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M.A. Nagy *

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Review Article

Drug repurposing against Covid-19 through anticytokine activity

M.A. Nagy [1*], M.M. Mahmoud [2], N A. Ibrahim [3]

[1] Head of Clinical pharmacy department, El minia hospital for mental health and addiction treatment.

[2] Head of Clinical research department,Manager of El minia hospital for mental health and addiction treatment.

[3] Lecturer of internal medicine department, University of deraya.

***Corresponding Author:** M.A. Nagy, Head of Clinical pharmacy department, El minia hospital for mental health and addiction treatment.

Received Date: April 05, 2023; **Accepted Date:** April 20, 2023; **Published Date:** April 27, 2023

Citation: M.A. Nagy, M.M. Mahmoud, N A. Ibrahim (2023), Drug Repurposing Against Covid-19 Through Anticytokine Activity, *Clinical Medical Reviews and Reports*, 5(3); **DOI:**10.31579/2690-8794/148

Abstract

Drug repurposing or repositioning is a well-known strategy that seeks to deploy existing licensed drugs for newer indications and provides the quickest possible transition from bench to clinics for unmet therapeutic needs. Given the current, urgent, and dire need for effective therapies against novel coronavirus-19, this approach is particularly appealing. The present review will focus on the repurposing efficacy of the currently used drugs against COVID-19 that act through anticytokine activity.

Keywords: drug repurposing; anticytokine drugs; COVID-19

Introduction

Currently, there are no treatment options available for the deadly contagious disease, coronavirus disease 2019 (COVID-19). Drug repurposing is a process of identifying new uses for approved or investigational drugs and it is considered as a very effective strategy for drug discovery as it involves less time and cost to find a therapeutic agent in comparison to the de novo drug discovery process? Anticytokine therapies have revolutionized the treatment of chronic inflammatory diseases, particularly autoimmune diseases such as rheumatoid arthritis. As the first introduced principle of cytokine blockade in the 1990s, tumor necrosis factor (TNF)-α antagonists still represent the leading anticytokine therapy. There are currently five TNF antagonists available with indications in the fields of rheumatology, dermatology, and gastroenterology **(McGonagle et al., 2020)**. Other therapeutic approaches have been introduced in the last 10 years, e.g., the blockade of interleukin (IL)-1, IL-6, and IL-12/23. The advantages of cytokine blockers are their rapid onset of action with high response rates and a tolerable safety profile **(Naumann et al, 2013).**

High concentrations of cytokines were associated with the pathogenesis of COVID-19. The mortality related to acute respiratory distress syndrome ARDS as well as multi-organ failure in COVID-19-infected patients may be connected with cytokine storm syndrome (CSS), an excessive immune response that severely damages healthy lung tissue. This response may lead to macrophage activation syndrome (MAS) or secondary haemophagocytic lympho histiocytosis (sHLH) with fulminant and fatal hypercytokinaemia **(Siddiqi and Mehra, 2020).** Cytokines primarily derived from mononuclear phagocytic cells and other antigen-presenting cells (APCs) are particularly effective in promoting the cellular infiltrate and damage to resident tissue characteristic of inflammation **(Prompetchara et al ,2020).** The processing of antigens as they are taken up by APCs, processed and presented to T-helper lymphocytes provides one pathway for this class of cytokine production **(Merad and Martin, 2020).** Alternatively, monocytes are potently triggered to produce cytokines through the innate immune system using pattern recognition receptors that recognize stereo typical components of pathogens that do not occur on mammalian cells Fig (1).

