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Materials Today: Proceedings xxx (xxxx) xxx

Contents lists available at ScienceDirect

Materials Today: Proceedings

journal homepage: www.elsevier.com/locate/matpr

Interleukin 6: A biomarker for COVID-19 progression

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Interleukin-6
SARS-CoV-2
Cytokine storm
COVID-19
Biomarker
Monoclonal antibodies

ABSTRACT

COVID-19 was discovered in China for the first time in December 2019 and was declared a pandemic by the World Health Organization on March 11, 2020. Due to its rapid geographic expansion over the last three years, it has now become a global health issue. The infection is caused by SARS-CoV-2, which is obtained from a zoonotic source and transmitted directly or through contact. Following exposure, the immune system becomes hyperactive resulting in the production of pro-inflammatory cytokines, particularly interleukin-6 (IL-6), a naturally occurring pleiotropic cytokine that plays a significant role in respiratory failure and multi-organ dysfunction. This massive inflammatory phenomenon is reminiscent of cytokine release syndrome (CRS) or "cytokine storm", which may be at the root of many severe complications. In fact, serum IL-6 levels are significantly high in patients with severe Covid-19 disease. The goal of treatment is to change the cytokine's concentration or activity. Interleukin-6 production could be inhibited, reducing inflammation and so serving as a therapeutic target. anti-interleukin-6 receptor monoclonal antibodies have been proven to reduce the severity of COVID-19 in clinical trials aimed at clarifying the function of immunoregulation. As a result, the Il-6 assay is a reliable predictor of morbidity and mortality at the time of infection diagnosis. The aim of our study is to highlight the role of interleukin 6 as biomarker of the COVID- 19 progression.

Selection and peer-review under responsibility of the scientific committee of the Fifth edition of the International Conference on Materials & Environmental Science.

1. Introduction

In December 2019, a new coronavirus was identified in the city of Wuhan, China, in patients who presented with unexplained severe pneumonia cases [1]. In February 2020, the World Health Organization (WHO) assigned the name COVID-19 to designate the disease caused by this virus, initially called nCoV-2019, then SARS-CoV-2 by the Committee on Taxonomy of Viruses [2]. After SARS-CoV-1 in 2002 in China, the MERS-CoV followed in 2012 in the Arabian Peninsula was responsible for often fatal respiratory distress syndromes. In fact, SARS-CoV-2 is the third global health threat linked to a coronavirus in less than twenty years [3]. SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as the primary cellular receptor to enter the host cell [4]. After an incubation period (five days), 70 % of infected patients develop cough, fever, or dyspnea [5]. This phase of viral invasion is followed, in some patients, by an inadequate immune response marked by worsening respiratory symptoms and inflammatory syndrome, usually-eight to ten days after the first symptoms [6]. This dysimmune phase, often called cytokine storm, can be associated with a coagulopathy, the whole corresponding, for some authors, to a viral sepsis [7]. IL-6, as well as other cytokines, leads to a stimulation of the inflammatory response with elevation of acute phase proteins CRP, ferritin, hyperleukocytosis with lymphopenia and thrombocytopenia, induction of the tissue factor gene with a procoagulant profile, increasing the risk of thrombosis, cytokine storm with endothelial damage, and tissue damage aggravating the acute respiratory distress syndrome. The current pandemic context, accompanied by a multitude of scientific publications, leads to a large and rapidly evolving literature. The aim of our study is to highlight the role of interleukin 6 as biomarker of the COVID- 19 progression.

2. Materials and methods

A literature search was done on PubMed, SCOPUS, and Google Scholar to identify articles discussing biomarkers in this review and its clinical implications on COVID-19 following the Preferred

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https://doi.org/10.1016/j.matpr.2022.07.387
2214-7853/
Selection and peer-review under responsibility of the scientific committee of the Fifth edition of the International Conference on Materials & Environmental Science.

Reporting Items for Systematic Reviews and meta-analysis (PRISMA) guidelines. Key words used were 'Interleukin-6′, 'SARS-CoV-2′, 'Cytokine storm', 'COVID-19′, 'biomarker' and 'Monoclonal antibodies'. Studies were included if they have reviewed a correlation between a biomarker and the severity of COVID-19. Exclusion criteria were studies with no particular definition of the role of biomarkers in COVID-19.

3. Pathophysiology of COVID-19 infection

COVID-19 is a global pandemic with a high mortality rate among critical cases. SARSCoV-2 infection causes hyperinflammation of the innate and adaptive immune systems, which results a cytokine storm (Fig. 1).

