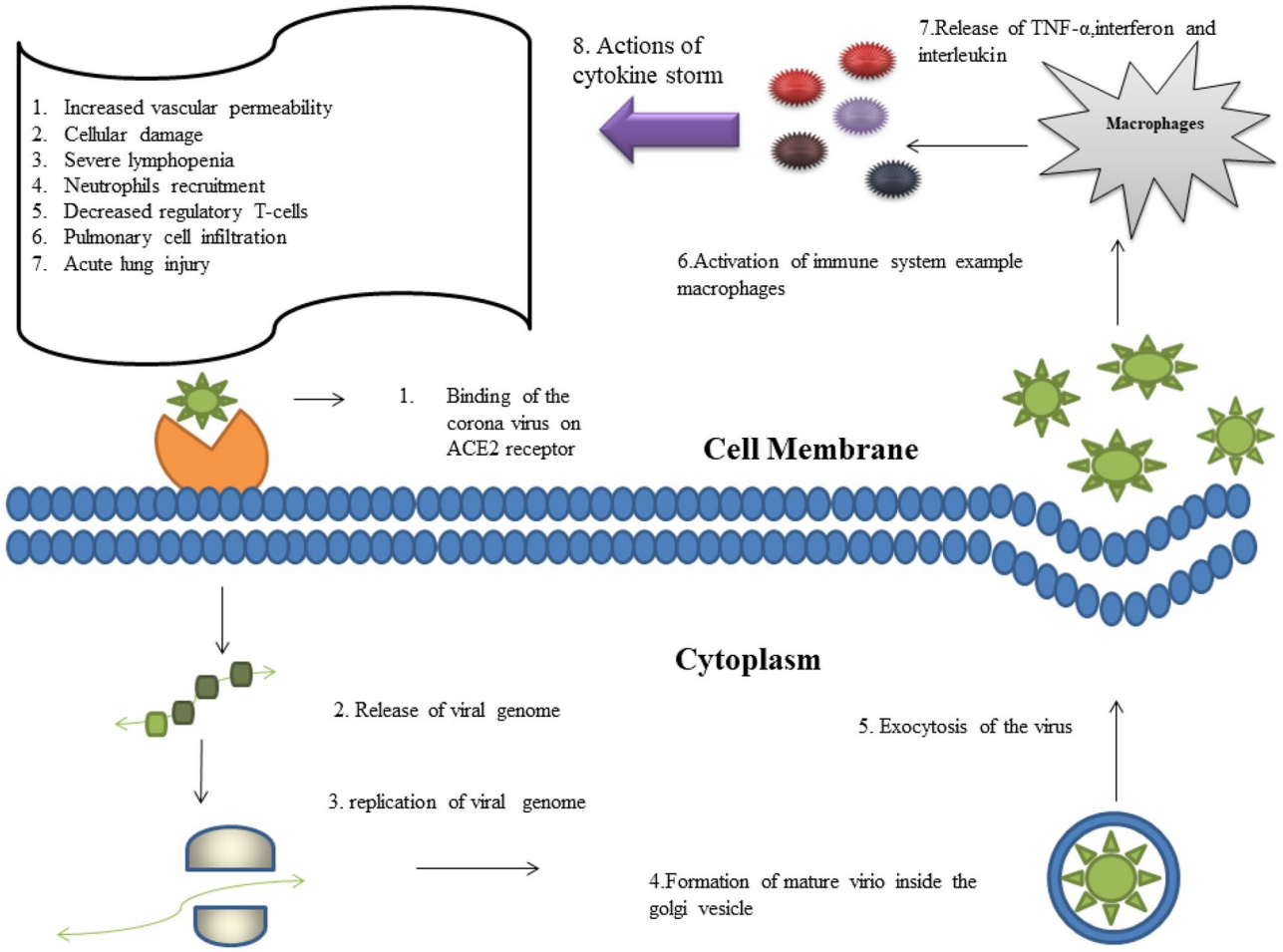

Fig. 1 Pathological effects of cytokine storm following the entry and replication of COVID-19 to host cells

producing interstitial and pulmonary edema, respectively. This will lead to dyspnea and hypoxemia (Ou et al. 2020). On the other hand, the damaged endothelial cells of alveoli release the prostaglandins and leukotriene. Leukotriene will cause bronchoconstriction while prostaglandins with other cytokines are the prime reason of fever, an important feature of Covid'19 (Bartee and McFadden 2013). Hypoxia will trigger the heart to pump faster for sufficient supply of oxygen that's why covid'19 patient suffers from tachycardia and tachypnea (Ståhlberg et al. 2021).

Cytokines, their production, types and properties

Cytokines types and their production

The word cytokine is the derivative of two words "Cyto" means cells and "kinos" means movement. These are low molecular weight regulatory proteins or glycoproteins and are cell signaling molecules. These are secreted by white blood cells and various other cells in the body in response to a number of stimuli. These are mainly activated by lymphocytes, macrophages, dendritic cells but also from connective tissue cells, epithelial and endothelial cells and mediate inflammatory and immune reactions. There are many types of cytokines depending on their functions and origin of secretions, e.g., chemokine has chemotactic activity, interferons are involved in antiviral response mostly and colony stimulating factors that support the growth of blood cells. Monokines and lymphokines are produced by monocytes and lymphocytes while interleukins are produced by one leukocyte and act on other leukocytes. It results in the immense activation of the protected system which includes uncontrolled release of pro and inflammatory mediators prompting in inflammation (Ye et al. 2020).