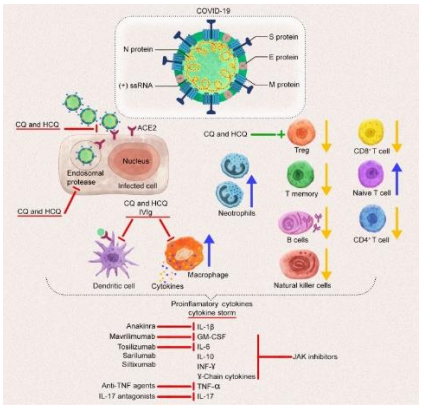

Figure 1: Proinflammatory cytokinee

IL-1 blockade

The pro inflammatory cytokine interleukin-1β plays multiple roles in the development of atherothrombotic plaque, including the induction of pro coagulant activity, the promotion of monocyte and leukocyte adhesion to vascular endothelial cells, and the growth of vascular smooth-muscle cells.

The damage-associated molecular pattern IL-1α (alarmin) liberated by necrotizing lung epithelial cells could be one of the initial cytokines produced during COVID-19 pathogenesis. IL-1α by further engagement to IL-1R leads to the production of an array of chemokines and cytokines. IL-1β, IL-6, TNF-α, GM-CSF, IL-17, CXC chemokine, CCL chemokines, etc. are some of the few upregulated cytokines/chemokines in severe COVID-19 responsible for exacerbating the lung pathophysiology by fueling up infiltration of macrophages/neutrophils, hypercoagulability, and fibrosis phenomena. Anakinra (IL-1α and IL-1β blocker) has shown greatly reduced mortality, need for invasive mechanical ventilation, and bettering oxygenation status in severe COVID-19 patients in smaller clinical studies as shown in Figure (2). Hence, anakinra might be effective in managing the severe pandemic state; more so, it is a well-tolerated molecule with no adverse effects (Gupta, 2020).

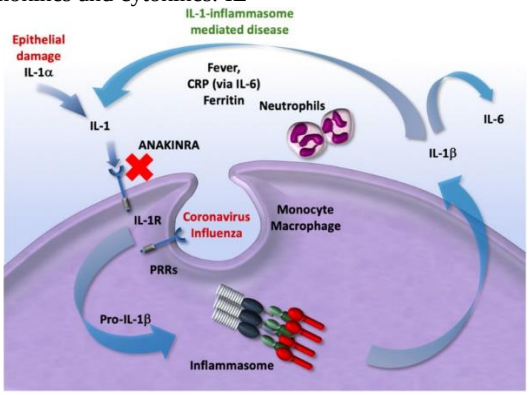

Figure (2)

Rational for use of anakinra in sever coronavirus (van de Veerdonk and Netea 2020). Diacerein (DAR), also called diacetylrhein, is an anthraquinone derivative used as a symptomatic slow-acting drug for the management of osteoarthritis (SYSADOA) licensed in countries of the European Union, Latin America and Asia for up to 20 years. The drug is administered orally and entirely converted to its active metabolite rhein, before reaching the systemic circulation. The main mechanism of action of DAR is inhibition of the interleukin-1 (IL-1) signaling pathway. In addition, several studies have described the inhibitory effect of this compound on IL-6 and TNF-α.

Canakinumab is a fully human monoclonal antibody neutralizing IL-1β with linear dose-dependent pharmacokinetics and a long elimination half- life of 26 days as shown in Figure (3). Canakinumab is approved to treat auto inflammatory diseases such as cryopyrin-associated periodic syn dromes (CAPS) and Familial Mediterranean Fever. In a large randomized trial of patients with atherosclerotic disease and increased inflammation, treatment with canakinumab led to a lower rate of recurrent cardiovascular events.

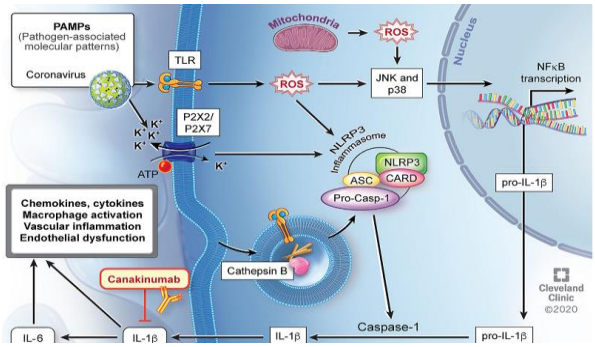

Figure (3):