Immune response: the pathways are initiated by the engagement of pattern recognition receptors (PRR). During PRR activation, signaling cascades trigger the secretion of cytokines. Among these, type I/III interferons (IFNs) are considered the most important for antiviral defense, but other cytokines, such as proinflammatory tumor necrosis factor alpha (TNF-a), and interleukin-1 (IL-1), IL-6 and IL-18 are also released. Combined, they induce antiviral programs in target cells and potentiate the adaptive immune response and are also responsible for the appearance of diffuse microthrombosis and signs of disseminated intravascular coagulation associated with thrombocytopenia [8]. Certain reports showed an increase in leukocyte and neutrophil counts that were significantly higher in severe patients, admitted to intensive care, while lymphocytes and platelets were lowered. Similarly, they observed a decrease in the number of CD4 + T and CD8 + T cells by acting on the lymphocytes, particularly the T lymphocytes [9,10]. While other reports indicate that leukopenia, leukocytosis and lymphopenia have been reported, although lymphopenia appears to be the most common [11]. Which could be an effective and reliable indicator of severity and hospitalization of patients with COVID-19 [12].

Thrombogenic risk: A model of the interaction between inflammation and coagulation was studied. All patients had elevated IL-6 values, with a clear association between IL and 6 and fibrinogen levels. IL-6 is a potent pro-inflammatory cytokine, which induces tissue factor gene expression in endothelial cells and monocytes, fibrinogen synthesis and platelet production, without affecting fibrinolysis. The tissue factor triggers the generation of thrombin, and the combination of these factors produces a pro-coagulant profile that was evident in patients [13]. SARS-CoV-2 infection can also directly or indirectly cause vascular endothelial dysfunction, increasing the risk of thrombosis [14]. The hypoxic vasoconstriction can itself cause occlusion of small vessels and is also at the origin of the synthesis of "Hypoxia Inducible Factors" (HIF) which modify and activate the synthesis of tissue factor and plasminogen-activator inhibitor 1 (PAI 1) [15].

Cytokine Storm Associated with COVID-19: In COVID-19, hypercytokinemia, also known as "Cytokine Storm (CS)", is characterized by an intense hyperinflammatory immune response and is the disease's main symptom [16]. Induced by the activation of *T*-cells, macrophages and ulterior release of cytokines, which further potentiates recruitment and activation of other immune cells [17]. CS is marked by elevated serum levels of pro-inflammatory cytokines and chemokines, especially IL-1, IL-6, IL-12, IFN-$_{\gamma}$ and TNF-α [18,19]. Increased levels of these pro-inflammatory cytokines in severe patients could be exploited as indicators for disease prognosis and as possible therapeutic targets [20]. According to several studies, CS has been correlated to multi-organ failure, lung

