IL-6: THE CHOIRMASTER ORCHESTRATING THE COVID-19 CYTOKINE STORM- SYSTEMATIC REVIEW

Pathology

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ABSTRACT

Background: Millions of people have died of acute lung injury, in the current global pandemic caused by SARS-CoV-2. An effective treatment regimen is yet to be established and will require an understanding of the intricate details of the disease pathophysiology. The death of patients is primarily attributed to the cytokine storm resulting from excessive activation of immune system, with a predominant role of IL-6. There is a divergence between its role in mild/moderate group and severe group. The need for a comprehensive understanding of IL-6 involvement in the pathophysiology of COVID-19 is imperative to control its spread and find its treatment. **Methods:** This systematic review was written after conducting a systematic search from 4 June, 2020 to 17 June 2020 in the PubMed database using the keywords Coronavirus COVID-19, IL-6, pathophysiology, and cytokine storm. Only articles written in English and those regarding the role of IL-6 in COVID-19 pathophysiology and correlating levels of IL-6 with severity of disease were included. **Findings:** The abstracts of 74 articles were screened, of which 23 full text articles were read and 6 articles were included in the review. **Interpretation:** IL-6 is one of the earliest indicators of the prognosis of COVID-19. It acts by classic signaling pathway in mild/moderate patients eliciting an anti-inflammatory response, and in severe patients, by trans-signaling pathway by which it elaborates a cytokine storm. Dysregulation in IL-6 regulating enzymes and NF-kB gene translation too play a role in the cytokine storm. Funding: None.

KEYWORDS

Cytokine Storm, IL-6, COVID-19, trans-signaling

INTRODUCTION

Since December 2019, outbreaks of viral pneumonia caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) leading to death of millions of individuals, began in Wuhan, China. As of October 1, 2020 there have been 34,172,820 cases and 1,018,957 deaths worldwide. SARS-CoV-2 is genetically very similar to two other coronaviruses, SARS-CoV-1 and MERS-CoV, both of which have caused pandemics in the last two decades. While SARS-CoV-1 and MERS-CoV were predominantly contained in China and Saudi Arabia respectively, SARS-CoV-2 has spread worldwide.

Although the disease remains asymptomatic or paucisymptomatic in most cases, it may progress to pneumonia, Acute Respiratory Distress Syndrome (ARDS) and septic shock ultimately leading to multi-organ failure and death. The disease commonly manifests as low-grade fever, dyspnoea, inflammatory reaction (most commonly as pneumonitis), even activation of intravascular coagulation; closely resembling Macrophage Activation Syndrome (MAS) or secondary Haemophagocytic lymphohistiocytosis (sHLH), implicating the role of cytokines in disease pathogenesis. The progression of Coronavirus disease-19 (COVID-19) from viral pneumonitis to ARDS is associated with a surge of cytokines referred to as 'cytokine storm'. Studies monitoring the levels of various biochemical and hematological parameters of COVID-19 patients, show greatly elevated levels of pro-inflammatory cytokines like Interleukins (IL-6, IL-1, IL-8, IL-12), Tumor Necrosis Factor α , d-dimer, ferritin. The elevation of serum IL-6 occurs several days before that of acute phase proteins, making it an effective early indicator of prognosis. IL-6 is greatly elevated in severe or critical patients while progressing from mildly affected patients. This review explains the role of IL-6 in the cytokine storm and inevitably the progression of disease, discussing the rationale of use of IL-6 pathway blockade in therapy regimens of COVID-19 patients.

COVID-19: TYPICAL CLINICAL PRESENTATION

The incubation period of the disease is 5-6 days on average but may extend to 14 days. Presenting signs and symptoms of COVID-19 vary greatly, barring some general manifestations. According to WHO, most symptomatic persons experience low grade fever (83-99%), cough (59-82%), fatigue (44-70%), anorexia (40-84%), dyspnoea (31-40%), myalgia (11-35%). Loss of smell (anosmia) or loss of taste (ageusia) may precede the onset of respiratory symptoms. Other non-specific symptoms such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported. Systemic

manifestations in adults caused by a dysregulated host immune response to suspected or proven infection appears with signs of acute life-threatening organ dysfunction such as altered mental status, dyspnoea, tachypnoea, low oxygen saturation, oliguria, tachycardia, weak pulse, cold extremities, hypotension, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, or hyperbilirubinemia.

