Immune Modulating Mechanisms Implemented To Control N-Cov Disease

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ABSTRACT: The n-CoV is a recent pandemic globally raising serious concerns on its exorbitance in both infection, transmission and mortality rate. It is an infectious disease driven by uncontrolled immune mediated inflammatory disease resulting in cytokine storms and acute respiratory respiratory syndrome. The virus affects the respiratory system and other organ systems and lower respiratory tract. Its initial symptoms include dry cough, nausea, fever, sneezing. In the virus and host interactions, both humoral and cellular immune response seem to play a vital role. Innate immunity is the first line of defence against virus invasion. Adaptive immunity also plays an important part in viral clearance via activated cytotoxic T cells that destroy virus-infected cells and antibody-producing B cells that target virus-specific antigens. With no proper medication to control the covid disease, researchers have implemented various immune mediated mechanisms to curb the viral replication and further establishment of the disease. This review thus highlights on the various immune-modulating mechanism implemented against covid disease with its limitations and challenges.

KEYWORDS- ARDS, Cytokine storms, Cov, Immune, Modulating mechanisms, SARS.

1. INTRODUCTION

The n-CoV is an infectious disease resulting in ARDS by uncontrolled immune mediated inflammatory response (Cascella et al. 2020). Magnified cytokine storm plays a vital role in inducing the inflammatory response in covid disease in the lungs leading to respiratory collapse. Many immune mechanisms have been proposed to induce the same. STAT1 is a key protein in interferon mediated immune response antagonized by virus that leads to increased response threshold of immune cells to interferons during CoV infections (Nezhad et al. 2019). Few medications and supportive remedies have been recommended to inhibit the viral replication and further inflammatory sequences. Systemic corticosteroids that are

known to potently dampen immune inflammation to specific efficient antiviral therapy for COVID19 (Prompetchara, Ketloy, and Palaga 2020). Chloroquine and its less toxic derivative hydroxychloroquine are well known for immunomodulating effects in COVID19 due to their intracellular action. Antimalarial drugs disrupt the virus replication and cytokine storm in COVID19 (Prompetchara, Ketloy, and Palaga 2020). Interferon gamma with interferon I is considered as a synergistic combination therapy. At later stages, the balance of immune reactions is disrupted and responses shift towards immunopathogenesis and cytokine storms. Acute alveolar injury is mediated by IL-6, TNF alpha, and IL-1 which then recruits neutrophils that damage the capillary endothelium of the alveoli (Conti et al. 2020). It later got transmitted from an infected human to normal humans.

The virus affects the respiratory system and other organ systems, lower respiratory tract. Its initial symptoms include dry cough, nausea, fever, sneezing. The incidence and mortality for the virus is higher for elder population and quite lower for childrens. It is widely recognized that respiratory symptoms of covid19 are heterogeneous. Covid-19 is more prevalent in immuno-deficient patients and causes death as they lack the immunity to fight against the virus. Viral infections can also be associated with other fungal pathogens like Candida albicans in immunocompromised patients (Shahzan et al. 2019) and bacterial pathogens like Enterococcus faecalis contributes to life threatening diseases as it affects the immunity (Marickar, Geetha, and Neelakantan 2014) (Geetha and Veeraraghavan 2016). Infections can also be propagated during dental treatments too (Renuka and Muralidharan 2017) (Ramesh et al. 2015). Many bacterial pathogens like Staphylococcus aureus and S.mutans causes involved with pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome, bacteremia, sepsis (Ashwin and Muralidharan 2015) (Sabarathinam, Muralidharan, and Others 2018) (Kurian and Geetha 2015) co-infection can still worsen the covid cases. With the advent of gene therapy, albeit costly and challenging (Paramasivam, Vijayashree Priyadharsini, and Raghunandhakumar 2020), immune-modulating mechanisms can be implemented with much care against covid cases. Though conventional antimicrobial measures with complementary and alternative medicines seem to be effective against microbial infections (Pratha, Ashwatha Pratha, and Geetha 2017), potent immune-modulators can enhance the control of covid disease. This review thus throws insights into all possible immune-modulating effects that can be implemented to curb the menace of n-CoV diseases.

Retrieval of data

The study setting of this research is scoping review. The approval from the research committee was not required since it is a review. The minimum number of articles were 40. In our research we reviewed a total of 50 articles excluding 10 irrelevant articles that showed general information on covid disease. The sampling and data collection done by search engines such as PUBMED, Google scholar, bioRxiv, medRx, chemRxiv, CON, Mesh. The period of duration considered was upto 2020. After collection of all articles, more specific articles were collected by using keywords.