Properties of cytokines

Cytokines have different properties for example Pleiotropic means different cell types which can secrete same cytokines or a single cytokine acting on several cell types. Cascade

induction, another cytokine property, is stimulation of target cells by one cytokine to make additional cytokines. Synergism, another property, not only combat with the infection but also damages the host cell (Varga et al. 2020). The immune system has an impressive ability to respond to various pathogens including COVID-19 that activates the inflammatory pathways of immune system that are part of the innate immune response including macrophages, dendritic cells, natural killer cells and the adaptive T and B lymphocytes. The cytokine response which leads to irreversible tissue damage as a result of the release of pro inflammatory mediators including IL-6, IL-1 and TNF-alpha. The cytokine storm may cause respiratory distress syndrome in COVID-19 patients. Normally this storm returns back to normal after clearing the infection but if it fails to return back, it may be alarming pathological conditions. The often-associated adverse effects with it are gangrene of extremities, vascular hyper-permeability, and hyper-coagulation (Henderson et al. 2020).

A brief overview of different cytokines and their physiological role

The main cytokine involves in the cytokine storm are discussed as followings.

Interleukin

The interleukins mediate the leukocytes functions. Almost up to 38 ILs have been identified so far and are numbered according to the order of discovering. These are involved in the human inflammatory and autoimmune responses. The interleukins having significant role are IL-1, IL-6 and IL-17. The cells involved in the expression of interleukins are monocytes, B lymphocytes, dendritic cells macrophages, T lymphocytes, and non-lymphocyte cells including fibroblast and endothelial cells. Specifically, the IL-6 is secreted by macrophages while IL-17 by T-lymphocytes. The IL-1 is involved in many physiological roles such as the stimulation of the expression of endothelial adhesion molecules, emigration of neutrophils and macrophages and secretion of other cytokines especially those involved in inducing fever. While the IL-17 is involved in the recruitment of neutrophils and monocytes, secretion of other cytokines, e.g., IL-6 and TNF-alpha (HAMBLIN A. J. I., 1988). Factors which stimulate the secretion of IL-6 in Covid patients are TNF-α and Toll like Receptors (TLR). In critical patients of COVID-19, it is usually released at high level and may be the early indicator of the cytokine storm and acute respiratory distress. IL-6 level helps in disease progression and to develop treatment plan (Ulhaq and Soraya 2020). Normally the different roles of IL-6 include that it acts on the hepatocytes and produces C-reactive protein, increase the serum level of amyloid leading to amyloidosis, increase the level of fibrinogen, increasing the cardiovascular events like heart diseases, releases hepcidin leading to iron deficiency or anemia, and also reduces the production of albumin that causes edema. Il-6 also elevates the platelet production by stimulating the bone marrow leading to blood clots, potentiating the chances of thrombocytosis.

The osteoclasts are also releases by IL-6 that will enhance the osteoclastic activity resulting in fractures (Coomes and Haghbayan 2020). The role of IL-6 in Covid-19 patients is that it binds to its α-IL-6 receptors which are widely present on the membrane of immune cells after the IL-6 is attached to the receptor. This causes the dimerization of β-receptors gp130 the signaling molecules or the co-receptors. This indirectly triggers the signal transduction by stimulating the JAK/STAT pathways. Resulting cascade leads to Covid-19 cytokine storm. It inhibits the production of T-regulatory cells T CD4, CD25 contributing in the development of autoimmune disease. IL-6 is also particularly important in inducing B cells to differentiate into antibody producing cells or plasma cells (Magro, 2020).

TNF-α

TNF-α is a protein consisting of 157 amino acids and is a homo-trimer. It is the pro-inflammatory cytokine and is the most important factor. It regulated different physiological and pathological processes. Its super family consists of 19 members of type Π transmembrane proteins (Filik and Avan 2020). It is mostly secreted by macrophages, fibroblast endothelial cells and few epithelial cells. It stimulates the adhesion of endothelial molecules. Emigration of neutrophils and macrophages, secretion of other cytokines and in inducing fever. It also regulates the energy balance by promoting lipid and protein catabolism or by suppressing the appetite. It plays an important role in rheumatoid arthritis and bone remodeling as it regulates the bone marrow level of osteoclast precursor by enhancing the signaling pathway of the receptor activator of NF-kB. It also functions in infection control and defending intracellular organism against invasion. It functionally trigger a series of inflammatory molecules including other cytokines and chemokines (Baugh and Bucala 2001).