Clinically, patients can be asymptomatic or symptomatic. Further categorization of symptomatic patients into mild, moderate and severe disease groups is done on the basis of WHO guidelines following three basic criteria – PaO₂/FiO₂ ratio, SpO₂, and Respiratory Rate.

- Mild patients: Those having laboratory confirmation of COVID-19 infection irrespective of clinical presentation without evidence of viral pneumonia or hypoxia.
- Moderate patients: Adolescents and adults presenting with clinical signs of pneumonia (fever, cough, dyspnoea, tachypnoea) without clinical signs of severe pneumonia, including SpO₂ $\geq$ 90% on room air.
- Severe disease: Adolescents and adults with clinical signs of pneumonia (fever, cough, dyspnoea, tachypnoea) plus one of the following, respiratory rate $>$ 30 breaths/min, severe respiratory distress, or SpO₂ $<$ 90% on room air. Patients falling under this category may progress to a critically hypoxic state presenting as ARDS within a week, requiring continuous monitoring and intensive clinical management, including mechanical ventilation.

Although symptomatic patients are divided into three distinct categories clinically, pathologically, with relation to IL-6 levels and its pathogenesis, no clear differentiation can be made between mild and moderate group.

Comparing the serum levels of various cytokines in patients of different severity on different days after disease onset, it is apparent that IL-6 plays a central role in COVID-19 pathogenesis. In mild to moderate patients, there is very little or no fluctuation in serum cytokine levels as opposed to greatly pronounced fluctuation in severe group patients. Most cytokines peak on the third or fourth day after disease onset, reducing to normal levels soon after, while IL-6 shows a sustained increase till the sixteenth day of disease onset, after which its

levels begin to reduce.¹

Wan et al, in their study found raised IL-6 levels in one-third of the patients with mild disease and three-fourth of those with severe disease.⁶ In another study, marked elevation of IL-6 was found in patients who succumbed to the disease rather than those who recovered.⁶ IL-6 has thus become an established prognostic indicator of COVID-19 in infected patients. Although the complete pathogenesis of this disease is unknown, evidence has revealed the role of elevated serum IL-6 in worsening the condition of patients.

II) GENERAL PATHOGENESIS

The SARS-CoV-2 virus enters the body through droplet inhalation. An immunogenic envelope protein, spike (S) protein of SARS-CoV-2 is first primed by host Transmembrane protease serine 2 (TMPRSS2), which then binds to human Angiotensin Converting Enzyme 2 (hACE2), a cellular receptor for SARS-CoV-2. The virus then enters the cell by endocytosis, releasing its RNA into the host cell cytoplasm. The viral RNA uses host enzymes to undergo translation and synthesize proteins and more nucleic acid, replicating. Assembled daughter virions so formed are released by exocytosis to infect other cells. Most commonly infected cells are hACE2 expressing cells which include type II alveolar cells, nasal mucosa, respiratory tract cells, cardiac, renal, endothelial and intestinal cells. Diabetic and hypertensive patients have an increased expression of hACE2 along with weak, inappropriate immune response explaining the poor prognosis and increased mortality in COVID-19 patients with these comorbidities.

