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Original
Covid-19 Cytokine Release Syndrome and Drugs / Sparavigna, Amelia Carolina. - ELETTRONICO. - (2020). [10.5281/zenodo.3820413]

Availability:
This version is available at: 11583/2822994 since: 2022-11-23T15:42:43Z

Publisher:

Published
DOI:10.5281/zenodo.3820413

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14 May 2024

Covid-19 Cytokine Release Syndrome and Drugs

Amelia Carolina Sparavigna
Politecnico di Torino

A survey of literature about the Cytokine Release Syndrome in Covid-19 and of some drugs used or proposed against it.

Keywords: Cytokines, Interleukins, TNF, Drugs.

Torino, May 11, 2020 - DOI: 10.5281/zenodo.3820413

Covid-19 is a disease resulting from the infection caused by virus SARS-CoV-2. This infection can have as its product "an excessive and aberrant host immune response", associated with what is defined as a "cytokine storm" [1]. This storm is characterized "by the plasma increase of many cytokines that produce long-term damage and fibrosis of lung tissue" [1].

Among the cytokines, there is the Interleukin 6 (IL-6), produced by a variety of cell types and involved in various physiological processes [1]. "Elevated tissue and serum levels of IL-6 are implicated in the pathogenesis of various inflammatory and autoimmune disorders including many forms of rheumatic diseases; they are also implicated in the cytokine release syndrome (CRS)" [1].

As told by Perrone F. et al. in [1], Chinese researchers (Xiaoling Xu et al., Effective Treatment of Severe COVID-19 Patients with Tocilizumab. ChinaXiv: 202003.00026v1 [2,3]) disclosed that 21 patients with severe or critical COVID-19 pneumonia were treated with a drug, the tocilizumab, with a reduction of oxygen requirement and other positive results. "These results are considered by the Chinese authors to be very positive".

Ref.1 is the first protocol in Italy about cytokine storm and the use of the Tocilizumab drug. The main source of information about other trials in Italy is given by the Italian Government [4-6]. In [7], we listed the drugs used in Italy. There we mentioned Tocilizumab, Sarilumab, Siltuximab, Canakinumab, Baricitinib, Methylprednisolone, Selinexor, Hydroxychloroquine, Enoxaparin sodium, Solnatide, Colchicine, Emapalumab, Anakinra, Remdesivir, Camostat, Nafamostat, Ivermectin.

In Refs. [8-22], some publications related to tocilizumab are given. In [23], a study is proposed. The research showed that prolonged treatment with tocilizumab has been associated with cases of severe hepatotoxicity with liver failure and hepatitis, characterised by elevated hepatic transaminases (GOT/AST and GPT/ALT). *In the case of Covid-19, the treatment is not prolonged.*

Cytokine

"Cytokines are a broad and loose category of small proteins important in cell signaling. Cytokines are peptides and cannot cross the lipid bilayer of cells to enter the cytoplasm. Cytokines have been shown to be involved in autocrine, paracrine and endocrine signaling as immunomodulating agents. Their definite distinction from hormones is still part of ongoing research. Cytokines include chemokines, interferons, **interleukins**, lymphokines, and tumour necrosis factors, but generally not hormones or growth factors (despite some overlap in the terminology). Cytokines are produced by a broad range of cells, ... They act through cell surface receptors and are especially important in the immune system; cytokines modulate the balance between humoral and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways.

They are different from hormones, ... Cytokines are important in health and disease, specifically in host immune responses to infection, inflammation, trauma, sepsis, cancer, and reproduction. The word comes from Greek: cyto, from Greek "κύτος" kytos "cavity, cell" + kines, from Greek "κίνησις" kinēsis "movement"." https://en.wikipedia.org/wiki/Cytokine

Cytokine storm

"Cytokines are small proteins released by many different cells in the body, including those of the immune system where they coordinate the body's response against infection and trigger inflammation. ... Sometimes the body's response to infection can go into overdrive. For example, when SARS -CoV-2 – the virus behind the covid-19 pandemic – enters the lungs, it triggers an immune response, attracting immune cells to the region to attack the virus, resulting in localised inflammation." When it happens that excessive or uncontrolled levels of cytokines are released, with a consequent activation of more immune cells, the body suffers a hyperinflammation, that is, a "cytokine storm".

