

# Multifactorial expression of IL-6 with update on COVID-19 and the therapeutic strategies of its blockade (Review)

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**Abstract.** Interleukin 6 (IL-6), a cytokine produced by various cells of the human body (macrophages, lymphocytes, astrocytes, ischemic myocytes, endothelial cells) has both pro-inflammatory and anti-inflammatory properties, being a key component in regulating various physiologic and pathological processes. The structure of this molecule and the receptor system it possesses are important due to the different activities that IL-6 can exert; through trans-signaling pro-inflammatory activities are mediated, while through classic signaling, IL-6 is responsible for anti-inflammatory and regenerative activities. IL-6 signaling is involved in coronary artery disease and the global COVID-19 pandemic. This proatherogenic cytokine reaches elevated serum

levels in the cytokine storm generated by SARS-CoV-2, and is also associated with smoking or obesity-classic cardiovascular risk factors which promote inflammatory states. IL-6 levels are proportionally correlated with dyslipidemia, hypertension and glucose dysregulation, and they are associated with poor outcomes in patients with unstable angina or acute myocardial infarction. IL-6 targeting for treatment development (not only) in cardiovascular disease and COVID-19 is still a matter of ongoing research, although tocilizumab has proven to be effective in reducing the proatherogenic effects of IL-6 and is suggested to improve COVID-19 patient survival.

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## 1. Introduction

Interleukin-6 (IL-6) is a cytokine produced by many cells of the body such as macrophages, lymphocytes, neutrophils,

adipocytes, astrocytes, mesothelial cells as well as cardiovascular components including endothelial cells, vascular smooth muscle cells and ischemic myocytes (1-4). In regards to its many properties and sources, IL-6 has been known for a long time under various names including interferon- $\beta$ 2, B cell stimulatory factor-2, 26 K factor, hybridoma growth factor, hepatocyte stimulatory factor, cytotoxic T cell differentiation factor, or plasmacytoma growth factor (5).

IL-6 regulates various physiological processes including hematopoiesis, immune response, acute phase response and the transition from acute to chronic inflammation (6). Despite the fact that IL-6 provides pro-inflammatory and anti-inflammatory properties, it is generally considered a pro-inflammatory cytokine (7), and dysregulation of IL-6 production represents a major contributor to the pathogenesis of chronic inflammatory and autoimmune diseases.

The role of IL-6 in the pathogenesis of many diseases, including rheumatologic, autoimmune, endocrine, cardiovascular or neurological diseases, its advantages and disadvantages and the therapeutic approach designed in order to inhibit the function of this specific inflammatory cytokine (anti-IL-6 therapeutic agents) are major topics of current research such that the number of related studies has increased substantially in the recent literature.

## 2. Literature review methodology

We performed an updated narrative review of studies published between 2000 and 2020 in the current literature which were focused on the cytokine IL-6 and its functional role, its intervention especially in the pathophysiology of inflammatory, autoimmune and cardiovascular diseases, the correlation between IL-6 and cardiac risk factors, the beneficial or detrimental cardiovascular outcome of anti-rheumatic therapies after IL-6 receptor blockade and its pathophysiological implications in various organ system diseases, including the novel COVID-19 global crisis.

Databases such as PubMed, Medline, ScienceDirect Freedom Collection, Elsevier were used in the search for related articles, by introducing the terms IL-6 and anti-IL-6 alone or in combination.

## 3. Interleukin-6

IL-6, a glycoprotein from the IL-6 family, involved both in health and disease, is present physiologically in the serum in picogram per milliliter (pg/ml) amounts. IL-6 can become elevated in basically any inflammatory state, even during exercise through skeletal muscle release of IL-6 or even after multiple trauma (proportional to the extent of the injury), being able to reach values of micrograms per milliliter ( $\mu$ g/ml) in severe conditions such as septic shock (8-10).

Multifunctional IL-6 is involved in many physiologic activities, disease initiation and progression, being more likely associated with the male gender (11); the pleiotropic quality of this cytokine makes it a key role player in many physiologic processes.

Physiologic processes in which IL-6 is involved are numerous, and include ageing, menses, spermatogenesis, bone strengthening, liver regeneration and skin proliferation (5).