Covid19 Pandemic- An Overview

Coronavirus is an infectious disease which causes ARDS and leads to uncontrolled immune mediated inflammatory response. The virion is an enveloped particle that contains spike,

membrane, envelope proteins. It can be classified into 4 genera of coronas namely alpha CoV, beta CoV, delta CoV and gamma CoV on the basis of phylogenetic relationships and genomic structures (Woo et al. 2012). Among these four genera, alpha coronaviruses and beta coronaviruses primarily cause respiratory and intestinal infection in mammals, whereas gamma coronaviruses and delta coronaviruses mainly infect birds (Perlman and Holmes 2007). They are large single stranded RNA viruses isolated from animal species. Covs are positive stranded RNA viruses with a crown appearance (Matoba et al. 2015). Coronavirus also causes ARDS (acute respiratory distress syndrome) which develops sepsis, pneumonia, aspiration of gastric content, major trauma. The symptoms of ncov include fever, cough, tiredness, shortness of breath, headache, chills and sore throat. The virus is easily spreadable through droplets of infected people. SARS- CoV-2 belongs to the genus of *Betacoronavirus*, and on the basis of evolutionary analysis, is most similar to the SARS-like coronavirus from the Chinese horseshoe bat, with a nucleic acid homology of 84% in reference to (Zheng 2020).

SARS-COV and Cytokine storm

SARS-Cov is a rapidly emerging pathogen which causes serious health consequences to the public. The overproduction of cytokines caused by aberrant immune activation is known as a cytokine storm. In fact, in the late stages of coronavirus disease, including SARS, MERS, and COVID-19, cytokine storms are a major cause of disease progression and eventual death (Mahallawi et al. 2018). Secondary hemophagocytic lymphohistiocytosis (sHLH) a disease entity characterised by an uncontrolled cytokine storm and expansion of tissue macrophages or histiocytes that exhibit hemophagocytic activity is associated with severe COVID-19 cases (Hutchinson, Tattersall, and Manson 2019). HLH can result from genetic defects in cytolytic pathways or other diseases such as infection, malignancy, and rheumatic disease.

The characteristics of HLH, including hypercytokinemia, unremitting fever, cytopenias, hyperferritinemia, and multi-organ damage, are commonly seen in seriously ill patients with COVID-19. Genome SARS-Cov encodes proteins which consist of spike protein, envelope protein, membrane glycoprotein, nucleocapsid protein (Mehta et al. 2020). Membrane glycoprotein envelopes host cells induce production of protective IFN-alpha to fight against viruses. Bananin converted to bananin 5 monophosphate and B6RA which inhibit infectious virion encapsidation (Groneberg, Hilgenfeld, and Zabel 2005). Targets BNP and B6RA are SARS associated with coronavirus therapy. Increased cytokine levels (IL-6, IL-10, and TNF-α), lymphopenia (in CD4+ and CD8+ T-cells), and decreased IFN-γ expression in CD4+ T-cells are associated with severe COVID-19 (Pedersen and Ho 2020). The alveolar macrophages expressing ACE-2 are the primary target cells for SARS-CoV-2 infection as these activated macrophages may play an important part in HLH-like cytokine storms during covid-19 (Wang et al. 2013).

Immunopathogenesis of n-CoV-19 disease

Viral entry relies on interplay between virion and host cell. Infection initiated by interaction of viral particles with specific proteins of cell structure. After initial binding to the receptor, enveloped viruses fuse their envelope to host cell membranes and deliver the nucleocapsid to

target cells (Belouzard et al. 2012). The spike protein has a dual role play in entry by mediating receptor binding and membrane fusion. The fusion process involves a large conformational change of spike protein. Coronaviruses have a wide set of receptors that trigger to activate fusion. The important role of spike protein is cell tropism. The first cov receptor identified by MHV which binds to adhesion molecule CEACAM1 to infect cells (Navas et al. 2001).

IL-1b causes inflammation of lungs and leads to fever, fibrosis and respiratory complications infecting the host (10). Virus, TLRs and pro IL-1 have inflammasome cells which affect innate adaptive immune system specific immune responses (Regla-Nava et al. 2015). Covid-19 has four stages: the first stage is where a pre-symptomatic phase of fever, cough, and generalized malaise heralded by high viral loads. The second stage manifests with viral pneumonia that involves the lower respiratory tract. The third phase develops symptoms of hypercytokinemia (cytokine storm) characterized by exaggerated levels of pro- inflammatory cytokines. The last stage leads to rapid onset of acute respiratory distress syndrome (ARDS) and multi-organ failure which leads to death (Girija et al. 2020a).

Immune modulating mechanisms

The invasion and pathogenesis of SARS-CoV-2 are associated with the host immune response. The spike glycoprotein (S protein) on the viral envelope binds to its receptor, angiotensin-converting enzyme 2 (ACE2), on the surface of human cells (Zhou et al. 2020). An analysis of the structure of the SARS-CoV- 2 S protein and its binding affinity for ACE2 using cryogenic electron microscopy and surface plasmon resonance showed that the structure of SARS-CoV-2 S protein is very similar to that of SARS, although with minor differences (Wrapp et al. 2020). The affinity of SARS-CoV-2 S protein binding to ACE-2 is 10 to 20 times higher than that of the SARS S protein, suggesting that SARS-CoV-2 might transmit more readily from person to person in reference to (14).