Putative mechanisms of SARS-CoV2 associated myocardial injury with increased inflammation and possible beneficial effects of canakinumab

IL-2 blockad

IL-2 signaling plays a central role in the initiation and activation of immune responses. Correspondingly, blockage of this pathway leads to inhibition of the immune system and would provide some therapeutic benefits. Basiliximab (Simulect), a therapeutic mAb drug with specificity against IL-2Ra of T cells, was approved by U.S. Food and Drug Administration in 1998. It has been proven to be effective in the suppression of the IL-2 pathway and hence has been widely used to prevent allograft rejection in organ transplantation, especially in kidney transplants (Du et al., 2010).

Daclizumab is a monoclonal antibody directed against the CD25 subunit of the interleukin-2 receptor, investigated as a disease-modifying therapy in relapsing-remitting multiple sclerosis (Bielekova B., 2019).

Interleukin-3

Interleukin-3 (IL-3) is a hemopoietic growth factor involved in the survival, proliferation and differentiation of multipotent hemopoietic cells. IL-3 has been shown to be a promising agent in the stimulation of bone marrow regeneration following myeloablative therapy. The biologic half-life of this agent is very short (5 to 15 minutes), which limits the effectiveness of low-dose therapy (Bessler et al., 2020).

Binding of IL-3 to its cognate receptors initiates rapid tyrosine phosphorylation of Janus kinases (JAKs) and of signal transducer and activator of transcription (STAT) proteins, as well as activation of the phosphatidylinositol-3 kinase (PI-3K)/Akt and Ras/Raf/MAPK kinase (MEK)/mitogen-activated protein kinase (MAPK) pathways. These signals culminate in induction of a constellation of antiapoptotic genes and prevent cell death from occurring. Thus IL-3 signaling has substantial effects on kinase activation and gene transcription (Yen and Yang-Yen, 2006).

Interleukin-4

Interleukin 4 (IL-4) mediates important pro-inflammatory functions in asthma, including T helper cell type 2 lymphocyte differentiation, induction of IgE production, up-regulation of IgE receptors, expression of vascular cell-adhesion molecule 1, promotion of eosinophil transmigration into the lungs, inhibition of T-lymphocyte apoptosis, and mucus hypersecretion. The role of IL-4 in the pathogenesis of asthma is supported by identification of polymorphisms linked to asthma in the IL-4 gene promoter and proteins involved in IL-4 signaling (Steinke and Borish, 2001).

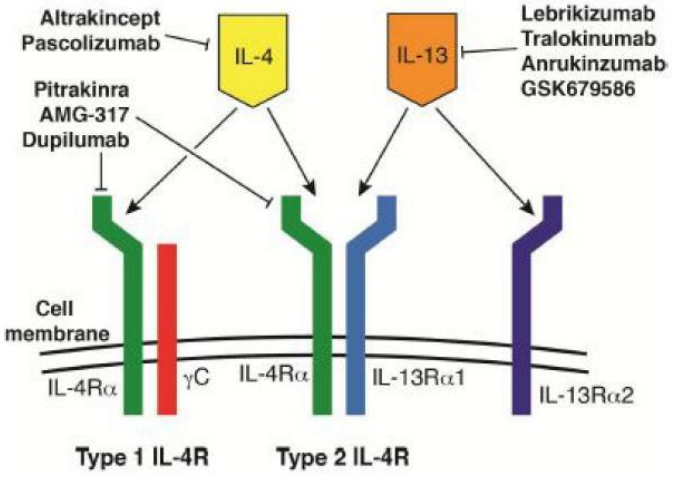

Figure 4: Diagram of IL-4 and IL-13 targeting medications

Altrakincept is a recombinant human IL-4 receptor delivered by aerosol and intended to act as an antagonist to IL-4 action as shown in Fig(4). While preliminary studies of altrakincept in steroid-dependent, atopic asthmatics appeared promising efficacy could not be demonstrated in phase III trials (Borish et al.,2001). Likewise, a humanized monoclonal antibody targeting IL-4, pascolizumab, was found to be ineffective in treating asthma (Hart et al.,2002).