IL-6 is involved in brain development including cognitive processes of memory formation and cognitive flexibility by promoting differentiation and proliferation of neurons (5,12). IL-6 is also involved in hematopoiesis, metabolism (13) and post-prandial glycemia improvement. Through delayed gastric emptying it regulates appetite and is such involved in body weight control, as a result of hypothalamic neuropeptide regulation (14). IL-6 also plays a role in immune modulation/host defense (acute phase reaction, B lymphocyte differentiation, T helper activation and T regulatory lymphocyte inhibition). In gut associated lymphoid tissue (GALT), IL-6 is the key factor in balancing Th17 and Treg cells (4,15-17).

Important pathologic processes with IL-6 involvement include inflammatory states. It is one of the earliest cytokines involved in inflammation, inducing acute inflammation, mobilizing neutrophils from the bone marrow and activating eosinophils; as an endogenous pyrogen, it can ensure the transition from an innate to an adaptive immunity, and also immunoglobulin secretion. It is involved in chronic inflammatory diseases including (osteo) arthritis, rheumatoid arthritis, pulmonary fibrosis, asthma, chronic obstructive pulmonary diseases (some with autoimmune background, such as vitiligo, for which piperine treatment seems to lower IL-6 levels) (18-23). IL-6 is also involved in cancer development and progression as is the case for head and neck squamous cell carcinoma, for which cumulative hydrochlorothiazide use seems to be a risk factor. It is frequently involved in liver and breast cancer, head and neck squamous cell carcinoma by exerting pro-angiogenic properties (this factor makes it also a valuable component in wound healing) and development of inflammation-associated cancers. In cancer prevention, IL-6 directs NK cells at the tumor site during exercise (4,14,15,24-26). IL-6 is involved in skin disorders including rosacea, vitiligo, lichen planus and contact allergy (19-22,27-30). IL-6 directly and indirectly inhibits human herpes virus-1 (HHV-1) infection. It is involved in humoral responses against influenza virus post-vaccination, registers high levels in advanced human immunodeficiency virus (HIV) infection, has antibacterial properties by inhibiting gram-negative bacteria and is involved in fighting parasitic infections such as filaria (31-37). It is involved in nervousness (13), osteoporosis (as a protective agent by promoting osteogenesis through angiogenesis) (4), cognitive dysfunction in neurodegenerative diseases (Huntington's, Parkinson's and Alzheimer's diseases, multiple sclerosis) and psychiatric disorders (major depression, schizophrenia, bipolar disorder) (12,38). IL-6 is involved in metabolic syndrome including obesity and type 2 diabetes (11,38), coagulation disorders (39), neuropathic pain, autoimmune disorders and ischemic injury (18).

*Structure and receptor system.* The structure of the IL-6 cytokine, of its receptors and receptor-complexes represents information valuable for understanding the basis of this cytokine's multifunction. This single chain glycoprotein has four helix bundles, A-D, which form a ribbon-like arrangement and run in opposite directions (A and B vs. C and D) (5).

The multifunctional activity of IL-6 is mediated by its cell surface type-I receptor complex consisting of two components-the  $\alpha$ -receptor subunit (CD126 or IL-6R), a type I transmembrane glycoprotein weighing 80 kDa, and the

signal-transducing  $\beta$ -receptor subunit (CD130 or gp130), a type I transmembrane protein of 130 kDa (13).

gp130 is an ubiquitous receptor, a signal transducer, commonly found on the surface of all cell types and shared between the IL-6 family members. IL-6R, on the other hand, is a specific receptor, found on a limited number of cell types including monocytes, macrophages, hepatocytes, B cells and T cells (few subpopulations) and is made up of a number of three domains-D1, D2, D3. D1, or Ig domain, and forms a link with the cytokine binding domain (CBD), made up of D2 and D3 (5,33).

IL-6R can be found in two forms, soluble (sIL-6R) and membrane-bound (mIL-6R). mIL-6R is found in liver cells, neutrophils, T cells or monocytes and is involved in physiological activities such as acquired immunity. sIL-6R is the product of proteolytic cleavage of members from the metalloproteinase gene family, ADAM10, ADAM17, or the result of the alternative splicing of IL-6R mRNA; it can also acts as a carrier for IL-6, taking it to the pathologic site which has gp130-the tallest cytokine receptor with an extracellular region with 6 domains (D1 to D6). As for IL-6R, D1 is the Ig domain, D2 and D3 form the CBD and D4, D5 and D6 bind with IL-6, being involved in other signaling mechanisms (5,33).