The virus is first detected by the innate immune system while replicating intracellularly. Infectious agents including SARS-CoV-2 virus express Pathogen-Associated Molecular Patterns (PAMPs) which are recognized by Pattern Recognition Receptors (PRRs) present on cells of host innate immune system. The PAMP for viruses are most commonly their nuclear proteins, which in case of SARS-CoV-2 is nucleocapsid (N) protein, detected by Toll-Like Receptor 7 and 4 (TLR-7, TLR-4), a type of PRR. Viral antigens once recognized by the immune system, are presented by antigen presenting cells to Natural Killer (NK) cells and CD8+ cytotoxic T-cells, activating both innate and adaptive immune systems. This in turn activates downstream signaling effectors like NF- κ B and Interferon Regulatory Factors (IRF 3/7) which mediate type I IFN dependent antiviral response. NF- κ B is a protein complex responsible for the expression of pro inflammatory genes encoding cytokines, chemokines and adhesion molecules.² (Fig 1)

Figure 1: General Pathogenesis of COVID-19 - Entry of virus and elaboration of IL-6

Another type of PRR is NOD-like Receptor (NLR), responsible for

detection of intracellular Danger-Associated Molecular Patterns (DAMPs). Binding of DAMPs activates NLRs leading to formation of inflammasomes where procaspase 1 is converted to caspase 1 further causing the conversion of pro-IL-1 β to IL-1 β , an important pro-inflammatory cytokine. It further stimulates the production of other pro-inflammatory cytokines including IL-6.³

Once the immune system is activated, virus-infected cells are usually destroyed by NK cells and CD8+ T-cells using perforin and granulysin cytotoxic granules leading to apoptosis of antigen-presenting cells and CD8+ T cells avoiding unnecessary activation and cytokine release after clearance of viral infection.³

Irrespective of the clinical group under which a patient falls, the above discussed pathway remains common amongst all COVID-19 patients.

III) SPECIFIC ROLE OF IL-6 IN THE PATHOGENESIS OF EACH CATEGORY

1) Mild and Moderate Group:

The presentation of COVID-19 in mild/moderate group patients is characterized by a slight rise in cytokine levels (hypercytokinaemia, a hallmark of COVID-19), lesser than that observed in severe disease. The activated innate immune response elicits a slight elevation of several acute phase proteins along with TNF- α , MCP-3, IP-10, MCP-1 and various interleukins (IL-1 β , IL-6, IL-10).

IL-6 binds to its alpha receptor, the transmembrane IL-6 receptor (IL-6R) on the target cell, which further binds to the co-receptor glycoprotein 130 (gp130), a homodimer. Though gp130 is present on all body cells, IL-6R is present only on surface of specific cells - hepatocytes, some epithelial cells and some leukocytes. This ensures controlled elicitation of IL-6 activity by selective cells. The binding of IL-6/IL-6R complex to gp130 causes its dimerization, initiating an intracellular signal transduction via Janus Kinase/ Signal Transducer and Activator of Transcription (JAK/STAT) (by STAT1 and STAT3 isoforms) and ras/Mitogen-activated protein kinase (MAPK) pathways.⁴ STAT3 induces suppressors of cytokine signaling- SOCS1 and SOCS3. SOCS1 binds to tyrosine-phosphorylated JAK and SOCS3 to tyrosine-phosphorylated gp130, creating a negative feedback loop ceasing IL-6 signaling.⁵ This pathway is called classic signaling pathway (Fig 2A).^{6,7}

Fig 2: Different signaling pathways of IL-6: A. Classic signaling pathway as seen in mild/moderate patients; B. Trans-signaling pathway as seen in severe patients

Through classic-signaling pathway, IL-6 has an anti-inflammatory and protective action, and some specific action on specific cells.

a) Intestinal epithelial cells:

IL-6 induces a STAT3-mediated regeneration of intestinal epithelial cells as well as inhibition of epithelial cell apoptosis, eliciting a

protective response.⁴

b) Hepatocytes:

During the initial phase of inflammation, the produced IL-6 acts on liver cells increasing the production of acute phase proteins like C-Reactive Proteins (CRP), SAA, ferritin, fibrinogen, haptoglobin, and depresses the production of fibronectin, albumin and transferrin.⁶ The rise in serum level of acute phase proteins occurs several days after the rise of IL-6.