It exists in transmembrane and in soluble form. It is initially synthesized in a precursor form and is converted to active form sTNF-α by TNF-α converting enzyme (TACE). This activated form activates the biological events of cascade, e.g., inflammation and cellular death by binding to TNF-α receptor 1 or 2 (TNFR1) and (TNFR2). The activation of TNFR1 can trigger different signaling complexes known as complex 1, 2a, 2b, and 2c that produces cellular responses. In this the TNFR1 binds to TNFR1-associated death domain called TRADD and results in further

interaction with different proteins called serine/threonine-protein kinase-1 (RIPK1), TNFR-associated factors 2 and 5 (TRAF2/5) cellular inhibitor of apoptosis protein 1 or 2 (CIAP1/2), ubiquitin chain. These all molecules triggering results in the activation of nuclear factor kB (NF-kB) and mitogen activated protein kinase (MAPKs). The functional end of the activation of TNFR1 is the induction of inflammation, tissue proliferation, cell survival and immune defense against pathogens. Whereas the formation of complex 2 by the TNFR2 allows the downstream activation of NF-kB, MAPKs, and protein kinase B leading to tissue regeneration, cell proliferation, cell survival and other homeostatic bioactivities. The extracellular proteolytic cleavage releases these proteins which act as TNF (Spriggs et al. 1992). These are produced by endothelial cells, monocytes, macrophages, neutrophils and activated lymphocytes. Its main function is the expression of the genes of growth factor, transcription factor and receptors. It is a prominent feature of severe covid-19 patients. It activates the HA-synthase-2 (HAS2) in lung alveolar epithelium and endothelium. This causes the fluid influx in the alveoli ending in deoxygenation or decreased oxygen saturation level (Mackay et al. 1993). During SARS-CoV-2 infection aggressive inflammatory response and cytokine storm contribute to the severe lung tissue damage and mortality. Recent research demonstrated that synergism between TNF-α and interferon triggers robust cell death during the activation of the JAK/STAT1/IFR1 axis in the human monocytic cells. The kinetic of lung cell death is proportional to the concentration of TNF-α and interferon. So blocking the inflammatory cell death pathway is beneficial to Covid patients or in other inflammatory diseases (Lau et al. 2013).

Interferon cell signaling pathway

Interferon is the proteins made and released by host cells in response to the presence of pathogens such as viruses, bacteria, parasites or tumor cells. They allow the communication between two cells to initiate the protective mechanism of immune system to eradicate tumor or pathogen. Interferon (IFNs) is the glycoproteins known as cytokines. These are basically named after their ability to "interfere" with the viral replication within the host cells (Sledz et al. 2003). They activate the immune cells, e.g., the natural killer cells or macrophages for engulfing. On the other hand, they also increase the recognition of infection or tumor cells by up regulating the antigen presentation to the T lymphocytes and also increases the ability of unaffected cells to resist to the pathogen. During infection some particular symptoms like muscle ache and fever is due to the IFNs release. Humans have almost seven types of interferon. Interferon is basically classified into two types based on the type of their receptors, e.g., Type IFN and Type 2 IFN. Interferon that binds to both of the receptors are important for combating the viral infection (Platanias 2005). Type 1 IFN binds to a specific cell surface receptor complex known as Interferon α/B receptor. This is made of two chains IFNAR1 and IFNAR2, these both are transmembrane proteins. Binding to these receptors activate the JAK-STAT pathway. The type interferon includes IFN-alpha, IFN beta, IFN epsilon and IFN omega. This type is usually produced by leukocytes, monocytes and fibroblasts. Interferon type 2 binds to interferon receptor 2 and this includes interferon-gamma. These are responsible for stimulating the macrophages so are also known as macrophage activating factor. In Covid-19, the virus in the lung cells activates the INF genes that act as defensive molecules against coronavirus. These interferons will bind respectively to their specific receptors on un-infected cells triggering the JAK/STAT signaling pathway to trigger nucleus to make anti-viral proteins so that when virus attacks to this particular cell it can combat the attack by degrading the virus. Interferon are involved in the initial stage of innate immunity (Lau et al. 2013; Caraglia et al. 2004). Lambda interferon is produced by the CD4 T helper cells, it promotes the differentiation of the CD8 T-cells and hence inhibits the entry of the coronavirus in the cells (Favalli et al. 2020).

Cytokine and the associated covid-19 comorbidities

The cytokine storm has a vital role in the exacerbation of the viral infection that directs to the comorbidities in the covid-19 patients. The most commonly found co morbidities are thrombosis, pulmonary complications and coagulopathy. The key contributors to these morbidities are IL-6, IL-2R, IL-1β and TNF-α. In the cytokine storm the blood serum level of inflammatory cells surges which causes the more recruitment of the immune cells at the target site. On the other site the inflammatory cells move out of the blood vessels to reach infected cells. Hence, due to these cellular changes the blood membrane becomes squeaky and hence more penetrable eventually contributing to more capillary escape. This substantial leak of the blood plasma into the surrounding environment forms a blood clot inside the vessels occasioning in coagulation or thrombosis. The state of hypoxia occurs due to decreased level of oxygen in the body (Favalli et al. 2020). The platelet activation or the conversion of fibrinogen into fibrin by thrombin stimulates the clot formation. In case the anticoagulation mechanism is impaired it can end up in micro thrombosis, multi-organ damage or disseminated intravascular coagulation (Jin et al. 2020). Similarly, the other co-morbidity usually seen is the pulmonary complications. The ACE 2 receptors are significantly present on the membrane of alveolar cells, bronchial epithelium and vascular endothelium. As the cellular cascade activated on activating these ACE-2 receptors by the coronavirus, it results in the fluid retention in the alveoli known

as pulmonary edema. This decreases the gaseous exchange capacity of the lungs so less oxygen reaches to the organs and shortness of breath is developed. Proper ventilation can also be needed if hypoxia is severe. Antibodies and fluid management are required to prevent secondary infections as immune system has got weak (Matthay et al. 2020).