The signal transduction mechanisms of IL-6 have been thoroughly investigated which include classic signaling, trans-signaling and cluster signaling; all of these rely on the process of mgp130 (membrane-bound gp130) homodimerization which then activates the following downstream signaling pathways: JAK/STAT, ERK and PI3K. By activating these two signaling pathways, ERK/MAPK and JAK/STAT, IL-6 can exhibit distinct, but also contradictory functions, explaining its antagonistic pro-inflammatory and anti-inflammatory activities (5,33).

On target cells which express both receptors, IL-6R and gp130, the first step which IL-6 takes, is to bind to mIL-6R, forming the IL-6/mIL6R complex and thus triggering the creation of a macromolecular complex with two identical proteins, mgp130, the homodimerization process mentioned earlier, part of the classic signaling (40).

The IL-6 trans-signaling is a pro-fibrotic transduction mechanism that uses sIL-6R in order to bind to IL-6 and form an IL-6/sIL6-R complex which detaches itself from the cell surface with the help of two metalloendopeptidases-disintegrin and metalloproteinase 17-ADAM17 (33,40); this complex then activates the cells expressing only gp130. The agonist activity of sIL-6R is thus revealed by amplifying IL-6 signaling in cells that lack IL-6R. Trans-signaling is an inflammation regulator involved in many diseases including rheumatoid arthritis, inflammatory bowel disease, pancreatic cancer, diabetes and pulmonary fibrosis (41).

Cluster signaling, a newly discovered type of signaling model, is a complex process described during the interaction between T helper17 (Th17) and dendritic cells. The IL-6/mIL-6R complex, found on the transmitter cells, sets off the activation of mgp130 on the receiver cells (13).

The importance of IL-6 signaling stems, on the one hand, from the molecular link that it creates between acute, chronic inflammation and fibrogenesis, IL-6 being a critical mediator in inflammatory processes by helping inflammatory cell recruitment to the affected area; trans-signaling, more

specifically, has been associated with pro-fibrotic processes and tissue remodeling (40,42). This fact is also strengthened by the IL-6 gene polymorphism which has been associated with acute and chronic inflammatory states, and, subsequently with fibrosis (31). On the other hand, IL-6 signaling is important due to the fact that, depending on the biochemical pathway that is involved, it has implications both in physiological and pathological activities (5), trans-signaling mediating pro-inflammatory activities of IL-6 and classic signaling mediating regenerative and anti-inflammatory activities (41).

#### 4. Interleukin-6 and the cardiovascular system

IL-6R signaling seems to have a determinant role in the development of coronary artery disease (CAD). Obesity, cigarette smoking, infection or stress are determinants in the development of elevated serum IL-6 concentrations and lead to different inflammatory responses. Increased IL-6 levels are strongly correlated with hypertension, dyslipidemia and glucose dysmetabolism, traditional cardiovascular risk factors which finally promote atherosclerosis, the main cause of cardiovascular disease (CVD) (43,44).

Over the last few decades, the role played by inflammation in the process of atherosclerosis development has been widely researched (45), making identification of detailed pathways which link inflammation with atherosclerosis and CVD, a promising basis for new possible therapeutic targets. In the pathophysiology of CVD, IL-6 plays a causative role, as a marker of inflammation related to cardiovascular risk (46,47) and as a significant proatherogenic cytokine (48).

Other studies have found that plasma C-reactive protein (CRP) levels are strongly linked with atherosclerosis, showing robust results as a marker of systemic inflammation associated with cardiovascular risk (49). Plasma CRP is produced primarily by liver cells in response to inflammatory stimulation exerted by cytokines, such as IL-6. Different research studies have reported IL-6 to be an upstream inflammatory cytokine that is responsible for chronic-inflammation-related atherogenesis (50).