"Cytokine storms are a common complication not only of covid-19 and flu but of other respiratory diseases caused by coronaviruses such as SARS and MERS. They are also associated with non-infectious diseases such as multiple sclerosis and pancreatitis. The phenomenon became more widely known after the 2005 outbreak of the avian H5N1 influenza virus, also known as "bird flu", when the high fatality rate was linked to an out-of-control cytokine response."

From "Cytokine storm - An overreaction of the body's immune system", by Alison George, New Scientist, https://www.newscientist.com/term/cytokine-storm/

"Cytokine storms are associated with a wide variety of infectious and noninfectious diseases. The term was popularized largely in the context of avian H5N1 influenza virus infection, bringing the term into popular media" [24].

Interleukin-6

"Interleukin 6 (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, it is encoded by the IL6 gene. In addition, osteoblasts secrete IL-6 to stimulate osteoclast formation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. IL-6's role as an anti-inflammatory myokine is mediated through its inhibitory effects on TNF-alpha and IL-1, and activation of IL-1ra and IL-10. There is some early evidence that IL-6 can be used as an inflammatory marker for severe COVID-19 infection with poor prognosis, in the context of the wider coronavirus pandemic. ... IL-6 stimulates the inflammatory and auto-immune processes in many diseases such as diabetes, atherosclerosis, depression, Alzheimer's Disease, systemic lupus erythematosus, multiple myeloma, prostate cancer, Behçet's disease, and rheumatoid arthritis. Hence, there is an interest in developing anti-IL-6 agents as therapy against many of these diseases. The first such is tocilizumab, which has been approved for rheumatoid arthritis, Castleman's disease and systemic juvenile idiopathic arthritis. Others are in clinical trials. ... The first FDA approved anti-IL-6 treatment was for rheumatoid arthritis." See https://en.wikipedia.org/wiki/Interleukin_6 and references therein.

Drugs used in Italy

As shown in [7], drugs used in Italy against Covid-19, are targeting cytokines.

"**Tocilizumab**, also known as atlizumab, is an immunosuppressive drug, mainly for the treatment of rheumatoid arthritis ... . It is a humanized monoclonal antibody against the **interleukin-6** receptor (IL-6R). Interleukin 6 (IL-6) is a cytokine that plays an important role in immune response and is implicated in the pathogenesis of many diseases, such as autoimmune diseases, multiple myeloma

and prostate cancer". https://en.wikipedia.org/wiki/Tocilizumab - Seee also "Tocilizumab" https://www.drugs.com/monograph/tocilizumab.html - "Atlizumab: anti-IL-6 receptor antibody-Chugai, anti-interleukin-6 receptor antibody-Chugai, MRA-Chugai". BioDrugs. 2003;17(5):369-72. https://www.ncbi.nlm.nih.gov/pubmed/14498766 - "Actemra/RoActemra (tocilizumab)" Roche https://www.roche.com/products/product-details.htm?productId=42bf9d08-8573-491a-944a-fdbc030ec44b - "Tocilizumab" by Adith Venkiteshwaran. MAbs. 2009 Sep-Oct; 1(5): 432–438. doi: 10.4161/mabs.1.5.9497. PMCID: PMC2759492 PMID: 20065633

"**Sarilumab** (trade name Kevzara) is a human monoclonal antibody against the **interleukin-6** receptor. ... US FDA approval on 22 May 2017 and European Medicines Agency approval on 23 June 2017." https://en.wikipedia.org/wiki/Sarilumab. "Sarilumab enters clinical trial for COVID-19, spotlighting 'key role' for IL-6". March 19, 2020. http://archive.is/PFldw "Sarilumab (Kevzara) — jointly developed Regeneron and Sanofi — is a fully human, monoclonal antibody that inhibits the interleukin-6 (IL-6) pathway by binding and blocking the IL-6 receptor. According to the pharmaceutical companies' joint statement, IL-6 may play a role in driving the overactive inflammatory response in the lungs of patients who are severely or critically ill with COVID-19."