Effect of existing inflammatory conditions on covid-19 patients

Although SARS-CoV-2 infection itself involves inflammatory condition but literature has revealed that pre-existing inflammatory conditions like diabetes, rheumatoid arthritis, inflammatory bowel diseases, asthma and tuberculosis may provoke the SARS-CoV-2 infection.

Asthma

The word asthma comes from the Greek word Panting. This involves the chronic inflammation of the airways making them narrow and more difficult to breathe through. People with asthma can have asthma attacks or asthma exacerbation triggered by the irritants in the environment that stimulate the immune cells in the lungs to produce inflammation of airways, making them narrower and potentially life threatening. In asthma the T-helper cells are involved as the allergens from the environment, triggers these helper cells to produce IL-4 and IL-5 (Maddox and Schwartz 2002). The IL-4 releases the production of IgE antibodies that causes the mast cells to continuously release chemicals like histamine, leukotrienes and prostaglandins. While the IL-5 secretes the eosinophil's which promotes immune response to release more cytokines and leukotriene. Asthma is a type 1 hypersensitivity reaction as IgE antibodies are involved. The exposure to allergen hence ultimately causes the smooth muscle spasm and increased mucus secretion making the airways narrower and ending up in the difficulty to breath (Barnes and Drazen 2002). There is also the increased permeability of the vasculature facilitating more immune cells especially eosinophil that release chemical mediators which damage the endothelium of the lungs. Initially these inflammatory changes are reversible but over the time they become irreversible accompanied by edema scarring and fibrosis (Sinyor and Perez 2019). The causes of asthma can be genetic like having family history or environmental factors like early exposure to bacteria/viruses or any allergens. The childhood asthma is usually due to genetic factors and later onset of asthma is due to environmental factors or at times medication like aspirin or beta blocker (Beasley et al. 2015). The symptoms of asthma include chest tightness, wheezing, dyspnea or coughing. This is a severe reparatory disorder and the important risk factor of Covid-19. Immune systems weaken in asthmatic patients and the delayed release of the IFN-lambda makes the patient more prone to Covid-19(Johnston, 2020). Moreover, the asthmatic patients are associated with increased level of expression of ACE-2 receptors and TMPRSS2. The use of oral corticosteroids decreases ACE-2 receptor expression. The asthma triggers the covid'19 infection and at times they both have quite same symptoms, e.g., dry cough and shortness of breath (Kimura et al. 2020). The treatment of asthma is recommended to be continued in the covid-19 infection as it decreases the severity of infection but the use of nebulizer is discouraged due to increased chances of viral transmission through aerosol route. Metered dose inhales or dry powder inhalers are suggested. The bronchodilators, anti-cholinergic and antihistamines are used in the treatment. In a study conducted on asthmatic patients revealed that adults with asthma history are more likely to infect with Sar-Cov-2 viruses than children (Abrams and Szefler 2020).

Tuberculosis (TB)

Almost 2 billion people worldwide are infected with mycobacterium tuberculosis. About 90–95% people initially are unaware that they are infected because virus is in a latent phase in which immune system restricts its multiplication. When the virus becomes active, it multiplies and can be spread to others. In the active phase the sign and symptoms appear. The mycobacterium is of rod shape and needs oxygen to survive. They are encapsulated by the waxy cell wall composed of mycolic acid so they can be dyed by acidic dye eosin staining into bright red color. The cell wall also protects it from disinfectant and helps to survive on dry surfaces for months (Flynn and Chan 2001). The bacteria are usually transmitted through inhalation and so enter into the lungs. The TB avoid the mucus air trap in the airways and enters into the alveoli. In alveoli, the alveolar macrophages are present that identifies and destroys the foreign molecules like TB. Normally the foreign molecule is being lysed by the hydrolytic enzymes produced by lysosome but TB produces proteins that inhibit action of hydrolytic enzymes allowing the mycobacterium to survive and proliferate to cause localized infection. This stage is called the primary tuberculosis usually asymptomatic or with mild flu like symptoms. After the 3 weeks of initial infection the cell mediated immunity activates forming a granuloma surrounding the mycobacterium, avoiding it from spreading. The tissue in the middle of the granuloma dies forming caseous necrosis and area is called as Ghon focus. This Ghon focus undergoes fibrosis and calcification. In some cases, the mycobacterium is killed by the immune system while in other cases, even after walled up they remain viable but dormant. If the person immune system becomes compromised like with AIDS or covid-19. The Ghon focus can reactivate and infection can spread to the upper lobes of the lungs because the oxygenation is

largest in these areas. Memory T cells release cytokines forming more caseous necrosis forming cavities allowing the bacteria to disseminate through air ways to other parts of the lungs causing broncho-pneumonia. It can also be spread through the vascular system to every other part of the body forming systemic Miliary-TB. Kidney, liver, adrenal glands, meninges of brain, lumber vertebrae and other vital organs of the body are also affected (Etna et al., 2014; VIJAYAN, V J. I. J. O. C. B. 2002). Usually, the treatment of TB includes isoniazid, rifampin, ethambutol, pyrazinamide. Tuberculosis is a severe bacterial infection characterized by the sputum cough (Stochino et al. 2020). These patients are strictly advised to follow the preventive measure of the covid-19 infection (He et al. 2020).