Interleukin-5

IL-5 is the most potent activator of eosinophils and is produced by Th2 cells and ILC2s. A role for IL-5 in eosinophil extracellular trap cell death, i.e., a proinflammatory cell death, has also been reported. Mepolizumab and benralizumab are humanized mAbs that target IL-5 and the IL-5 receptor α, respectively, and their therapeutic efficacy for severe asthma has been established. Although consistent differences in the efficacies of those drugs have not been proven, benralizumab extensively depleted eosinophils via Ab-dependent cell-mediated cytotoxicity (Poblete et al.,2018).

Mepolizumab is a humanised monoclonal antibody (IgG1) that binds with high affinity to free IL-5 and thus prevents IL-5 from binding to IL-5Rα. At present, mepolizumab is the most studied anti-IL-5 in the treatment of severe asthma. Mepolizumab has also been investigated for the treatment of atopic dermatitis, FIP1L1/PDGFRA-negative hypereosinophilic syndromes, eosinophilic oesophagitis, nasal polyposis and Churg–Strauss syndrome (Michael et al.,2012).

Benralizumab (MEDI-563; Kyowa Hakko Kirin/AstraZeneca) is a humanised anti-IL-5Rα monoclonal antibody. Benralizumab targets the effector cells that are driven by IL-5 (eosinophils/basophils) rather than the numerous cells that only produce IL-5. *In vitro* experiments demonstrated that benralizumab directly targets eosinophils for antibody-dependent cell-mediated cytotoxicity (Roland et al., 2010)

Reslizumab is a humanised IL-5 monoclonal antibody that has been previously investigated in the treatment of nasal polyps and is currently in clinical development for the treatment of asthma (Roland et a, 2010)

IL-6 blockade

The chief perpetrator of this cytokine storm is interleukin-6 (IL-6), a proinflammatory molecule, that acts on a large number of cells, releases acute phase reactants, and is capable of causing extensive tissue damage. IL-6 is clearly implicated in the causation of cytokine release syndrome (CRS), which is characterized by rapid inflammatory cascade leading to fever, septic shock, and multiple organ failure, the most common of which is ARDS – the leading cause of mortality (Huang et al.,2020).

Tocilizumab (TCZ) is a potential recombinant monoclonal antibody against IL-6 and currently is under investigation for the management of acute respiratory distress syndrome (ARDS) in patients with COVID-19 (Radbel J, Narayanan N, Bhatt PJ, 2020). In this cohort of mechanically ventilated COVID-19 patients, tocilizumab was associated with lower mortality despite higher superinfection occurrence (Somers et al., 2020).

Tocilizumab treatment showed inspiring clinical results including temperature returned to normal quickly and respiratory function improved. Therefore, we suggest that Tocilizumab is an effective treatment in severe patients of COVID-19 to calm the inflammatory storm and reduce mortality (Fu et al ,2020).

It was reported that 42-year-old male suffering from respiratory failure due to SARS-CoV-2 infection. After 4days of TCZ treatment, the CRP decreased from 225 to 33 mg/L and ultimately clinically fully recovered. Similarly, some case reports showed TCZ is an efficacy and safety approach in COVID-19, even patients with other diseases combined, such as multiple myeloma, end-stage renal disease, and sickle cell disease **(Luo etal.,2020).** On other hand, Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19 (Stone et al, 2020). Nevertheless, anticytokine therapy can cause increased rates of tuberculosis and hepatitis B infections or reactivation.

Interestingly, previous studies conducted in interleukin-6 deficiency showed susceptibility to systemic *Candida albicans* infection, also a decreased survival and an increased fungal load in their organs (Spinello antinor et al.,2020)

Sarilumab is a human anti-IL-6 receptor monoclonal antibody licensed for the treatment of rheumatoid arthritis. It is a safe and well-tolerated drug. The most common side effects are respiratory tract infections, neutropenia, hypercholesterolemia and mild hepatotoxicity. The most serious side effects are gastrointestinal infections and perforations **(León López et al., 2020)**.