"**Siltuximab** (INN, trade name Sylvant; also known as CNTO 328, anti-IL-6 chimeric monoclonal antibody or cCLB8) is a chimeric (made from human and mouse proteins) monoclonal antibody. It binds to **interleukin-6**. Siltuximab has been investigated for the treatment of neoplastic diseases." https://en.wikipedia.org/wiki/Siltuximab - "Il Siltuximab è un anticorpo monoclonale che agisce sull'IL-6, è studiato come antitumorale. E' commercializzato come Sylvant; noto anche come CNTO 328. E' studiato per il trattamento di tumori metastatici come il carcinoma a cellule renali, tumore alla prostata, e per la malattia di Castleman, tra altri tipi di tumore." https://it.wikipedia.org/wiki/Siltuximab - "Sylvant è un medicinale contenente il principio attivo siltuximab." https://www.my-personaltrainer.it/farmaci/sylvant.html

"**Canakinumab** (INN, trade name Ilaris, previously ACZ885) is a human monoclonal antibody targeted at **interleukin-1 beta**. Canakinumab was approved for the treatment of cryopyrin-associated periodic syndromes (CAPS) by the U.S. Food and Drug Administration (FDA) in June 2009 and by the European Medicines Agency in October 2009. CAPS is a spectrum of several autoinflammatory syndromes. ... Canakinumab was being developed by Novartis for the treatment of rheumatoid arthritis, but this trial was completed in October 2009. Canakinumab is also in phase I clinical trials as a possible treatment for chronic obstructive pulmonary disease, gout, and coronary artery disease." https://en.wikipedia.org/wiki/Canakinumab

"**Baricitinib**, sold under the brand name Olumiant among others, is a drug for the treatment of rheumatoid arthritis (RA) in adults whose disease was not well controlled using RA medications called **tumor necrosis factor (TNF) antagonists**. It acts as an inhibitor of janus kinase (JAK), blocking the subtypes JAK1 and JAK2." https://en.wikipedia.org/wiki/Baricitinib - About TNF, see the discussion "**In the Lancet**".

Other drugs are used in Italy, see [7].

In the Lancet

In "The Lancet", "The Lancet Rheumatology", we find discussed the cytokine storm syndrome related to Covid-19, such as in Ref.25.

In [26], it is told that "SARS-CoV-2-induced pneumonia is marked by hyperactivation of effector T cells and excessive production of inflammatory cytokines, particularly IL-6. This reaction, known as a cytokine storm, was initially described as a life-threatening complication in patients receiving antibody-based immune therapy. **In addition to IL-6, other cytokines (ie, IL-1, TNF, and interferon-γ), which are produced during the cytokine storm,** contribute to the pathological process that leads to plasma leakage, **vascular permeability, and disseminated intravascular coagulation**. ... In the case of viral infection, these events increase dissemination of the virus, ... In

line with these events, blockade of IL-6 function with a monoclonal antibody against its receptor (eg, tocilizumab) is useful for the initial treatment of patients with a so-called cytokine storm, and preliminary evidence suggests that such a therapy can help to prevent the detrimental inflammatory response in some cases of SARS-CoV-2-induced pneumonia (unpublished)".

