

## Review

# Interleukin-2 Level for Normal People and COVID-19 Infection: Is It Our Concern is COVID-19 Infection or Interleukin-2 Level Before the Infection?

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### Abstract

The newly discovered Coronavirus severe acute respiratory distress syndrome virus-19 (SARAS-COV-2, COVID-19) has become a pandemic issue across the globe. Until now, many investigations are taking place to look for specific, safe, and potent anti-viral agents. Upon transmission and entry into the human body, SARS-COV-2 Trigger multiple external players to be involved in the protection against the viral infection. These include Masks, Gloves, Sanitizing and social distancing.

On the other hand, multiple internal body players to be involved in the protection against the viral infection. These include Angiotensin converting enzyme inhibitors or (ACEI) or Angiotensin receptor blockers or (ARB).

Also, immune players to be involved in the fight against the viral infection. These include Vaccines, plasma from the Recovered patients and cellular immune players such as B, T and natural killer (NK) Cells, as well as the soluble Cytokines and Chemokines. In this review, we will propose the best way to protect ourselves against COVID-19 infection using Interleukin-2, based on evidences we have.

**Keywords:** COVID-19, drugs, Helper-T cells, Interleukin 2, experimental autoimmune encephalomyelitis, Treg cells and natural killer cells.

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Coronaviruses (CoVs) are large positive stranded enveloped RNA viruses that cause enteric and mild or severe respiratory diseases in animals and humans.<sup>[1]</sup> Coronaviruses are named based on their morphology as spherical virions with a core shell and surface projections, that are classified into four subfamilies, namely alpha, beta, gamma and delta. SARS-CoV-2 belongs to the beta-coronaviruses and is closely related to the severe acute respiratory distress syndrome virus (SARS-CoV), that emerged earlier this century.<sup>[2-4]</sup> Recently, COVID-19 infection was reported to be caused by SARS-CoV-2 in Wuhan, China.<sup>[5]</sup> Additionally, it was as-

sociated with mortality in a ratio of the patients similar to other previously reported CoVs.<sup>[6]</sup> COVID-19 could be transmitted through huge droplets caused by coughing and/or sneezing.<sup>[7]</sup> Similar to SARS-CoV, SARS-CoV-2 uses a unique receptor for cell entry, which is angiotensin converting enzyme 2 (ACE2).<sup>[8-11]</sup> The clinical symptoms could vary from fatigue, fever, headache, dyspnea, nasal congestion and cough, as well as gastrointestinal symptoms including nausea, vomiting, diarrhea and abdominal pain.<sup>[2,12]</sup> In severe cases, these symptoms are aggravated to shortness of breath and pneumonia that could lead to acute respiratory

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distress syndrome (ARDS) and other complications.<sup>[13,14]</sup> A study performed on hospitalized patients with SARS-CoV-2 associated pneumonia reported that the most common symptoms were fever (83%) and cough (82%), followed by shortness of breath (31%).<sup>[15]</sup> As part of the inflammatory process, markers such as C-reactive protein, erythrocyte sedimentation rate and proinflammatory cytokines are elevated.<sup>[13]</sup> The extremely high concentration of cytokines “cytokine storm” was recorded in plasma of severe cases of COVID-19 patients and was associated with disease severity.<sup>[16]</sup> The inflammatory cytokines include granulocyte colony stimulating factor (G-CSF), IL-2, IL-7, IL-10, TNF $\alpha$  and the chemokines CCL2, CCL3, and CXCL10.<sup>[16,17]</sup>

Various current therapeutic agents are currently being investigated for treatment of COVID-19. Use of intravenous immunoglobulins has been described to show great efficiency especially in severe and deteriorating patients infected with SARS-CoV-2.<sup>[18]</sup> Also, anti-viral agents such as Remdesivir have been examined as potential candidates for COVID-19 therapy. Hydroxychloroquine and chloroquine have been suggested to inhibit viral replication and activity.<sup>[19]</sup> Since antiretroviral drugs previously showed efficacy against SARS-CoV, lopinavir/ritonavir may have potential therapy in COVID-19 patients.<sup>[20,21]</sup> For instance, the JAK inhibitor Baricitinib that is used for treating rheumatoid arthritis patients was suggested to control viral replication and treatment of COVID-19 infection,<sup>[22]</sup> but with all of these studies that we have we still need to know if there is any specific treatment we can use it against the COVID-19. In this review, we are going to explain the role of interleukin-2 during homeostasis and activation of the immune system and how we can use it against the COVID-19.