This clinical trial tests the hypothesis that early blockade of IL-6 could halt the progression to severe respiratory failure in hospitalised patients infected with SARS-CoV-2. The early use of sarilumab, in addition to standard therapy, can attenuate the detrimental host immune response in patients with elevated markers of inflammation by reducing the development of severe respiratory failure and other organ damage

Siltuximab could be considered as a therapeutic strategy to treat severe cases of SARS-CoV-2 infection with increased IL-6 levels. Siltuximab is a human–murine chimeric monoclonal antibody that forms high affinity, stable complexes with soluble bioactive forms of human IL-6. The drug prevents the binding of human IL-6 to both soluble and membrane bound IL-6 receptors, thus inhibiting the formation of the hexameric signalling complex with gp130 on the cell surface and avoiding activation of the Janus kinase/signal transducer and activator of transcription signalling pathway.Siltuximab is indicated for the treatment of adult patients with multicentric Castleman's disease, a rare lymphoproliferative disorder driven by dysregulated production of IL-6 (Palanques-Pastor et al.,2020).

IL-10 blockade

IL-10 is the founding member of a family of cytokines that also IL-20, IL-22, IL-24, IL-26, IL-28A, IL-28B, and IL-29. The cytokine IL-10 is a key anti-inflammatory mediator ensuring protection of a host from over-exuberant responses to pathogens and microbiota, while playing important roles in other settings as sterile wound healing, autoimmunity, cancer, and homeostasis.

IL-10was discovered 30years ago as a secreted cytokine synthesis inhibitory factor, produced by T helper (Th) 2 cell clones shown to inhibit cytokine production by Th1 cells. High IL-10 levels in severely infected patients may be responsible for the negative feedback of systemic and local inflammation.

The role of IL-10 clearly exceeds the regulation of intestinal inflammation, as a function for this molecule has been also described in several other settings, from inflammatory or neurodegenerative diseases to infection or cancer.

There is recent evidence that IL-10 may play a previously underappreciated dual role, in some contexts stimulating the immune response instead of suppressing it. This depends on specific cell types and contexts.

IL-12 &23 blockades

Ustekinumab is a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23 that has been approved for use in the treatment of psoriasis and psoriatic arthritis (Gisbert JP, Chaparro M, 2017).

IL-17 blockade

Secukinumab (Cosentyx®), a first-in-class fully human monoclonal antibody against interleukin-17A, is approved in several countries, including the USA and those of the EU, for the treatment of ankylosing spondylitis (AS). Subcutaneous secukinumab significantly improved the clinical signs and symptoms of AS versus placebo in three of four phase III trials. The benefits of secukinumab were generally seen regardless of whether patients had or had not received previous tumour necrosis factor (TNF) inhibitor therapy, and were sustained during longer-term (up to 5 years) treatment. Secukinumab was also associated with improvements in spinal mobility, physical function, health-related quality of life and work productivity in some of the trials (Blair HA, 2019).

IL-18 blockade

IL-18 is a member of the IL-1 family of cytokines which play roles in both the innate and adaptive immune responses, fibrosis and hemato poiesis. It is synthesized as an inactive precursor, pro-IL-18, requiring processing by caspase-1 into an active cytokine. IL-1β and IL-18 are mainly produced by monocytes/macrophages in response to harmful stimuli including viruses (Zalinger ET AL., 2017). IL-18 is produced by macrophages at very early stages of viral infections and induces production of IL-6 and IFN-γ which are considered critical for optimal viral host defense. However, aberrant IL-18 production can also lead to severe pathological injury as shown in Fig (5). Upon viral infection, IL-18 release induces ferritin, explaining the

frequently observed hyperferritinemia in viral infections **(Shah,2020)**. Identification of the role of IL-18 will shed light on disease pathogenesis of COVID-19 which is also characterized by hyperferritinemia and cytokine storm. Moreover, serum concentrations of IL-18 might serve as a biomarker to predict disease outcome (Vecchié etal.,2021)