2) Severe group:

The severe group characteristically shows its manifestation in the form of a 'Cytokine Storm', an ill-defined phenomenon related to several infectious and non-infectious diseases, associated with excessive and uncontrolled release of various pro-inflammatory cytokines causing a systemic inflammatory response, beginning with the immune system failing. With context to COVID-19, cytokine storm indicates a full-blown disease state presenting as aggravation of several symptoms and potentially fatal ARDS, septic shock and multi-organ failure. The cytokine profile of COVID-19 patients closely resembles that of MAS/sHLH, showing elevated serum IL-1, IL-6, IL-17, IL-8, TNF- α .⁸ Another key feature of cytokine storm is the immune dysregulation caused by IL-6.

Certain predisposing factors for the development of cytokine storm have been proposed. It includes a high viral load along with long viral shedding period and impaired viral clearance due to impaired anti-viral immune response. Reduced levels of type I IFN, the first line of defense against viral infection and increased neutrophil extracellular traps (NETs and NETosis) also play a role. NET is an extracellular fibril matrix composed of fragments of neutrophil DNA released from the neutrophil by NETosis, an alternative type of apoptosis. Pyroptosis, a Caspase-1-dependent special apoptosis resulting from rapid viral multiplication leading to release of copious amounts of inflammatory mediators, also influences the development of cytokine storm.³

The generation of the cytokine storm in severe disease is through dysregulated host immune responses. The initial host response to infection consists of local production of IFN- α/β and IL-1 β by infected epithelial cells which protect surrounding cells by expressing Interferon-stimulated genes and simultaneously activating NK cells, increasing their lytic potential and IFN- γ production. The IFN- γ so produced activates resident macrophages around the infected region amplifying subsequent TLR-mediated translation of the regulatory element of the NF- κ B region on IL-6 promoter gene.⁴ The released cytokines further modulate NK cells. Dysregulation of certain pathogenic factors like pathogen load and host anti-inflammatory responses cause enhanced elaboration of IL-6 and other pro-inflammatory cytokines, generating the cytokine storm⁹ and subsequent organ damage (Fig 3). The main activators of IL-6 are IL-1 β and TNF- α , other contributors being TLRs, prostaglandins, adipokines, and other cytokines.⁵

Activated T lymphocytes can further exaggerate the cytokine storm by stimulating innate immune cells. T-cells with expression of IL-1 β , Colony Stimulating Factor 1 or 2 (CSF1 or CSF2) bind to IL-1R or CSF receptor on monocytes, activating them. Zhou et al have reported that in patients with severe disease, Th1 cells induced IL-6 elaboration by CD14⁺ and CD16⁺ monocytes, causing hyperinflammation.⁹

In critical patients, IL-6 exhibits a pro-inflammatory response instead of normal anti-inflammatory response, using an alternative signaling pathway, seen in COVID-19 and various inflammatory diseases like rheumatoid arthritis. Here IL-6 binds to another form of the transmembrane IL-6R, soluble IL-6R (sIL-6R), derived from IL-6R mainly by action of protease ADAM17 on it, yielding a soluble protein. Another minor pathway yielding sIL-6R is by translation of IL-6R-mRNA. sIL-6R is present in circulation and binds easily to serum IL-6. The IL-6/sIL-6R complex binds to gp130 with a similar affinity as that of the normal complex. Since the complex of IL-6 and its receptor is formed in the circulation and gp130 is ubiquitously expressed, IL-6 mediated intracellular signaling is activated in every cell leading to an unrestrained pro-inflammatory cytokine elaboration by most cells. This alternative pathway of IL-6 action is called trans-signaling pathway (Fig 2B) which generates the so called 'Cytokine Storm'.⁵

Several molecules and enzymes regulate IL-6 signaling pathway.