## Interleukin-2

### Interleukin 2 and the Immune Response

Cytokines are produced by various immune system cells and perform several functions, including mediation of the immune and inflammatory responses. The effects of cytokines on the immune response depend on a number of factors, such as their local concentrations, receptor expression patterns and the integration of multiple signaling pathways in response to immune cells.<sup>[23]</sup> The immune system includes proinflammatory cytokines that can enhance the functions of other cytokines and the immune response and anti-inflammatory cytokines that suppress this response; various interleukins (ILs) stand out in these responses.<sup>[24]</sup> ILs are small protein molecules that signal specific cells to regulate the immune systems of organisms. They are primarily synthesized by T cells, monocytes, macrophages and endothelial cells. The functions of ILs

include the facilitation of communication among immune system cells, regulation of transcription factors, and control of inflammation, cell differentiation, proliferation and antibody secretion.<sup>[25]</sup> The characterization of interleukin 2 (IL-2) as a T-cell growth factor was consolidated in 1975 at the Second International Lymphokine Workshop. The number of studies on this molecule increased quickly; by 1983, the IL-2 gene was cloned, and in 1992, the IL-2 crystal structure was described.<sup>23</sup> Analysis of the three-dimensional structure of the IL-2 molecule shows that it is composed of four “packed”  $\alpha$ -helices. The first and fourth helices are connected by a long upper loop to form a typical structure known as “up-up-down-down”. Within this configuration, the first two  $\alpha$ -helices are turned upward, and the last two helices are turned downward. Importantly, the disulphide bond between the cysteines at positions 58 and 105 (Cys 58-105) of the second helix and the inter-helix region of the third and fourth  $\alpha$ -helices are necessary to ensure the stability of the protein.<sup>[25]</sup> IL-2 is a monomeric glycoprotein with a molecular weight of approximately 15 kDa that is primarily produced by activated CD4+ T cells, CD8+ T cells and dendritic cells.<sup>[26]</sup> IL-2 is a proinflammatory cytokine that is secreted by Th-1 cells, and it effectively participates in the activation of T cells to produce the cytokines tumor necrosis factor alpha (TNF- $\alpha$ ) and interferon gamma (IFN- $\gamma$ ); IL-2 can also enhance the cytolytic activity of natural killer cells (NK).<sup>[27,28]</sup> Therefore, IL-2 is used therapeutically to stimulate the immune system.<sup>[29]</sup> IL-2 also contributes to the development of regulatory T cells, which control the expansion and apoptosis of activated T cells.<sup>[26,29]</sup> Furthermore, IL-2 influences cell survival, differentiation<sup>23</sup> and the formation of immune memory cells<sup>[23,32]</sup> and acts as a negative regulator of immune activation.<sup>[23]</sup> Recent studies showed that IL-2 played a critical role in the differentiation and survival of regulatory T cells, thereby ensuring their significance in the control of the immune response.<sup>[30-31,33]</sup> Cytokines effectively participate in the pathogenesis of several pathological conditions, such as cancer and metabolic, infectious, autoimmune and inflammatory diseases.<sup>[34,35]</sup> Thus, IL-2 plays multiple roles in immune functions by contributing to the generation and propagation of antigen-specific immune responses.<sup>[36]</sup> Studies conducted with animals and humans showed that low doses of IL-2 induced expansion of regulatory T cells in vivo and suppressed autoimmune diseases; this phenomenon is representative of a novel therapeutic approach to modulate the immune response for the treatment of these types of illnesses.<sup>[37]</sup> Anti-humoral therapy associated with IL-2 administration led to the remission of metastatic renal cell carcinoma in up to 30% of patients and increased the sur-

vival of patients with melanoma and acute myeloid leukemia.<sup>[38]</sup> In these situations, the administration of high doses of IL-2 was associated with improved survival, although the related adverse effects were considerably severe in most patients.<sup>[39]</sup> Cases of cellular and humoral immunodeficiency exhibited satisfactory outcomes following IL-2 administration.<sup>[39]</sup>