Diabetes mellitus (DM)

It is the protracted auto immune disease in which blood glucose regulation system is impaired. The insulin production decreases and insulin resistance develops resulting in increased glucose level in the body. The cells do not have sufficient glucose which is the source of energy, so the cells starve for energy (Kaul et al. 2013). Normally the insulin and glucagon maintain the level of glucose in the cells and blood respectively. Both of these hormones are produced by the pancreas. The insulin is secreted by the beta cells and glucagon is secreted by the alpha cell of the Islets of Langerhans. The insulin transports the glucose into the cells from blood and glucagon triggers gluconeogenesis or the breakdown of glycogen to glucose that is transported to the blood. In both cases of DM (type I and II), the blood glucose level increases and patient develop symptoms like urination, thirsty, lethargy, fatigue and losing weight abruptly. There is a greater risk of mortality and infection in DM patients in comparison to other patients (Muniyappa et al., 2020). In diabetic patients there is decreased T cell activity and the hyper inflammation which increases the susceptibility of COVID-19 infection (Guo et al. 2020). Factors that potentiate the virus uptake in DM patients are the increased expression of the ACE-2 receptors and the protease enzymes which facilitates the entry of virus into host cells. This can be controlled by administering ACE inhibitors or ARBs that are also the part of DM therapy. These all factors make the diabetic patient more prone to the COVID-19 infections and special precautions must be taken by these patients (Maddaloni and Buzzetti 2020).

Rheumatoid arthritis (RA)

This is a chronic inflammatory disorder that mostly affects the joints. It is a serious autoimmune inflammatory disorder (Grassi et al. 1998). The healthy joint includes two bands of articular cartilage at the ends of the joint. The articular cartilage is a type of connective tissue that protects and lubricates the joint. The knee joint is a type of synovial joint that connects the two band with fibrous joint capsule and continues with the outer layer called periosteum. The fibrous capsule is lined with synovial membrane composed of synovial cells that produces synovial fluid that is of jelly like consistency, helps to lubricate the joint. Synovial membrane is also covered with lymphatic's and blood vessels (Sweeney and Firestein 2004). The causative agents of RA include pathogens or human leukocyte antigen causes the modification of the antigen such as IgG antibodies, type 2 collagen or vimentin through citrullination. In this the arginine is converted into citrulline which is not recognized by the immune cells as self-antigens. These antigens are picked by the antigen presenting cells and carried to the lymph nodes where CD4 cells and B cells are activated producing antibodies against these self-antigens. In RA the T-helper cells and antibodies enter the circulation reaching the synovial fluid of joints. There the T cells secrete cytokines and recruits more macrophages, TNF-α, interleukins and interferon, rheumatoid factor therein (Table 1).

The synovial cells proliferate and the combination of these cells along with cytokines forms pannus. This pannus damages the cartilage, soft tissues of joint and also erodes bone. The joint is damaged by the rubbing and inflammation

Table 1 Types of cytokines, their sources and possible mechanism of action

Cytokines	Source	Possible mechanism of action	References
Interleukin-1	Monocytes and Dendritic Macrophages	Stimulation of the expression of endothelial adhesion molecules	(HAMBLIN, A. J. I, 1988)
Interleukin-17	Macrophages and B lymphocytes	Recruitment of neutrophils and monocytes	(HAMBLIN, A. J. I., 1988)
Interleukin-6	Macrophages and monocytes	Triggers JAK/STAT pathway	(Ulhaq and Soraya, 2020; MAGRO, G. J. C. X., 2020)
TNF-α	Macrophages and endothelial cells of alveoli	Activation of HA synthase-2 (HAS2)	Baugh and Bucala, 2001, Mackay et al. 1993)
Interferon	Host cells	Promotes the secretion of anti-viral protein	(Sledz et al. 2003; Platanias 2005; Caraglia et al. 2004)

(McInnes and Schett 2011, RHEUMATISM, 1959). This inflammatory cytokine can also affect the healings forming scar tissues by the action of fibroblasts in the interstitial or the pleural cavities, can be filled with fluid causing breathing difficulties and weakening of lungs ultimately (D'Silva and Wallace 2021). The corticosteroids impair the immune system hence delaying the clearance of the COVID-19 virus potentiating the chances of infection (Schett et al. 2020).

Inflammatory bowel disease (IBD)

The two main IBD are Crohn's diseases and ulcerative colitis, both are characterized by chronic inflammation. These both diseases differ each other by the site and the extent of inflammation, e.g., the ulcerative colitis affects the colon while the Crohn's disease can affect the entire digestive system (Baumgart and Carding 2007). The symptoms of IBD may come and over go and most commonly the symptoms are stomach pain, diarrhea, decreased appetite, weight loose, fever, night sweats and extreme tiredness. The ACE-2 receptors are also present in the terminal ileum and colon while in this disease the expression of ACE-2 receptor increases due to inflammatory condition. In the inflamed gut, the level of proteases enzymes also increases facilitating the binding and uptake of the virus, respectively (Monteleone and Ardizzone 2020). The treatment of IBD also increases the susceptibility to the infection but still discontinuing the therapy is not recommended. That's why people with IBD are at more risk of Covid-19 in comparison to the people without IBD (Rubin et al. 2020).