Adaptive immunity also plays an important part in viral clearance via activated cytotoxic T-cells that destroy virus-infected cells and antibody-producing B cells that target virus-specific antigens (Huang et al. 2020). TNF-alpha converting enzyme inhibitors cause therapeutic antibody inhibitors to host the immune system (Barnard and Kumaki 2011). CR3014 humanised monoclonal neutralizing antibody for specific SARS-Cov and recombinant IFN-alpha-2b and type-1 IFN-beta are interferon inducers. The 6- mercaptopurine and 6-thioguanine are specific inhibitors of SARS coronavirus (Balzarini et al. 2006). The carbohydrates binding agents block the enveloped viruses of coronaviruses. Oncolytic virotherapy infects tumour cells lyses due to viral particle production and enhances sensitivity to conventional therapy and the immune system clears virus before the therapeutic effects. The putative vaccine peptides targeting the bapAB mediated TCS in A.baumannii using immune-informatics approach suggests promising results but it requires further experimentation and clinical trials. Since co-occurrence of the drug resistant strains can worsen the situation (Girija et al. 2020b) (Girija, Jayaseelan, and Arumugam 2018) (Girija As and Priyadharsini J 2019) (Smiline, Vijayashree, and Paramasivam 2018)**,** immune-modulating effects can be a potent measure to control covid disease.

Role of pro-Inflammatory cytokines and its control:

Proinflammatory cytokines in particular IL-1 are important mediators in local and systemic inflammations (Dinarello, Conti, and Mier 1986). Stimulated IL-1 in viral infections mediates lung and tissue inflammation, fibrosis and fever (Kritas et al. 2020). Macrophages activated by ncov are crucial for pathogenesis of fibrosis, since macrophages perform phagocytic activity on debris of dead cells and tissue, releasing inflammatory substances. These reactions can be related to danger associated molecular patterns (DAMPs) which have receptors called pattern recognition receptors (PRRs) which also include TLRs. IL-6 and IL-8 are SARS-Cov induced epithelial cytokines inhibiting T-cell priming of dendritic cells (Yoshikawa et al. 2009). Infections exacerbated inflammatory cascades causes severe tissue damage in SARS patients.

The binding of COVID19 to Toll-like receptors (TLR) causes release of pro IL-1 beta which is cleaved by caspase-1 followed by inflammasome activation. Production of active mature IL-B which is a mediator cytokine IL-37 suppresses innate and acquired immune responses by acting on mTOR and increasing the adenosine monophosphate (AMP) kinase. IL-37 cytokine inhibits formation of class-II histocompatibility complex (MHC) molecules and inflammation in inflammatory diseases by suppressing MyD88 and subsequently IL-1β, IL-6, TNF and CCL2. The suppressing IL-1β by IL-37 in its inflammatory state that is induced by coronavirus-19 can have a new therapeutic effect which was previously unknown. IL-38 the newest cytokine of the IL-1 family member which is an inhibitory cytokine is produced by several immune cells including B cells and macrophages. IL-38 is also a suppressor cytokine which inhibits IL-1β and other proinflammatory IL-family members. Potential therapeutic cytokine effect is exhibited by IL-38 which inhibits inflammation in viral infections including that caused by coronavirus-19, providing a new relevant strategy.

2. CONCLUSION

n-CoV being a newly emerging virus, with no approved effective drug or vaccine, an intimate understanding of n-CoV immunobiology is essential to implement novel therapeutic strategies. In addition, knowledge on the host-viral interaction is also a vital factor to design mechanisms related to the enhancement of the viral immunity. This review had thus highlighted the various immune-mechanisms involved with covid pathogenesis and the immune-modulating mechanisms implemented to curb the spread of covid disease.

AUTHOR CONTRIBUTIONS

Tahreem Fathima 1.Execution of the work 2.Data Collection
3. Drafting of manuscript

Smiline Girija AS

1.Concept and design of the study 2.Validation of data collection 3.Revision and proof-reading of the view

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1.Validation of data collection 2.Revision and proof-reading of the view

Conflict Of Interest
The authors have no conflict of interest.

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Table 1- Immune-modulating mechanisms to control covid-19 disease

nune Modulating Therapies	**Actions**
Cell therapy- Stem cells	Suppression of inflammation; proviral silencing
2. Plasma Therapy- Convalescent plasma	Promotion of virus elimination via virus-specific antibodies
3. Baricitinib	JAK inhibitor; blockade of viral invasion through the inhibition of AAK1; immune suppression

4.	Ruxolitinib	JAK inhibitor; immune suppression activity
5.	Leflunomide	Inhibition of virus replication
6.	Tocilizumab	Blockade of IL-6 receptor and its downstream signalling pathways
7.	Anakinra	Blockade of IL-1 receptor and its downstream signalling pathways
8.	Thalidomide	Reduction of inflammatory cell infiltration; reduction of cytokine storm; reduction of lung damage and pulmonary interstitial fibrosis