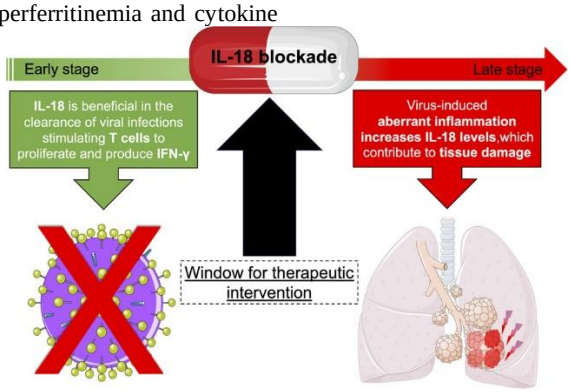

Figure 5: Prognostic value of IL-18

IL-23 blockade

Interleukin 23 is a heterodimeric cytokine consisting of the p19 and p40 subunits . The IL-23 p40 subunit is shared with IL-12. The p40 subunit is the target of another biological drug for psoriasis – ustekinumab. Recent clinical trials suggest that a drug targeting exclusively IL-23 and the p19 subunit may result in a more favorable safety profile compared to targeting both IL-23 and IL-12. Interleukin 12, as shown by studies, may be of beneficial importance for the organism and participate in the protection of the organism against the action of intracellular pathogens, and what is more, it also probably participates in immune surveillance in the development of cancer.

It is also worth noting that inhibition of the p40 subunit is also associated with the inhibition of IL-39, which is still a poorly studied factor, and it is not known whether it performs beneficial functions in the human body.

The novel biologic medication tildrakizumab is among the first drugs with specific action against IL-23 that has recently been approved by the United States Food and Drug Administration and the European Medicines Agency for moderate-to-severe psoriasis. Tildrakizumab has been shown in large randomized controlled trials to be effective in improving skin manifestations as well as enhancing quality of life outcomes in patients with psoriasis.

Tildrakizumab is a humanized monoclonal IgG1κ antibody. This antibody selectively binds to the p19 subunit, thereby inhibiting the interaction of IL-23 with its receptor, and thus inhibits the release of IL-23 mediated proinflammatory cytokines.Recent studies show that the IL-23/IL-17 axis plays a key role in the etiopathogenesis of psoriasis . IL-23 is involved in stimulation, and what is more, it also affects the functioning of Th-17 lymphocytes, which play an important role in the pathogenesis of psoriasis.

IL-17 blockade

Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease (van der Heijde et al.,2018).

IL-23 blockade

Interleukin (IL)-23 inhibitors are a new class of biologics currently undergoing clinical trials for the treatment of moderate-to-severe psoriasis **(Gordon et al., 2015)** . Guselkumab (CNTO1959; Janssen Research & Development, Spring House, PA, USA) is a fully human IgG1 lambda monoclonal antibody that binds to the p19 subunit of IL-23. Phase I and II studies have shown promising safety and efficacy in the treatment of moderate-to-severe psoriasis (Sofen et al ,2014).

Conclusion:

In conclusion, we used a novel approach of grouping separate anticytokine drugs with different pharmacological uses on the basis of a common targetable pathogenic mediator, provided evidence of a pathogenic role of interleukins in COVID-19. It also showed that the inhibition of interleukins was efficacious in controlling COVID-19.

Acknowledgements:

The unit of clinical research thanks Prof.Dr. Menan rabie secretary general of mental health and addiction treatment. Ministry of Egyptian health for her kind support. Also, Clinical Pharmacy department appreciate the great efforts and encouragement of Dr Monsef Mahfouz, Manager of El minia hospital for mental health and addiction treatment.

Conflict of interest:

The Authors have declared that there are no conflicts of interest in relation to the subject of this work.

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DOI: 10.31579/2690-8794/148