### Search Strategy

Articles were searched in the literature using the keywords: Interleukin 2, experimental autoimmune encephalomyelitis, drugs, COVID-19, Helper-T cells, Treg. cells and natural killer cells. These articles were checked thoroughly, and any unnecessary or irrelevant information was removed. Subsequently, included articles were used to search for a possible link between Interleukin 2, COVID-19 and the action of various drugs. Research articles and reviews were included from those published in the past 15 years from papers using the keywords “COVID-19 and Immune System”, “the role of Interleukin-2 during homeostasis and activation of the immune system”, “drugs for increasing the IL-2 Levels”, or “COVID-19 and T cells”.

### COVID-19 and T-Cells

With the new studies which have been carried out by researchers at La Jolla Institute for Immunology and have been published in the journal *Cell*, and confirmed that T cells play an important role in the body's response to COVID-19, and The findings show that a multi-layered, virus-specific immune response is important for controlling the virus during the acute phase of the infection and reducing the severity of the disease, with the bulk of the evidence pointing to a much bigger role for T cells than antibodies.<sup>[40]</sup>

### COVID-19 and the Immune System

When COVID-19 enters the body, the innate immune system launches a broad and unspecific attack against the intruder, releasing waves of signaling molecules that incite inflammation and alert the immune system's precision forces to the presence of a pathogen. The 'adaptive immune system' then launches a more specific attack against the virus, intercepting viral particles and killing infected cells. The adaptive immune system consists of antibodies, helper T cells, which assist B cells to make protective antibodies, and Natural Killer T cells which seek out virus-infected cells and eliminate them.<sup>[40]</sup> The researchers suggest from the findings that potential vaccines should elicit a broad immune response that includes antibodies, help, and killer T cells to ensure immunity.

Dr. Alessandro Sette, who co-led the study with Shane

Crotty, both professors in LJI's Center for Infectious Disease and Vaccine Research, said: “What we didn't see was any evidence that T cells contribute to a cytokine storm, which is more likely mediated by the innate immune system.”<sup>[41]</sup> The researchers wanted to capture the whole range of disease manifestation to identify differentiating immunological factors, finding that fully recovered individuals had measurable antibody, helper, and killer T cell responses, while the adaptive immune response in acute COVID-19 patients varied more widely with some lacking neutralizing antibodies, other helper or killer T cells, or any combination thereof.<sup>[41]</sup> Co-first author and postdoctoral research, Carolyn Moderbacher, commented: “When we looked at a combination of all of our data across all 111 measured parameters we found that in general, people who mounted a broader and well-coordinated adaptive response tended to do better. A strong SARS-CoV-2 specific T cell response was predictive of milder disease. Individuals whose immune response was less coordinated tended to have poorer outcomes.”<sup>[41]</sup>

### COVID-19 in the Elderly

'Naïve T cells' are inexperienced T cells that have not met their viral match yet. As we age, the immune system's supply of these types of T cells reduces, and fewer cells are available to be activated to respond to a new virus.<sup>[41]</sup> Crotty said: “Our observations could also explain why older COVID-19 patients are much more vulnerable to the disease. With increasing age, the reservoir of T cells that can be activated against a specific virus declines and the body's immune response becomes less coordinated, which looks to be one factor making older people drastically more susceptible to severe or fatal COVID-19.”<sup>[41]</sup> The research shows that instead of antibodies, T cells and helper T cells are associated with protective immune responses.<sup>[41]</sup> “This was perplexing to many people, but controlling a primary infection is different from vaccine-induced immunity, where the adaptive immune system is ready to pounce at time zero.” Crotty continued. “These findings indicate it is plausible T cells are more important in natural SARS-CoV-2 infection, and antibodies more important in a COVID-19 vaccine, although it is also plausible that T cell responses against this virus are important in both cases.”<sup>[41]</sup>

### Interleukin-2: Potential Therapeutic Target

Since Helper-T Cells, Treg. Cells and NK cells are key antiviral players, they could be utilized as a therapeutic tool in fighting COVID-19. A study by Osman et al. reported that T cells are not only important for the viral clearance of SARS-CoV-2 but they also limit the severe cytokine storm associated with COVID-19.