Treatment regimens for covid-19

Currently, there is non-specific therapy for treating COVID-19 virus, only supportive aid is being used. The classes of drugs being used in treatment of COVID-19 as described in Table 2. Mostly used drug classes for treatment are antivirals, antibiotics, antipyretic, anti-inflammatory drugs, corticosteroids, anti-tussive drugs and few nutrients are also used as well. In the initial stages of Covid-19, anti-viral are mainly used to restrict the advancement of the disease whereas in later or critical stage the combination of immunomodulators and anti-viral drugs are used. Now there are some emerging herbal medicines as well that also plays an effective role in the treatment. The different therapeutic regimen used for controlling of Covid-19 is as following.

Antivirals

Many anti-viral being used for the HIV infection are also prescribed to Covid-19 patients as these inhibit the protease activity that is fundamental for the viral replication. The antivirals are used from the initial stage till the chronic stage so it is a fundamental part of the covid-19 regiment. The different anti-viral being used are.

Table 2 An overview of therapeutic interventions for treatment of COVID-19

Class	Drugs	Mechanism of Action	References
Anti-viral	Remdesivir	RNA dependent polymerase inhibitor	(Sheahan et al. 2017)
	Lopinavir	HIV-1 protease inhibitor	(Chu et al. 2004)
	Ritonavir	HIV-1 Protease inhibiter	(Hung et al. 2020)
	Favipiravir	RNA polymerase inhibitor	(Agrawal et al. 2020)
Disease modifying ant rheumatic drugs (DMARDs)	Hydroxychloroquine chloroquine	Hinders the viral access into the host organism	(Mehra et al. 2020)
Anti-inflammatory drugs	Glucocorticoids	Inhibition of the production of prostaglandin leading inflammation	(Ronchetti et al. 2018)
	Tocilizumab	Antagonist of IL-6 receptor	(Luo et al. 2020)
JAK\STAT inhibitors	Baricitinib	Inhibits the type 1 and 2 receptors of cytokine	(Richardson et al. 2020)
Anti-fibrotic drugs	Ninetedanib	It causes the downstream signaling cascade of fibroblast growth factor receptor to prevent pulmonary fibrosis	(Rangarajan et al. 2016)
	Pirfenidone	Inhibits the fibroblast proliferation by inducing the phosphorylation of mediators	(Conte et al. 2014)
Antibiotic drugs	Azithromycin	Obstructs the protein synthesis by inhibiting the translocation step in protein synthesis	(Echeverría-Esnal et al. 2021)
	clarithromycin	Inhibits protein synthesis by preventing the translation of peptides	(Ohe et al. 2020)
Bronchodilators	Albuterol	Relaxes the bronchial smooth muscles by binging to the Beta-2 adrenergic receptors	(Weber et al. 2020)

Remdesivir

It is a nucleotide analogue which is RNA dependent polymerase inhibitor previously used for treating the Ebola virus pandemic in Africa and used for Covid-19 patients. It is a prodrug having a broad spectrum range against the viruses example Filoviridae, paramyxoviridae, pnemoviridae, MERs and SAR coronavirus (Sheahan et al. 2017). According to the stage of coronavirus the days of anti-viral administration are suggested like patients at initial stage can be cured with 5 days of administration while chronic patients may have to continue it for up to maximum 14 days. The day varies between 5 and 14 days depending on the condition of the patient. This is also concluded by a case study conducted on 397 people in which 67% people at initial stage were cured within 5 days of regiment, 54% were cured with 10 days of medication and 74.4% were treated with 14 days of regiment (Goldman et al. 2020).

Lopinavir and ritonavir

These are the protease inhibitor drugs and usually used in combination with other drugs for the HIV treatment and is the HIV protease inhibitor (Chu et al. 2004). The combination these drugs with the ribavirin reduces the risk to the adverse drug reactions such as respiratory distress syndrome or death. Recently a study concluded that the mild to moderate patients of Covid'19 received 14 days combination of Lopinavir 400 mg and Ritonavir 100 mg every 12 h was effective in bringing the negative nasopharyngeal swab for COVID-19 with RT-PCR (Hung et al. 2020). Another study proved that at initial stage the combination of drugs can combat the virus in 5 days in comparison to each drug being administrated separately, but this combination is not effective for the patients critically ill and being hospitalized or are on respiratory support (Wölfel et al. 2020).

Favipiravir

This is an oral broad spectrum RNA dependent RNA polymerase (RdRp) inhibitor that causes chain termination and mutation (Agrawal et al. 2020). In vitro studies have demonstrated that a therapeutic dose can be effective against COVID-19 infection. It is mostly used for mild to moderate patients. It has a broad range against viruses like influenza virus, Arenavirus, phlebovirus, Hantaviruses, flaviviruses and Ebola viruses. The dosing is 1600 mg at first day, then 400 mg BD a day from day 2 to 6 continued by 400 mg once daily at 7th day. Precautions must be taken while administering theophylline, famciclovir and pyrazinamide (Chu et al. 2004).