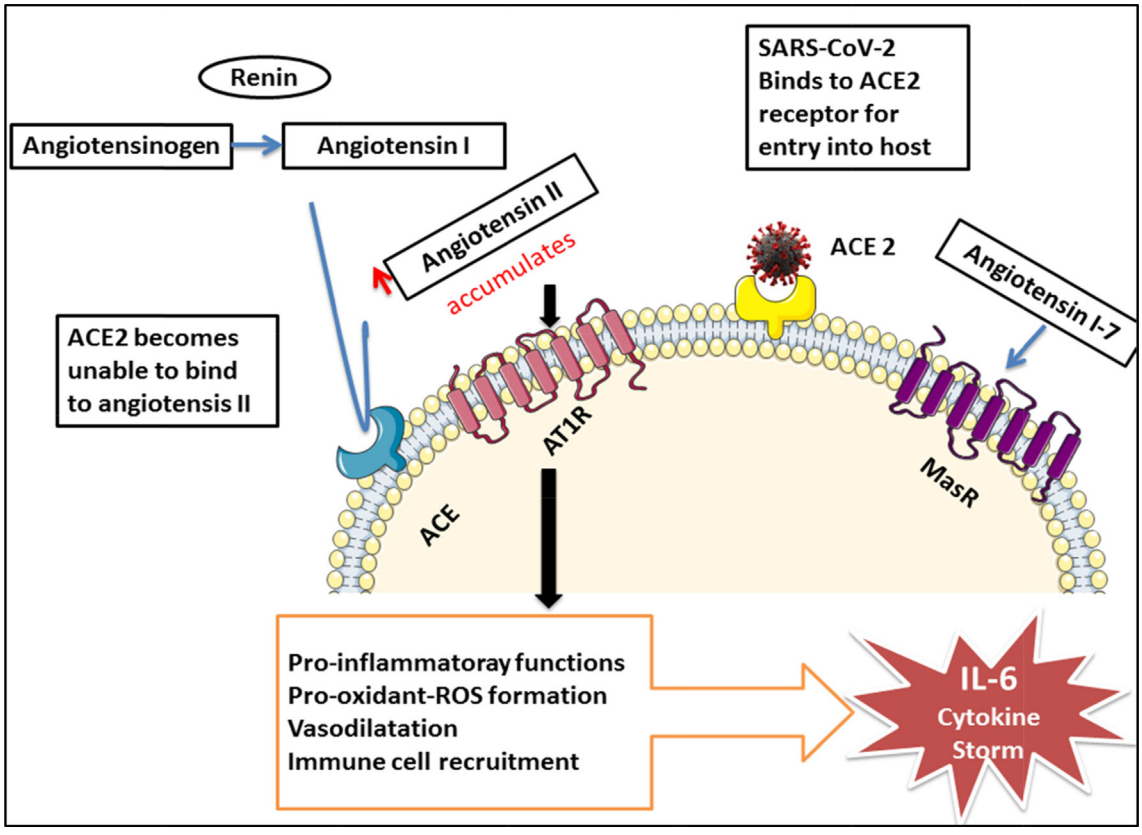

Fig. 1. In healthy state, the Angiotensin II –Angiotensin I Receptor axis and the Angiotensin 1–7-Mas receptor axis are in a state of dynamic equilibrium to maintain the blood pressure. The former causes an inflammatory response while the latter suppresses inflammatory responses. In SARS-CoV-2 infected state, viral binding to ACE2 renders it unavailable to bind to Angiotensin II causing an imbalance between the two axes and a shift towards the proinflammatory functions [22].

injury, ARDS (acute respiratory distress syndrome), need for mechanical ventilation and unfavorable disease prognosis [20,21]. Besides cytokines, elevated levels of serum lactate dehydrogenase, C-reactive protein, creatinine, procalcitonin, ferritin, D-dimer and White Blood Cell count are crucial parameters for predicting respiratory failure and need for supplementary oxygen in COVID-19 patients [21]. IL-6 has been reported as the most reliable predictor of disease progression and mortality in SARS-CoV-2 infected patients. Furthermore, therapeutic options targeting IL-6 or its signaling have showed promise in COVID-19 patients [22].

4. Interleukin 6 levels in severe COVID-19 infection versus non-severe infection

Several authors have reported that IL-6 plasma concentration increased with the severity of the disease and was a poor prognostic factor. The following Table 1 summarizes the IL-6 serum levels. A study established an IL-6 predictive level of a severe form of Covid-19, for a value greater than 24.3 pg/mL measured on Cobas e601 Roche. According to these authors, a plasma IL-6 concentration above this level and D-dimer levels above 0.28 mg/L predicted respiratory complications of Covid-19 with a sensitivity of 66.7 % and a specificity of 96.4. In addition, IL-6 is a simple assay to implement in the laboratory, by sandwich Eclia technique, automated, and for a reasonable cost [23]. A retrospective study conducted on ICU patients found significantly high levels of IL-6 in nonsurvivor group compared to survivor with AUROC of 0.73 [24]. It was also linked with elevated levels of GGT, ALT and AST during hospitalization of COVID-19 patient [25]. A study conducted on 225 COVID-19 patients in Southwest quaternary United states hospital reported that a positive correlation between IL and 6 levels and adverse cardiac events or deaths [26]. Recent data from COVID-19 patients with diabetes have found elevated levels of systemic IL-6 compared to patients without diabetes [27]. Likewise, obese COVID-19 patients had a higher risk of developing severe respiratory distress syndrome. Both in the steady state and in disease, they have higher levels of pro-inflammatory cytokines [28]. Furthermore, obese patients have higher levels of IL-6 in their adipocytes, which leads to a reduced antiviral immune response by neutrophils and, as a result, uncontrolled viral multiplication in the early stages of infection [27]. Age is another risk factor for poorer prognosis in COVID-19 [4]. This age-related susceptibility is most likely owing to increased ACE2 expression, with older patients having a greater mortality rate [29]. Smoking has also been identified as a risk factor for SARS-CoV-2 infection [30]. 19.2 % of the patients were smokers, reported a Chinese cohort on evaluation of risk factors associated with COVID-19 [31]. IL-6 levels were significantly elevated in males compared to females. Furthermore, it was reported that a higher number of males were reported to experience lymphopenia. In fact, the immune-modulatory effects of hormones like estrogens help women infected with SARS-CoV-2 to have a lower susceptibility and a better prognosis [32].

5. Anti-IL-6 therapy agents

For the treatment and control of COVID-19 infection, a wide range of pharmacological treatments are currently being used. Tocilizumab, a monoclonal antibody that targets the IL-6 receptor, has been recommended for treatment [38,39]. Since IL-6 is observed to be considerably increased in COVID-19 infection, MoAbs that can counteract its effects could be used as a therapy option [40]. Tocilizumab is a recombinant humanised monoclonal antibody of the IgG1 class that targets the interleukin-6 (IL-6) receptor in both soluble and membrane-bound forms [38]. Retrospective studies patients affected by severe COVID-19 showed that treatment with Tocilizumab improved their COVID-19 clinical profile [41]. the National Health Commission of China via "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)" has recommend the use of Tocilizumab in severe or critically ill patients with confirmed elevated levels of IL-6 has been recommended for use in severe or critically ill patients with confirmed elevated levels of IL-6 [42].