## Effects of Ultra Low dose of Interleukin-2

Low-dose interleukin-2 (IL-2) expands regulatory T cells (Tregs) and natural killer (NK) cells. However, the safety, dose level, and immune signatures of ULD IL-2 in immune-competent healthy subjects remain unknown, but the main concern for us using this method is, we cannot keep giving the healthy people ULD IL-2 during their life.<sup>[42]</sup>

## Effects of FTY720 “fingolimod” or “Gilenya” Therapy on Interleukin-2

The drug FTY720 “fingolimod; 2-amino-2-(2-[4-octylphenyl]ethyl)-1,3-propanediol” is an immunosuppressive drug derived from myriocin, a fungal metabolite that is similar to sphingosine. This drug has been tried on RRMS patients where it showed a reduction in MS lesions and relapse rates.<sup>[43, 44]</sup> Regarding its activity on NK cells, FTY720 upregulated the expression of the activating receptors NKp30, NKp44 and NKG2D on NK cells. Moreover, FTY720 enhanced IL-2-activated Treg. Cells, Helper-T Cells and NK cell lysis of immature and mature DCs, impeding autoreactive T cell activation,<sup>[45]</sup> in addition to activating NK cell lysis of tumor target cells.<sup>[46]</sup> It is worth mentioning that FTY720 is currently under clinical trial to assess the efficacy of fingolimod for treatment of COVID-19 (NCT04280588). Although not yet examined, however, it is highly plausible that FTY720 might induce robust NK cell activity in COVID-19 patients. This is based on FTY720 effects on NK cells described in vitro.<sup>[45]</sup>

## Effects of Glutathione and 2-mercaptoethanol (2-ME) Therapy on Interleukin-2

It is known that glutathione (GSH) has an immunological effect on several features of the immune system. The present study investigated the effects of GSH on interleukin-2 (IL-2) production from normal human peripheral blood lymphocytes (PBL). The results showed that both exogenous GSH and 2-mercaptoethanol (2-ME) significantly increased intracellular GSH levels after PBL were incubated with both agents. IL-2 production from PBL was markedly increased at the presence of exogenous GSH (0.5-8 mmol/l) or 2-ME (12.5-50 mmol/l) which corresponded to 1.57-2.82 nmol/10(6) cells and 1.41-1.80 nmol/10(6) cells of intracellular concentrations of GSH, respectively. However, IL-2 production seemed to reach a steady level when exogenous GSH concentrations in cell culture were between 2 and 8 mmol/l. The findings also showed that there was a positive correlation between the IL-2 concentrations and intracellular GSH levels. This study indicated that both exogenous GSH and 2-ME were able to elevate intracellular GSH levels and the increased intracellular GSH could increase IL-2 production in vitro. It is suggested that GSH may exert its effects on the immune system via the regulation of IL-2 synthesis.<sup>[47]</sup>

## Hypothesis

Interleukin-2 deficiency appears to be a crucial factor in SARS-CoV-2-infection and, as a result, leads to serious manifestations, such as Weak response for our Immune system against the Virus, acute respiratory distress syndrome, multiorgan failure, and death in COVID-19 patients. When the level of Interleukin-2 before the infection is considered, individuals with Interleukin-2 deficiency seem to have a higher susceptibility for uncontrolled replication of SARS-CoV-2 virus and thereby suffer from an increasing viral load. The severity of clinical manifestations in COVID-19 patients is apparently determined by the Level of Interleukin-2 before the infection in COVID-19. This assumption can be supported by our findings. In particular, COVID-19 patients with moderate and severe illness had lower levels of T Cells activation than COVID-19 patients with a mild illness. This finding suggests that the virus cannot actively replicate at steady levels of Interleukin-2 before the infection, and therefore, milder clinical symptoms are observed with lower viral loads.

## Disclosures

**Conflict of Interest:** None declared.

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