Chloroquine or hydroxychloroquine

These drugs have activity of antimalarial as well as immunomodulators activity so this synergistic effect enhances its effect. It is already widely used for rheumatoid arthritis and malaria. They hinder the entrance of the viral into host cell by neutralizing the pH of the endosomes and lysomes to restrict the effect of protease enzyme in order to prevent S protein cleavage that facilitates the entrance of virus (Mehra et al. 2020). These can be used with or without the macrolide example azithromycin and clarithromycin. It was concluded that it can also cause cardiac adverse drug reaction like onset of ventricular arrhythmias or prolongation of QT interval, due to this on June, 2020 the World Health Organization announced to discontinue these drugs for the treatment of Covid-19 (Cortegiani et al. 2020).

Anti-inflammatory drugs

As the pathogenesis of the Sar-Cov-2 involves the cytokine storm or the expression of pro-inflammatory mediators like IL-1.IL-8, IL-6 and TNF-α so the anti-inflammatory drugs are also used to manage COVID-19 virus. These drugs are also used in in the inflammatory diseases like rheumatoid arthritis and etc. (Conti et al. 2020). This class includes following drugs, e.g.

Glucocorticoids

This is used for the treatment of coronavirus pneumonia or influenza pneumonia without any consequence. In 2003 it was declared as a main drug in immunomodulators therapy and can also be used in small doses in septic shock. In COVID-19, it is used in severe complications as no effect was being observed at mild stage (Yam et al. 2007). The glucocorticoids binds to its receptor and up regulates the lipocortin that inhibits the production of phospholipase A2 and it also down regulates the COX2 hence the prostaglandin production is inhibited. A case study reported that patients treated with glucocorticoid have one third lower mortality rate than those treated without it. Hence they are proven to improve the outcomes at the critical stage that involves the cytokine storm (DHASMANA D. J. J. N. E. J. O. M. 2021).

Tocilizumab

This was authorized by AIFA on 3rd April in phase 3, double blind, multicenter and randomized study to appraise the efficacy and safety. This is an antagonist of the IL-6 receptor hence inhibiting the IL-6 mediated cell signaling. It is already being used for the Crohn's disease and Castleman disease and is also seen beneficial in the management of severe Covid'19 patients. The recommended dose is 8 mg/kg

by IV drip every 4 weeks and for the body weight less than 30 kg dose given is 12 mg/kg for every 2 weeks. Patients who had SaO2 less than 93% and a partial oxygen pressure (Pao2)/inspired oxygen fraction (FiO2) is less than 300 mmHg in 24 h of proceeding in the hospitals are recommended (Luo et al. 2020).

Janus kinase signal transducer and activator of transcription. (JAK/STAT) inhibitors

This is a promising approach for the patients in the hospitals. These are the biological agents that inhibit the type 1 and 2 cytokine receptors present on the immune cells (Seif et al. 2017). FDA approve the Tofacitinib an effective oral JAK inhibitor for the handling of rheumatoid arthritis in 2012. Tofacitinib can effectively block IL-2, IL-6, IL-7. Nevertheless no treatment of SAR-Cov-2 virus with Tofacitinib has been reported (Lee et al. 2014). Baricitinib is a selective JAK 1 and 2 inhibitors and is approved for rheumatoid arthritis. These classes of drugs can improve the condition of the Covid'19 patients. A dose of 4 mg daily orally of Baricitinib is administered to the critical patients. In a case study it was reported that 113 patients treated with Baricitinib had two weeks case fatality rate less than 78 people treated with usual care. The therapy with Baricitinib was recommended at the initial stage of the disease resulting in decreased number of admission in intensive care unit and deaths (Richardson et al. 2020). Other jakinibs include ruxolitinib, memolitinib, oclatinib, Fedratinib and Gandotinib are the JAK inhibitors that can potentially affect signaling pathway downstream of the receptor involved in Covid'19 development (Furqan et al. 2013).

Anti-fibrotic drugs

The patients of Covod-19 are at greater risk to develop the pulmonary fibrosis that can be treated by administering the anti-fibrotic drugs, namely ninetedanib and pirfenidone. These drugs can reduce the complications at the severe stages associated with the fibrosis (George et al. 2020). The ninetedanib binds to the fibroblast growth factor receptor inhibiting its phosphorylation hence its downstream signaling cascade to prevent pulmonary fibrosis (Rangarajan et al. 2016). The pirfenidone reduce the TGF-β induced phosphorylation of the key mediators example Smad3, p38 and Akt of the fibrosis pathway (Conte et al. 2014).

Antibiotic therapy

The macrolides like azithromycin and clarithromycin are widely used in the Sar-Cov-2 virus. These drugs are basically used for protecting the patient from secondary infections as the immunity of the person has gotten weak due to the viral infection (Ali et al. 2020). The azithromycin binds to the 23S rRNA unit of 50S ribosome and obstructs the protein syntheses by inhibiting the transpeptidation and translocation step (Echeverría-Esnal et al. 2021). The Clarithromycin inhibits the protein syntheses by preventing the translation of peptides (Ohe et al. 2020).

Bronchodilators

These are not the part of the standard therapy but can be used as per need. Nebulizers associated with the aerosolization should be avoided as it can be a way of transmission. The most effective bronchodilator used for Covid patients is albuterol which binds to the beta-2 adrenergic receptors to relax and dilate the bronchial smooth muscles. Additionally it also inhibits the release of hypersensitivity mediators from the mast cells (Weber et al. 2020). Whereas metered dose inhalers (MDI) can be used in asthma or bronchospasm and Chronic obstructive pulmonary disease (COPD). If nebulizer is to be used then special care and personal protective equipment is recommended. Patients with severe hypoxia need bronchodilators to improve the ventilation perfusion. Improvement in oxygenation is seen within few hours of administering the bronchodilators (Levin et al. 2020).