Inflammatory biomarkers are known for their association with many cardiovascular events (51-53). These markers, including IL-6, have a predictive value demonstrated in patients with pre-existing CAD and cerebrovascular disease (54,55). The existing extensive literature aids in supporting the role of chronic inflammation in the development and progression of atherosclerosis (56), as various reports state that elevated levels of these inflammatory agents (IL-6 including) have been linked to acute ischemic conditions and are by far predictors of recurrent events in those with CAD (51,52,56).

There are multiple mechanisms by which circulating IL-6 contributes to the development of CAD including endothelial, coagulant and metabolic mechanisms. Serum IL-6 is a main stimulator of hepatic acute-phase response (associated with increased blood viscosity and increased platelet number and activity). Autocrine and paracrine activation of monocytes by IL-6 in the vessel wall activates the deposition of fibrinogen (CRP and fibrinogen are both strong risk factors for CAD). Circulating IL-6 also stimulates the hypothalamic-pituitary-adrenal (HPA) axis which is associated with central obesity, hypertension, and insulin resistance (57,58).

The positive association between IL-6 serum concentration and mortality risk from CAD has been reported by several studies (51,55,59,60). Elevated serum IL-6 levels are linked to an increased risk of CAD patient mortality but the cytokine's direct causal role in death is yet to be confirmed (61). Serum IL-6 levels are a major predictor for short- and long-term death rates, being a possible mortality biomarker in CAD patients.

The first association between IL-6 and the development of cardiovascular disease was shown thirty years ago in a case of cardiac myxoma (62). Although acute IL-6 response can protect and preserve myocardial tissue, the chronic elevation of IL-6 induces depressed myocyte function (58). Increased levels of IL-6 have been associated with a detrimental outcome concerning all CVDs (63). IL-6 can cause cardiac hypertrophy through gp130 activity. Continuous and excessive production of IL-6 promotes myocardial injury, congestive heart failure (1) and a higher risk of future myocardial infarction even in apparently healthy young men not only in older people (64).

A recent report which highlighted IL-6 involvement in CHD development also reported that IL-6R blockade reduced systemic and articular inflammation (47); whether this could decrease the risk of CVD, or not, is yet unknown. Furthermore, this causal association between IL-6R-related pathways and coronary heart disease is also strongly supported by a collaborative randomized analysis (47). As such, targeting IL-6R may be a novel therapeutic approach for the prevention of CHD.

The serum level of IL-6 is also associated with unfavorable clinical outcomes in patients hospitalized for unstable angina and ST-elevated myocardial infarction (STEMI) (47,55). Many chronic conditions (common causes of death in the elderly) may stimulate and maintain a systemic inflammatory state which can be measured by increased levels of serum IL-6 or other pro-inflammatory cytokines (65).

Associations between serum IL-6 and death rates have been researched by many studies in the past, but with important conflicting results. The Women's Health and Aging study revealed that among women with prevalent CVD, those who registered higher plasma levels of IL-6 had an increased mortality risk (more than 4-fold) as compared to those found in the lowest tertile; this study did not manage to find such an association among female patients without CVD (65). IL-6 has been found to be more strongly associated with an all-cause and cardiovascular death rate than CRP (54).

Other recent studies have shown that elevated levels of serum IL-6 provide valuable information for the risk assessment of long-term cardiovascular mortality in patients with STEMI and are a powerful predictor of cardiovascular and all-cause mortality (55,66).

Plasma IL-6 level has been shown to be good predictors for short- and long-term mortality in patients with acute heart failure (HF); also, two prospective studies have associated serum IL-6 levels with CHD. Increased IL-6 concentrations can be a predictive factor for mortality in elderly patients with HF (64,67); plasma IL-6 is a stronger and more powerful predictor for total and cardiovascular mortality in patients undergoing hemodialysis, even more than CRP (68).

Gender-specific aspects concerning death rates is still a problematic aspect, this including the issue of inflammatory

markers (69). It is thus necessary to further study the gender specificity of mortality in relation to the inflammatory hypothesis and CAD.