SOCS1 and SOCS3 produce a negative feedback loop to inhibit IL-6 action; Regnase-1 degrades IL-6 mRNA stopping IL-6 production; Arid 5a stabilizes IL-6 and counteracts the destabilizing function of Regnase-1. Together, Regnase-1 and Arid 5a regulate IL-6 mRNA stability. A dysregulation and imbalance between the actions of the two could cause overproduction of IL-6, causing cytokine storm.⁵

Figure 3: Pathway for elaboration of IL-6 in severe patients

IL-6, through the trans-signaling pathway, has specific actions on specific cells.

a) T- lymphocytes:

Lymphopenia is a prominent feature of COVID-19 affecting all subsets of T-cells along with B cells. According to published data, SARS-CoV-2 can infect T cells directly by binding of Spike (S) protein to hACE2 in spite of an insufficient expression of hACE2 on T-cell surface owing to high S protein affinity for hACE2. However, another receptor has also been recorded allowing entry of the virus. SARS-CoV-2 cannot replicate inside T-cells and instead causes cell death, impairing cell mediated immunity (CMI).⁸ T-cell apoptosis is achieved by enhancing P53 and Fas signaling pathways.⁹ CD4⁺ and CD8⁺ T-cells in blood of severe group patients show hyperactivity due to an increased expression of HLA-DR4 and CD38, although decreased in numbers.⁹ IL-6 elicits a non-protective T helper cell 2 (Th2) response instead of a protective Th1 response, further reducing the ability of immune system to clear the virus. Following T-cell apoptosis, there occurs an infiltration of macrophages and neutrophils in the target tissue (especially lungs), causing dysregulation of pro-inflammatory cytokines.¹⁰

The IL-6/sIL-6R complex inhibiting the differentiation of T-cells, causes an efficient suppression of regulatory T-cells (Treg) and induction of Th17 cells, indicating the significance of trans-signaling pathway in severe disease.⁷

As discussed above, NK cells and CD8⁺ cytotoxic T-Cells kill virus

infected host cells by perforin mediated granulysin secretion. SARS-CoV-2 infection inhibits cytolytic activity of immune cells resulting in uninhibited elaboration of several pro-inflammatory cytokines like IL-6, TNF, IFN, IL-18, IL-33 creating a cytokine storm presenting as ARDS, multi-organ failure and possibly death.³

b) Monocytes:

IL-6 trans-signaling causes massive recruitment of monocytes by upregulation of monocyte-attracting chemokines. It also influences the differentiation of monocytes into macrophages by an upregulated M-CSF receptor expression.⁷ Following depletion of CD4⁺ and CD8⁺ T-cells, a massive recruitment of monocytes or macrophages and neutrophils triggers exudation in lung tissue and ARDS, resulting in a vicious circle of cytokine release leading to cytokine storm and further lesions.¹⁰

Some studies have demonstrated that CD169⁺ macrophages being unresponsive to activation by type 1 IFN, contribute to developing immunity by controlling viral replication. Infection of CD169⁺ macrophages might channelise the transfer of SARS-CoV-2 to spleen and lymph nodes where they are mainly found, a potential cause for additional systemic viral replication contributing to lower immunity.⁹

Although monocytosis is not observed in severe patients; morphological features such as expression of CD14, CD163 and CD206 on monocytes represent their activation linked to hyperproduction of cytokines.⁹

c) Hepatocytes:

The cytokine storm mediated dysregulation of protein synthesis leads to coagulative disorders, a feature of cytokine storm and MAS.⁶

Severe group patients primarily show disease manifestation in the form of severe pneumonia and ARDS. The pathogenesis for the same involves binding of IL-6/IL-6R complex with gp130 resulting in recruitment and phosphorylation of the latent transcription factor STAT3, activating it. It induces genes involved in cell differentiation and proliferation, as well as inhibitors like SOCS3, all of which result in tissue fibrosis in the targeted lung tissue.^{11,12} IL-6 mediated trans-signaling is also involved in the infiltration of granulocytes and macrophages during the late phase of acute inflammation due to the secretion of MCP-1 in endothelial cells. Infiltration of granulocytes and macrophages is possibly a cause of tissue damage in acute lung injury.⁴ COVID-19 patients also show exudation and mass mucus aggregation, especially in the distal respiratory tract, with IL-6 having a central role. IL-6 stimulates predominant mucin genes (MUC5A, MUC5B) expressed in tracheobronchial epithelial cells, causing excessive mucus production.¹³ The pro-inflammatory cytokines released via type-I-interferon response, acting on innate immune cells, generate a feedforward loop resulting in the cytokine storm, including coagulopathy and ARDS.¹⁴