In [27] it is told that "Cytokine upregulation is documented in COVID-19. In patients with COVID-19, there is upregulation of pro-inflammatory cytokines in the blood, **including interleukin (IL)-1, IL-6, TNF, and interferon γ,** and patients in intensive care units have increased concentrations of many cytokines. Preliminary data from Salford Royal Hospital and the University of Manchester in the UK document the presence of proliferating excess monocytes expressing TNF by intracellular staining in patients with COVID-19 in intensive care (Hussell T, Grainger J, Menon M, Mann E, University of Manchester, Manchester, UK, personal communication). ... Initial reports comprising a trial of 21 severe and critical COVID-19 patients in China (ChiCTR2000029765) and a case study from France [28] of clinical benefit with the anti-IL6 receptor antibody10 tocilizumab in COVID-19 suggest that cytokines are of importance in the "cytokine storm" and further controlled clinical trials are in progress. Although there are many potential drug candidates for reducing inflammation in COVID-19, only a few drugs such as the anti-TNF antibodies infliximab or adalimumab are potentially effective, widely available, and have a well established safety profile. The potential role of anti-TNF therapy thus warrants consideration".

In [29], the author is discussing [27], where it is suggested the potential use "of **anti-tumor necrosis factor (TNF)** therapy to inhibit development of a cytokine storm in patients with coronavirus disease 2019 (COVID-19). Following this Comment," David J M Wright writes "to propose that the opioid, meptazinol, might be a possible alternative or addition to anti-TNF therapy, particularly in the UK, where meptazinol is a licensed drug (current licenced supplier Almirall, Barcelona, Spain) and thus could be easily prescribed." The basis of his suggestion is [30].

TNF and TNF inhibitors

"TNF inhibitors are drugs that help stop inflammation. They're used to treat diseases like rheumatoid arthritis (RA), juvenile arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, ulcerative colitis (UC), and Crohn's disease. They're also called TNF blockers, biologic therapies, or anti-TNF drugs. ... TNF inhibitors are antibodies made in a lab from human or animal tissue. ... Your immune system makes a substance called tumor necrosis factor (TNF). Usually, your body keeps your TNF levels steady. But if you have an autoimmune disease like RA, something goes wrong. You start making too much TNF, and that leads to inflammation. ... Because TNF inhibitors tamp down your immune system to stop inflammation, they can make it harder for you to fight off infections. You may be at higher risk for getting colds, flu, urinary tract infections, or even tuberculosis (TB)". https://www.webmd.com/rheumatoid-arthritis/tnf-inhibitor-inflammation#1

"Tumor necrosis factor (TNF) is a multifunctional cytokine that plays important roles in diverse cellular events such as cell survival, proliferation, differentiation, and death. As a pro-inflammatory cytokine, TNF is secreted by inflammatory cells, which may be involved in inflammation-associated carcinogenesis." [31].

"Tumor necrosis factor (TNF) is a critical cytokine, which contributes to both physiological and pathological processes." [32]. This reference "will briefly touch the history of TNF discovery, its family members and its biological and pathological functions".

Potential therapeutic candidates

In [33], we find a work which is summarizing "the current potential therapeutic approaches for diseases related to COVID-19 infection and introduce their mechanisms of action, safety, and effectiveness". Keywords are "ACE2 blocker, Antimalaria, Antiviral, Chinese traditional medicine,

COVID-19, Immunoenhancer, Monoclonal antibody, Vaccine". "SARS-CoV-2 binds to the ACE2 receptor on the surface of cells using the Spike protein, which subsequently triggers endocytosis". ACE2 is the angiotensin-converting enzyme 2, an enzyme attached to the outer surface (cell membranes) of cells in the lungs, arteries, heart, kidney, and intestines.

In [33] tocilizumab (TCZ) and sarilumab are considered. TCZ and sarilumab efficiently inhibit IL-6 through both membrane-bound and soluble IL-6R. "TCZ has been approved by the FDA for treating cytokine release syndrome marked by excessive cytokine production ... COVID-19 disease severity depends on the increase in pro-inflammatory factors [IL-6, IL-1, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-γ-inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein-1 alpha, and TNF-α] (Huang et al., 2020, Ruan et al., 2020, Zhou et al., 2020a), suggesting that cytokine storms are involved in the development of COVID-19".