Acute myocardial ischemia/reperfusion (I/R) has been proven to be associated with an inflammatory response which may contribute to I/R-induced injury of the heart. Upon cardiac I/R, one of the major inflammatory mediators that are quickly released is IL-6. Chronically elevated IL-6 levels is a factor associated independently with acute coronary syndromes, thus suggesting an etiologic involvement of this cytokine in myocardial injury (70-72). IL-6 is a contributing factor in the adverse remodeling which takes place at 35 days following I/R (73).

On the other hand, the NOMAS/Northern Manhattan Study has assessed the relationships between high-sensitivity CRP (hsCRP)/IL-6 and stroke. The stroke risk associated with the inflammatory biomarkers (hsCRP and IL-6) depended on the relationship to one another. When hsCRP-quartile dominated the IL-6 quartile, risk was increased, and when IL-6 was over hsCRP, the risk was decreased. Having combined panels of inflammatory biomarkers might help in predicting ischemic events; this is also valid even when their individual measurements are not capable of doing so (74). IL-6 contributes to the determination of the severity of ischemic stroke and that it affects clinical outcomes in this pathology (74); thus being said, more studies are needed in order to evaluate this risk classification and to assess the importance of inflammatory markers in stroke evolution.

Treatments that lower systemic inflammatory markers such as IL-6 show beneficial effect on atherosclerosis and, respectively, on its complications. The blockade of IL-6 by neutralizing IL-6R with monoclonal antibody tocilizumab (an interleukin-6 receptor antagonist) reduces systemic and articular inflammation (75-77).

## 5. Cardiovascular system and rheumatoid arthritis link

In several clinical human trials, elevations in serum lipid levels were found among those receiving tocilizumab (TCZ). This treatment, although it develops significant dyslipidemia and increases body weight, also significantly reduced IL-6 activity and provided dramatic improvement in endothelial function in a high risk rheumatoid arthritis (RA) population (78-80).

In a head-to-head randomized controlled trial (RCT) of TCZ monotherapy vs. adalimumab monotherapy that enrolled 325 patients with RA, TCZ proved to be superior to adalimumab in attenuating signs and symptoms of RA; more patients in the TCZ group had increases of 17 to 25% in total cholesterol, low- and high-density cholesterol, and triglyceride levels, more than those in the adalimumab group. Nonetheless, although increases in lipid levels with TCZ treatment compared with treatment with other biologic agent were registered, an excess risk for cardiovascular events, stroke, heart failure hospitalization, or cardiac death has not been yet determined (80,81).

Patients with RA have an increased risk of sudden cardiac death, a fact which is not entirely explained by RA disease characteristics. Corrected QT (QTc) interval prolongation is a marker more frequently found in patients suffering from RA, than in those without RA. TCZ treatment in patients with RA decreases the QTc interval by reducing systemic inflammation.

Furthermore, given the anti-arrhythmic potential of TCZ treatment, it may have beneficial effects in those RA patients (82).

RA is associated with an increased risk of congestive heart failure possibly through inflammatory mechanisms. Studies have tested the hypothesis that the powerful anti-inflammatory effect of anti-IL-6 TCZ therapy might lead to a reduction in left ventricular dysfunction in patients with RA. It demonstrated that the improvement in left ventricular regional function by TCZ treatment may correlate with reduction in RA disease activity (83).

## 6. Interleukin-6 and the gastrointestinal system

The cytokine IL-6, part of the inflammatory cascade and an indicator of systemic injury, is involved in immunologic signaling, in reticulo-endothelial system activity, the acute phase response in the liver and is part of the liver's regenerative process. After partial liver resection, IL-6 serum levels were found to increase as early as 30 min post-resection and were maintained at an increased level for several days afterward (84,85). The effects of IL-6 on the liver have also been linked to the muscle-liver axis-which is involved in metabolism homeostasis, with protection against non-alcoholic fatty liver disease through the activation of the autophagy-lysosomal liver pathway and evasion of liver steatosis (86).

IL-6 is a potent vascular relaxer and it is involved in sepsis at the intestinal level through the dilatation of the constricted vasculature; it allows proper oxygenation and inhibits the processes of necrosis and apoptosis of intestinal epithelial cells which are induced through hypoxia. In the intestines, IL-6 has also proven to have antibacterial effects, lowering the load of pathogenic *Campylobacter* even before IgA is involved, thus implying the involvement of a non-immune mechanism (87). As a critical factor for the survival and differentiation of T cells, IL-6 is a key player in irritable bowel disease (a T cell-mediated immune disorder) and by participating in chronic inflammation it continuously stimulates the production of growth factors and cytokines which in turn allow the growth and survival of malignant cells. In consequence, besides it being involved in colitis, both Crohn's disease and ulcerative colitis, IL-6 is also linked to the development of colorectal cancer (88,89).