III) EMERGING THEORY FOR TREATMENT OF COVID-19 ON THE BASIS OF IL-6:

From the above discussion it is abundantly clear that IL-6 plays a central role in cytokine storm, characteristic to the severe group of COVID-19 patients. Blockade of IL-6 release or action may alleviate symptoms of cytokine storm, preventing a fatal outcome. Studying the pathway of IL-6 release, its stimulators and inhibitors could provide us with insight about various elements which can be targeted to achieve an IL-6 blockade.

There are some experimental treatment options currently available under trial specifically targeting IL-6.

a) Drugs like Tocilizumab, Sarilumab, Siltuximab – They block IL-6R, inhibiting both the classic and trans-signaling pathways. In a mouse model infected by SARS-CoV-2, Tocilizumab however provided only limited degree of relief from symptoms without preventing the death of mice.⁴

b) Baricitinib and Ruxolitinib – They inhibit the JAK-STAT pathway and have been proposed for preventing cytokine storm.⁹

c) Myo-inositol – It downregulates IL-6 and STAT3, a molecule regulating IL-6. Unpublished preliminary results indicate its mechanism of action to be an epigenetic effect.^{3,15}

d) Chloroquine and Hydroxychloroquine – These antimalarials are established autoimmune disease drugs as immunomodulators and potential broad-spectrum anti-virals. Both drugs increase the endosomal pH inhibiting virus-cell fusion; reduce glycosylation of ACE-2 receptors. Data also suggest that they decrease IL-6 and TNF- α .^{3,16}

e) Certolizumab – It is a specific monoclonal antibody to TNF- α , a major IL-6 stimulant.^{3,17}

IL-6 transitions from having a protective function (classic signaling) to pro-inflammatory effect (trans-signaling) as the disease progresses. It is crucial to determine the stage of COVID-19 to provide a prognosis and before administering IL-6R blockers, as inhibiting its early protective effect may prove fatal.

A possible new modality of treatment is sgp130Fc, a selective trans-signaling inhibitor formed by fusion of gp130 with the Fc portion of human immunoglobulin antibody. Sgp130Fc offers 100% improvement in the survival of patients in various inflammatory diseases, acute and chronic, including infections of *Listeria*, *Mycobacterium*, and *Malaria*. COVID-19 primarily being an inflammatory disease resulting from IL-6 trans-signaling, sgp130Fc is a potentially effective treatment, since it preserves the anti-inflammatory properties of the IL-6 classic pathway, and blocks the pro-inflammatory actions mediated by trans-signaling pathway.

Several other elements of IL-6 pathway from the stage of elaboration to its action remain unexplored as targets for drug trials. Some potential targets are the regulators of genes encoding IL-6 like Regnase-1, Arid-5a; IL-1 β and TNF- α as the main stimulators of IL-6; blockade of ADAM17, preventing the production of sIL-6R, thus inhibiting the trans-signaling pathway. One important mechanism inducing the cytokine storm is the feed-forward loop acting on the innate and adaptive immune system. The grave symptoms of COVID-19 can be evaded by targeting the elements of this loop, specifically STAT1 and type I IFN which amplify the signaling pathways, contributing to cytokine storm. This would not only provide a possible treatment for COVID-19, but also other autoimmune and inflammatory diseases whose pathogenesis revolve around IL-6 signaling dysregulation.

CONCLUSION

IL-6 is a predominant driver of cytokine storm in COVID-19 and an established prognostic determinant. In spite of the available trials, treatment for COVID-19 is only supportive and no single drug or combination has been established till date as complete cure. Hence studying the intricacies of role of IL-6 in pathogenesis of cytokine storm is necessary and highlighted in this review as elements involved in the IL-6 release and signaling pathway may be potentially effective targets for treatment.

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