In [33] it is also told that "**Hydroxychloroquine sulfate** (HCQ) shares a similar chemical structure and mechanisms of action with CQ [**Chloroquine**] but with lower ocular toxicity (Lim et al., 2009) and has proven efficacious in containing SARS-CoV-2 in vitro (Liu et al., 2020a). CQ and HCQ exert antiviral function through various mechanisms. CQ has been shown to interfere with the glycosylation process of ACE2 in host cells, thereby inhibiting the efficiency of the binding of S protein with ACE2, in turn disrupting the virus/cell fusion process (Savarino et al., 2006). CQ can increase the pH of acidic cellular organelles required for virus entry into host cells (Savarino et al., 2003). **In addition to its direct antiviral activity, CQ and HCQ can attenuate major "cytokine storms" (an overreaction of the immune system causing inflammatory "storms") by decreasing cytokine production (interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF], etc.)** (van den Borne et al., 1997 [34]). ... the immune-modulating activity of HCQ might partially account for its efficient control of SARS-CoV-2 infection. CQ and HCQ are therefore promising drugs of choice for large-scale use due to their low cost, ... CQ and HCQ need to be administered with caution when treating COVID-19 infection to prevent toxicity".

Also the **Traditional Chinese Medicine** (TCM) is proposed, and that " the integration of traditional Chinese and western medicine is a unique scheme in China. Approximately 85% of Chinese COVID-19 patients underwent TCM treatment as reported by XuNanping, the vice minister of Science and Technology of China (China's State Council, 2020). In clinical practice, several kinds of TCM have demonstrated their beneficial effects in treating patients with COVID-19 pneumonia (Ren et al., 2020). **Lianhua Qingwen** (LHQW) has a broad-spectrum antiviral effect on a host of influenza viruses, such as influenza A (H1N1), and HPAI A (H7N9) viruses, by inhibiting viral propagation and regulating immune function (Ding et al., 2017, Dong et al., 2014). LHQW has been commonly used for treating viral influenza clinically and played a key role in controlling SARS-CoV during the 2003 outbreak. Recently, LHQW was reported to have inhibitory activity against SARS-CoV-2 and anti-inflammatory effects in vitro (Table 1) (Runfeng et al., 2020). **Xuebijing** (whose chemical composition includes safflower yellow A, paginin, ferulic acid, and salvianolic acid B) functions as an endotoxin antagonist, anti-inflammatory agent, and anticoagulant (He et al., 2013, Sun et al., 2010, Xu et al., 2009, Zhang et al., 2006) ... A clinical trial showed that injecting Xuebijing improved the symptoms of severe pneumonia (Wang et al., 2016). Given the cytokine storms in severe COVID-19 infection, administering Xuebijing could turn critically ill cases into mild ones by attenuating the overactivated immune responses and preventing progressive pathological deterioration. Two clinical trials aimed at testing the efficacy and safety of Xuebijing injection for COVID-19 have been registered in the Chinese Clinical Trial Registry (ChiCTR2000030388 and ChiCTR2000029381)".

What are the components of Lianhua-Qingwen, for instance?

In [35], we find that **Lianhua-Qingwen** capsule (LQC) is a "commonly used Chinese medical preparation to treat viral influenza and especially played a very important role in the fight against severe acute respiratory syndrome (SARS) in 2002-2003 in China". After analysis, the authors found "A total of 61 compounds including flavonoids, phenylpropanoids, anthraquinones,

triterpenoids, iridoids, and other types of compounds were unambiguously or tentatively identified by comparing the retention times and accurate mass measurement with reference compounds or literature data. Among them, twelve representative compounds were further quantified as chemical markers in quantitative analysis, including salidroside, chlorogenic acid, forsythoside E, cryptochlorogenic acid, amygdalin, sweroside, hyperin, rutin, forsythoside A, phillyrin, rhein, and glycyrrhizic acid".