This cytokine is also produced by hematopoietic and epithelial neoplastic cells, as in pancreatic carcinoma, and it modulates the behavior of these cells by interacting with vascular endothelial cells and acting as a regulator for vascular permeability. The increased values in obesity have been in direct link with type 2 diabetes; a paradoxical observation was made which stated that through stimulation of glucagon-like peptide-1 (GLP-1) in the pancreas by IL-6 administration insulin secretion was stimulated, improving plasma glucose levels (90,91).

IL-6 is also involved in gastro-duodenal diseases, the gastric mucosal levels of this cytokine being increased in *Helicobacter pylori*-associated chronic gastritis and also in individuals with gastric cancer which are positive for this bacteria (another chronic inflammation-cancer development cascade with which IL-6 is linked) (92). High levels of IL-6 have been proven to be involved in delayed gastric emptying, with lower postprandial glucose levels in normal and type-2 diabetes individuals (93).

## 7. Interleukin-6 and cancer

IL-6 is involved in pancreatic cancer which is supported by immunohistochemistry studies which revealed overexpression in the tissues examined. Here, the tumor cells act as secretory cells for this cytokine. IL-6 is a key player in cancer progression by supporting the proliferation and ensuring the survival of neoplastic cells through the JAK/STATs pathways; this plays a further role in metastatic progression, establishing the poor prognosis of pancreatic cancer, but also that of breast cancer (94).

Tumor-derived IL-6 is multifaceted through the many activities in which it is involved, acting not only on the tumor itself, but also on the immune system. Thus, it acts as a growth factor in breast and prostate cancers, as a differentiation-inducer for neoplastic cells in lung adenocarcinoma (95). It promotes angiogenesis and tumor invasion (important factors in local and systemic tumor extension and metastasis), having an important role in hepatocellular carcinoma and Wilms tumor. IL-6 is also involved in colon cancer where it facilitates tumor immune escape by regulating tumor resistance to cytotoxic cells (determining decreased cell death receptor expression) and it drives and maintains pro-tumorigenic inflammatory loops. High levels of serum IL-6 (and the associated worse prognosis) have been found in patients with metastatic renal cell carcinoma, lung, breast and prostate cancers, Hodgkin's disease, multiple myeloma or ovarian carcinoma. However, cancer-bearing animal-based studies have shown that exogenous administration of IL-6 has antitumor properties, in direct contrast with the pro-tumorigenic activities described (96-99).

As in the pro-inflammatory-anti-inflammatory dichotomy described earlier in this article, the former antagonistic activities might be linked to the different signaling pathways that IL-6 and its receptor system use.

## 8. Interleukin-6 and COVID-19

The most recent global pandemic of the 21st century, which originated in the city of Wuhan, Hubei Province, China, was caused by the highly contagious novel beta-coronavirus-SARS-CoV-2 (the third lethal human coronavirus), the etiologic agent of a pneumonia causing severe respiratory acute syndrome (100,101). Almost 19% of cases are severe or in a critical state (100).

The World Health Organization (WHO) named this deadly outbreak COVID-19, an acronym for COronaVIrus Disease from 2019, spreading extremely fast between continents and having severe consequences on everyday life (100,101). On April 21, 2020, the WHO revealed in its 92nd Situation report a total number of more than 2,300,000 people infected, with over 160,000 deaths worldwide (102).

The pathogenesis of COVID-19 is the subject of current research and until now a dysregulated immune response, the cytokine storm, seems to be one of the main culprits. The cytokine storm, or the cytokine release syndrome (CRS), is a systemic inflammatory response to various factors (SARS-CoV-2), signifying the overwhelming and uncontrolled release of high levels of pro-inflammatory cytokines, a specific finding in the critically ill patients infected with the novel virus. The importance of this overly active immune system

response stems from the fact that those with high cytokine concentrations have a severe and rapid progression towards cardiovascular collapse, multiple organ dysfunction syndrome (MODS) (including renal and liver failure) and, finally, exitus. The specificity of the organs affected resides in the fact that this virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor which is particularly massively expressed on the cell surfaces of the lung, kidney and heart (103-105).