Sarilumab, a human monoclonal antibody targeting the IL-6 receptor, was found to have a considerable improvement effect on respiratory function (30 % lower oxygen need than baseline) [43]. The anti-IL-6 antibody siltuximab was tested in the Siltuximab in Severe COVID-19 (SISCO) study. Mortality rates were examined in two cohorts of patients getting treatment with or without siltuximab, and it was reported that patients receiving siltuximab had a lower mortality rate [44,45]. Clazakizumab, another anti- IL-6 MoAb is suggested to be efficient treatment option, respiratory functions, inflammatory markers and oxygen require-

Table 1
Studies that compare IL-6 for COVID-19.

Author	Study design	Cohort size	Level in non-severe patient	Level in severe patient	Confidence interval (CI) range and p value	Comments
Chen et al (2020) [33]	Retrospective cohort; single centre	99	34 ± 7	72 ± 12	P < 0.0001	Increased expression of IL-2R and IL-6 in serum to predict the severity of COVID-19
Li et al (2020) [34]	Retrospective cohort; single centre	132	2.4 (2.1–2.9)	36,5 (30.8–42)	P < 0.0001	Severity of COVID-19 could be predicted with baseline IL-6 levels
Diao et al (2020) [35]	Retrospective cohort; multi-centre	552 COVID; 40 healthy	51 ± 74	186 ± 283	P < 0.0001	Significantly higher baseline levels of IL-6 in those requiring ICU compared to those do not
Huang et al (2020) [6]	prospective	41	5 (0–11.2)	6.1 (1.8–37.7)	P < 0.0001	Significantly higher baseline levels of IL-6 in those requiring ICU compared to those do not
Qin et al (2020) [36]	Retrospective cohort; single centre	452	13.3 (3.9–41-1)	25.5 (9.5–54.5)	P < 0.0001	Significantly higher baseline levels of IL-6 in sever critical COVID-19. Surveillance may help in early screening of critical illness
Wu et al (2020) [37]	Retrospective cohort; multi-centre	150	6.3 (5.4–7.8)	7.4 (5.6–10.9)	P < 0.0001	ARDS development in COVID-19 is related to rise in IL-6

ARDS = Acute Respiratory Distress Syndrome; ICU = intensive care unit.

ments have been improved in COVID-19 patients with significantly elevated levels of CRP and IL-6 after treatment with Clazakizumab [43].

CS is mediated via the JAK/STAT cascade. As a result, JAK inhibitors can be used to treat CS in SARS-CoV-2 (JAKi). Ruxolitinib is the first JAK inhibitor approved by the FDA, and it inhibits both JAK1 and JAK2 [46]. Ruxolitinib showed a faster clinical, chest CT improvement and significantly decreased levels of cytokines compared to control group. Furthermore, no deaths were reported in the Ruxolitinib receiving group (n = 20), against three patients in the control group (n = 21) due to respiratory failure [47]. Baricitinib, another JAKi, has been recommended as a potential treatment for SARS-CoV-2. All clinical characteristics (fever, cough, and dyspnea) as well as respiratory function improved in baricitinib treated COVID-19 patients compared to baseline [48]. A large number of anti-IL6 drug trials are now being conducted, which will pave the way for treatment techniques in the future.

6. Conclusion

Overall, the role of IL-6 in the immunopathology of COVID-19 is crucial. IL-6 takes centre stage in initiating and potentiating the dreaded CS. It also aids predicting disease severity and mortality in COVID-19. Elevated IL-6 levels were correlated with ARDS, increased requirement of mechanical ventilation, prolonged hospital stay, worse SOFA score (Sequential Organ Failure Assessment), multiple organ impairment and intensive care unit admission. Because anti-IL-6 antibodies and IL-6 receptor inhibitors have already been in vogue for the treatment of autoimmune illnesses, and have now been repurposed for the treatment of COVID-19 with some success, this review focused on IL-6 levels rather than other cytokines increased in cytokine storm. JAK inhibitors are also being tested for the treatment of COVID-19 in clinical trials. Further studies on genetic polymorphisms in various ethnic groups which affect IL-6 levels need to be conducted for stratification of COVID patients into mild, moderate and severe. Delineating such genetic polymorphisms may also pave the path for pharmacogenomic database for the exhibition of anti-IL-6 antibodies.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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