New emerging drugs for treatment of covid-19

Few emerging therapeutic regimens for treatment of COVID-19 has been shown in Table 3.

Lactoferrin

Lactoferrin is an iron interacting glycoprotein that consist of 703 amino acid residues and is secreted by glandular cells in the mammalian milk. It plays a vital role in non-specific host defense molecules against wide range of viruses including cytomegaly virus, herpes simplex virus, rotavirus, poliovirus, hepatitis C virus Human papillomavirus, and influenza virus. It is in the phase 1 of the clinical trials in prospective randomized double-blind placebo controlled designed trial. It has anti-inflammatory as well as immunomodulators activity because of which it is being considered in the treatment of covid'19. It can trigger the immune system to respond the entry of virus (Ng et al. 2015). It inhibits the virus to enter into the host cell by binding to the cell surface molecules namely Heparan Sulphate Proteoglycans (HSPGs) that facilitated the entry of virus into the host cells. The anti-inflammatory and the down-regulation of the cytokines including IL-6 and TNF-α helps in reducing the severity and mortality associated with COVID-19. The range of dose is 100-1000 mg/kg is such a way that 32 mg if administered at three to four doses per day for ten days with zinc 10 mg

Table 3 Emerging therapeutic interventions with possible role in treatment of COVID-19

Classification	Name of drug	Mechanism of action	Clinical trial	References
Anti-viral	Lactoferrin	Inhibits the entry of coronavirus by binding with the receptor	Phase 1	(Ng et al. 2015)
Anti-coagulant	Nafamostat	Protease inhibitor	Phase 2	(ORGANIZATION, W. H., 2018)
Anti-inflammatory	Ruxolitinib	JAK-2 inhibitor	Phase 3	(El Bairi et al., 2020)
Anti-inflammatory drug	Infliximab	JAK-2 inhibitor	Phase 2	(Stallmach et al. 2020)
Chelating agent Anti-Fibrotic agent	Deferoxamine	Binds to the iron making it unavailable for fibrosis process	Phase 2	(Georgiou et al. 2000)

twice daily resulted in COVID-19 recovery in the experimental studies (Serrano et al. 2020).

Nafamostat mesylate

Nafamostat Mesylate is being used in the therapy of acute Pancreatitis in Japan. Transmembrane protease serine 2(TMPRSS2) plays a critical role in the entry of Sar-Cov-2 and Nafamostat Mesylate is a protease inhibitor inhibiting the (TMPRSS2) thus interfering with the entry of Sar-Cov-2. In Japan this drug has been approved as a novel medicine influenza virus disease. This drug is being used in combination with Favipiravir in clinical trial (Yamamoto et al. 2016). This is in phase 2 of clinical trials for Covid disease. The Favipiravir is an antiviral drug exhibiting activity against RNA viruses thus is used against COVID-19. This combination of drugs inhibits the virus entry as well as its replication. Furthermore, the Nafamostat is also used in treating hyper-coagulation associated with COVID-19. This is prescribed to the patients in combination with Nafamostat 0.2 mg per kg per hour by continuous intravenous infusion for 14 days and Favipiravir 3600 mg daily for 14 days treated COVID-19 patients (Organization, 2018).

Ruxolitinib

This is an anticancer drug. It is a potent inhibitor JAK 2 interfering with the JAK STAT signaling pathway which is important in in cell proliferation that's why used in managing malignancy. As this pathway is also involved in the pathogenesis of Sar-Cov-2, is used also combating it. Ruxolitinib is in the Phase 3 of clinical Trials for COVID-19 treatment (El Bairi et al. 2020).

Infliximab

This is a TNF inhibitor and is used to treat severe COVID-19. In a case study, 433 patients were treated with this drug. The recorded patient mortality was three, while others were successfully treated. It is in the phase 2 of the clinical trial for coronavirus disease. The dose administered is a single infusion of infliximab of 5 mg/kg (Stallmach et al. 2020).

Deferoxamine

Recent studies showed that one of the pathogenic pathways includes the direct damage of hemoglobin by coronavirus. The hemoglobin molecule consists of four globulin subunits, two beta and two alpha chains and each of these subunits binds to heme group which consist of iron and porphyrin (Drakesmith and Prentice 2008). It is in the phase 2 of clinical trials for COVID-19. Through the iron chelating effect, deferoxamine reduces the iron availability and could avoid the fibrosis and lung injury following the Covid'19. An in-vitro study concluded that in combination with the anti-viral drug it produces a synergistic effect on reducing the viral load and its associated damage (Georgiou et al. 2000).

Conclusion

Cytokines and interleukins play a very important role in the pathogenesis of COVID-19 after the virus gets entry to the body and replicates there. The release of cytokines may provoke the onset of cytokine storm. This condition may get worsened in the presence of other co-morbidities especially if they are involving underlying inflammation such as RA, diabetes, tuberculosis, inflammatory bowel disease, etc. There is a dire need for such patients to take all the necessary precautions. On the hand, all the therapeutic interventions for the COVID-19 are also discussed here with their possible underlying effect on cytokines.

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