Recent Chinese clinical experiences incriminate IL-6 as one of the main cytokines involved in such coronavirus-induced storms, being produced mainly by activated macrophages. One study even reports severe cases as having lymphopenia-diminished numbers of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes (with a more accentuated decrease in CD8<sup>+</sup> cells), accompanied by increasing levels of inflammatory cytokines and chemokines in the peripheral blood including IL-6, IL-1 $\beta$ , IL-2, IL-10, IFN- $\delta$ , IP10 (induced protein 10) and MCP-1 (monocyte chemoattractant protein-1) (103-105).

A cohort study found that IL-6 blood levels correlated with mortality in patients suffering from severe forms of COVID-19, being an important biomarker for predicting disease severity and prognosis (along with IL-2R which seems to have the same predictive value) (105). In this complex pathogenic mechanism, IL-6 plays an essential role in generating T helper cells (more specifically Th17 lymphocytes which seem to be overly activated) in the process of interaction between T cells and dendritic cells. IL-6 levels were reported to vary between the severely affected patients (having highly elevated levels), who were admitted in the Intensive Care Unit (ICU)-ICU patients and those who had milder disease manifestations (non-ICU patients). This is important for the therapeutic decision: whether IL-6 blockade is effective in all patients or only in those suffering from CRS, and for the ability of classifying patients according to disease severity, thus being useful in establishing risk stratification and evaluating patient prognosis (105).

As such, IL-6 being the key molecule in CRS, it is of utmost urgency and importance to find a suitable treatment that will ensure patient survival, especially in the case of those critically ill patients. Until now, therapeutic agents are scarce, patients having limited options for treatment.

## 9. Anti-interleukin-6 therapy

Anti-IL-6 therapeutic agents are a class of biologic immune modulators which includes antibodies directed against the IL-6 receptor/ligand (tocilizumab, sarilumab) and also inhibitors of IL-6 signal transduction (JAK inhibitors such as baricitinib, tofacitinib), making them useful in many chronic inflammatory conditions. Targeting IL-6 pathways is a more global approach, which includes targeting two of the three pathways: classic signaling and trans-signaling (more specifically sIL-6R and mIL-6R); this is not a novel approach, but an attractive one nonetheless due to the many activities exerted by this cytokine.

**Tocilizumab (TCZ).** TCZ is a humanized monoclonal antibody (mAb) directed against the IL-6 receptor (IL-6R), more specifically against its  $\alpha$  subunit and is approved for use in diseases such as systemic juvenile idiopathic arthritis and RA, having seemingly positive effects in Crohn's disease and Castleman disease (79,104,106).

A phase III study involving 623 patients (79) revealed that this therapeutic agent has significantly improved the clinical and laboratory signs in RA patients-the OPTION study. TCZ administered as 8 mg/kg/dose (alone or in combination with methotrexate) registered a significant decrease in CRP levels, even as low as their normal range. Improvement concerning the hemoglobin levels (which are low in those suffering from a chronic inflammatory disease, with the characteristic secondary anemia) was also shown. Another positive effect of TCZ, administered at the same dosage, was revealed by the LITHE study where the radiographic findings in those with RA were significantly improved (106). All of these studies, including ACT-RAY, FUNCTION and SURPRISE have shown a more beneficial outcome in those following combination therapy, rather than monotherapy. Other positive effects of such treatment were registered in the physical and mental scores of RA patients (79,106,107).

In what concerns the new COVID-19 pandemic, IL-6R blockade seems to be a key treatment option for the critically ill patients who suffer from CRS (IL-6 being a key cytokine). CRS inhibition could be possible through the use of TCZ because it binds to both forms of IL-6R (membrane-bound and soluble) and because it also inhibits the signal transduction that these two receptors mediate (100). It is suggested that a combination between immune modulation agents and antiviral agents might be more beneficial for patient survival. The results reported major improvements in elevating the peripheral blood lymphocyte numbers and in reducing the patient's fever and lung opacities, all the while reducing the IL-6 blood levels which had an initial spike increase followed by constant decrease.