Other proposals

In [36], **melatonin** as a potential adjuvant treatment is proposed. "Melatonin, - it is told in [36] - a well-known anti-inflammatory and anti-oxidative molecule, is protective against ALI/ARDS[1] caused by viral and other pathogens. Melatonin is effective in critical care patients by reducing vessel permeability, anxiety, sedation use, and improving sleeping quality, which might also be beneficial for better clinical outcomes for COVID-19 patients. Notably, melatonin has a high safety profile. There is significant data showing that melatonin limits virus-related diseases and would also likely be beneficial in COVID-19 patients. Additional experiments and clinical studies are required to confirm this speculation." Melatonin is also mentioned in [37], where it is reviewed "the melatonergic pathway role in viral infections, emphasizing influenza and covid-19 infections. Viral, or preexistent, suppression of pineal melatonin disinhibits neutrophil attraction, thereby contributing to an initial “cytokine storm”, as well as the regulation of other immune cells".

"Melatonin is a hormone that regulates the sleep–wake cycle. ... While it is known that melatonin interacts with the immune system, the details of those interactions are unclear. An antiinflammatory effect seems to be the most relevant. There have been few trials designed to judge the effectiveness of melatonin in disease treatment. Most existing data are based on small, incomplete trials. Any positive immunological effect is thought to be the result of melatonin acting on high-affinity receptors (MT1 and MT2) expressed in immunocompetent cells. In preclinical studies, melatonin may enhance cytokine production (Wikipedia gives reference [38], and by doing this, counteract acquired immunodeficiences. Some studies also suggest that melatonin might be useful fighting infectious disease including viral, such as HIV, and bacterial infections, and potentially in the treatment of cancer." https://en.wikipedia.org/wiki/Melatonin

Of course, it is necessary to investigate the cytokines on which melatonin is acting. In [39], it is told that "The report shows that melatonin enhances IL-2 and IL-6 production by two human lymphocytic (Jurkat) and monocytic (U937) cell lines via a nuclear receptor-mediated mechanism".

Vitamin D

In [33], it is told that "**Lopinavir/ritonavir** and **favipiravir** inhibit the proteolysis of polypeptide chains. **Remdesivir** inhibits RNA-dependent RNA polymerase. **EIDD-2801** could inhibit SARS-CoV-2 replication. **NO** and **Zinc** might inhibit SARS-CoV-2 replication. **Vitamin D** might induce antimicrobial peptides to reduce SARS-CoV-2 replication. **Ivermectin** could effectively block SARS-CoV-2 growth. **Baricitinib** could interrupt the passage of SARS-CoV-2 entering cells through inhibition of AAK1-mediated endocytosis. **CQ and HCQ** inhibit virus/cell fusion process. LHQW and IFNs could block the process of virus replication (RNAs transcription, protein translation, and post-translational modification)". Of Remdesivir, Baricitinib, Hydroxychloroquine Ivermectin we told in [7]. We find Vitamin D too.

Let me report a part from abstract of [40], entitled "Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19?". "Like tocilizumab, Vitamin D appears to modulate the activity of an interleukin (IL-6), which may explain the seasonal variation in prevalence of influenza. ... A retrospective comparison of Vitamin D levels in previously obtained blood samples between

1 Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

survivors and confirmed fatalities could establish a rationale for implementation of widespread Vitamin D supplementation. This would be far cheaper and simpler than tocilizumab as a therapeutic option to trial". In the article it is also written: "given that Vitamin D appears to have similar modulating effects on an interleukin, it offers a realistic alternative treatment option which may save many lives." No references are given in [40], about the similar effect on interleukins. However, studies exist [41-44].

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