In 2017, TCZ was approved by the Food and Drug Administration (FDA) for the treatment of CRS in the case of a pediatric female patient suffering from acute lymphoblastic leukemia (ALL) treated with chimeric antigen receptor T-cell immunotherapy (CAR-T therapy). The CRS caused by CAR-T therapy was successfully treated with TCZ, improving the patient's overall health status and without affecting the ALL therapy (100,103,104).

As any other therapeutic agent, TCZ has the capacity of causing adverse effects such as: Infections, hypertension, dermatitis, rashes, dyspepsia, abdominal pain, oral and peptic ulcers, headaches, increases in lipid levels (hypercholesterolemia) and liver function tests such as aminotransferases, and leucopenia (79,106,107). Some trials even reported TCZ to be a CVD risk factor, as patients who underwent treatment with this agent were much more likely to suffer from major cardiovascular events (104).

**Sarilumab.** Another human mAb targeting IL-6R $\alpha$ , sarilumab (SAR153191/REGN88), binds with high affinity sIL-6R $\alpha$  and mIL-6R $\alpha$ , without any cell-mediated toxicity.

It showed promising results in studies which enrolled patients suffering from moderate to severe RA-such as MOBILITY, MONARCH and TARGET, where it lowered CRP levels and stopped joint damage progression in a dose-dependent manner, as monotherapy or combined therapy (41,106).

The adverse effects ranged from infections, hypersensitivity reactions (no anaphylaxis) to laboratory abnormalities including hypercholesterolemia, increased liver function tests, leucopenia and thrombocytopenia (41,106,108).

*Olokizumab and sirukumab.* As a humanized anti-IL-6 mAb, olokizumab has proven to be as effective as and with similar side effects as TCZ in various clinical trials. This anti-IL-6 agent has the property of blocking the final assembly of this cytokine's signaling complex. Olokizumab registered a very low increase in triglyceride blood levels, without any increases in the total cholesterol levels or its low density and high density subunits, as opposed to TCZ findings. Sirukumab, a human mAb, reported similar side effects in human trials as with TCZ (especially regarding laboratory abnormalities), but without the presence of opportunistic infections. The safety and efficacy profiles of TCZ, sarilumab, olokizumab and sirukumab have proven to be similar in reported studies (109,110).

Besides the treatment possibilities listed, what could be of use concerning the COVID-19 pandemic are adequately implemented preventive measures, such as: early detection of those infected, implementation of national procedures for the detection and management of the virus, the continuous up-dating of the latest scientific discoveries concerning this disease with international collaboration and assistance (111); having these in mind, the most important step in disease prevention remains the development of a vaccine, although it has been a difficult task to manage due to the many unknowns concerning SARS-CoV-2 (112).

## 10. Conclusions

Long term elevated levels of IL-6 have now been proven to be associated with cardiovascular risk and to be involved in the pathogenesis of cardiovascular diseases, a causality link being established between this cytokine IL-6 and CHD; thus being said, an etiological link between serum IL-6 levels and mortality in patients with arterial heart disease yet remains to be proven. Targeting IL-6R in order to decrease cardiovascular risk needs further studies for confirmation, as clinical research has proven monoclonal antibodies to have an increasing effect on serum lipid levels, a well-known factor for CHD development and progression.

More studies are indeed needed in order to evaluate the entirety of the positive and adverse effects of tocilizumab, sarilumab, olokizumab and sirukumab in the field of cardiovascular diseases, although in the case of tocilizumab it appeared to significantly reduce the proatherogenic effect of IL-6. Concerning the novel COVID-19 global crisis and the CRS this virus generates, it is necessary to better understand the pathogenesis of this viral disease in order to find suitable immune therapies.

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## Availability of data and materials

All information is documented by relevant references.

## Authors' contributions

ALT, VC, ODB, MD, MM and CB contributed to the acquisition, analysis and interpretation of data. MC, FB, DSR and EN made substantial contributions to the conception and design of the work, while EM, AME, MA, LCN and AN supervised and substantially revised this work. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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