A combination of Immunotherapies and Micronutrients May Relieve the Severe illness in COVID19 Patients: Review Article

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ABSTRACT

Seven months with COVID19 pandemic, the prevalence passes twenty million and the deaths have reached more than three quarter of millionworldwide. The pandemic began in Wuhan, China in January 2020, then transferred vigorously to Europe and the USA. Failure of the conventional therapies in the treatment of severe illness of COVID19 patients and lack of a specific vaccine or therapies target for SARS-CoV-2 infection, the drug repositioning in treatment of COVID19 patients is the only opportunity to face this pandemic. It is reported that the cytokine storm is the main reason for severe illness and high mortality. Thus, we discuss the implication of immunotherapies in combination with micronutrients (Zinc, Selenium, and vitamin C) and antioxidants such as Glutathione (cysteine pro-drug) in counteracting SARS-CoV2-induced cytokine storm as a possible insight to improve the clinical outcomes. The present review highlights the importance to widen the scale of researches on immunotherapies in combination with micronutrients to involve different doses, route of administration, molecular targets, and different populations worldwide. Particularly, polymorphisms are attributed to the noticed variations in the risk factors to COVID19 as well as the response to therapies. Thus, global studies about applications of different immunotherapies plus micronutrients are recommended to establish different regimens in the treatment of different populations. Also, we need to study the mode of actions of the immunotherapies beyond their immunosuppression role. Finally, global cooperation in either innovation or repositioning therapies is warranted since the response to therapies differs among the population.

Key Words: *SARS-CoVist, COVID19, immunotherapies, micronutrients, Pneumonia, cytokines storm.*

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INTRODUCTION

To date, COVID19 prevalence still progresses rapidly and attacks about twenty million persons with more than three quarter of million worldwide[1, 2]. The majority were reported in Europe, the USA, and China, especially, in patients with advanced chronological age. In addition, it is still hindering all life activities of the humanitarian [3, 4]. Recognizing the enemy helps us to overcome it. When Scientists recognized the nature of oncoviruses, they update their researches and introduce target therapy specific for each protein encoded by a mutated gene [5, 6]. Also, understanding HIV as an immunodeficiency virus helps scientists to deal with it [7]. In the current pandemic, strong evidence revealed that vigorous activation of the immune system (cytokines storm) in response to infection with SARS-CoV-2 is correlated with the severe illness and deaths. Subsequently, a novel treatment strategy based on immunomodulatory therapies to counteract COVID19-induced cytokine storm is widely used to improve the clinical outcomes [8, 9]. Accordingly, we face a new class of viruses that may be classified as a stimulator of the immune system and may be called Human immunostimulator virus (HISV) in contrast to HIV. This makes us to hypothesize a specific suffix to add to the name of current SARS-CoV-2; SARS CoVist as the

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addition of "ist" as a symbol to express specifically about the confirmed immunostimulatory action of SARS-CoV-2 in 2019-2020. Also, we may speculate that with time and updating evidence may emerge its role as a mutagenic virus that targets the genetic materials of immune elements in such manner causing disturbance of immune balance.

The human body is created in a homeostatic pattern within a delicate balance in everything such as oxidants-antioxidants & cell proliferation and cell death & pro- and anti-angiogenic & pro- and anti-inflammatory cytokines and electrolytes balance. Any disturbance in these balances results in disorders that may lead to diseases and sometimes to death. Also, all these pathways and their signal transducers and responded genes are intersected and very complex. None can resolve their network. Of note, to date, despite the progressive scientific development, there is no vaccine against HIV since 1982, no therapy completely cures diabetes, no therapy specific for coronaviruses since their first isolation in 1932 or first pandemic since 2002-2003 [10, 11]. In this aspect, the treatment of immune disorders is very difficult and needs more effort to resolve their intersected lines and maintain its balance. Therefore, we focus on a new strategy in the treatment of COVID19 patients who did not respond to the conventional treatment protocol, particularly elderly ones who suffer from diabetes, cardiac disease, and hypertension. Finally, more researches are required to study SARS-CoV-2 target genes, cells, and the affected signal cascades. Also, the world needs to widen the researches among different populations since polymorphic variations in cytokine themselves or any related factors such as proteins, enzymes, transcription factors, growth factors affect the response to therapies.

In contrast to Influenza viruses that are usually restricted to the respiratory tract and cleared efficiently in most cases [12], SARS-CoV-2 causes acute fatal infections that are associated with systemic spread of the virus. Despite the respiratory system is the core target for SARS-CoV-2, the clinical manifestation present a wide spectrum range from asymptomatic or paucisymptomatic types to clinical conditions characterized by respiratory failure and multiple organ dysfunction syndromes (MODS). These include thrombotic complications, eventual multi-organ failure, respiratory distress syndrome (ARDS), cerebrovascular accidents, acute kidney injury (AKI), myocarditis, and finally death. Huang et al. showed that patients suffered from fever, dry cough, malaise, and dyspnea, pneumonia with abnormal results in all cases were about a third of those needed ICU care, and there were fifteen percent fatal cases [13,14]. It is well known that lung function is one of the strongest predictors of cardiorespiratory and cardiovascular health and mortality. There is strong evidence of an association between cardiovascular diseases (CVD), hypertension, diabetes, autoimmune diseases with the risk and severity of SARS-CoV-2infection [15]. Day by day, new non-specific symptoms were described such as hypercoagulability resulting in macro and microthrombi formation in the vessels because of higher levels of D-dimer, fibrinogen, and fibrinogen degradation products leading to MODS [16]. In May 2020, scientists reported additional non-specific symptoms in the skin. Pityriasis Rosea, exanthematous rash, urticaria, chickenpox like vesicles, petechiae, and acute hemorrhagic edema were reported in a patient infected with SARS-CoV-2 [17]. All of these confirm that SARS-CoV-2 infectivity extends beyond being an influenza virus. Symptoms of influenza virus infection may last for 7–10 days and self-limiting due to the induction of protective immune response [18]. Years ago, scientific research focused on understanding the immune response to viral infection to induce protective immunity in populations at the extremes of age and in immune-compromised subjects, the most liable targets for infectious induced-severe illness and high mortality [19]. Worldwide, the clinical trials are based on: a) interfering with viral infection by vaccines [20], b) providing Abs or enhancing the immune response to impair viral replication [21], c) counteracting the severe cytokines storm [8].

Obstacles impair discovering of specific vaccines for COVID19

The virulence of SARS-CoV-2 that enables it to interfere with the discovering of specific vaccines is attributed to several items. Firstly,SARS-CoV-2 belongs to Betacoronavirus that are characterized by the largest positive single-stranded RNA (ssRNA) viruses approximately 30 kb in length, with a 5′-cap structure and 3′-poly-A tail. They generate a significant amount of dsRNAs as replicative and transcriptive intermediates [22]. This large RNA genome in CoVs exerts extra plasticity in genome modification due to mutations and recombination, thereby increasing the probability for interspecies co-evolution [23]. The most frequent mutation in SARS-CoV-2 samples isolates from China, USA, and Europe is deletion and substitution in structural and non–structural proteins [24, 25]. Secondly, coronaviruses can constantly evolve and cross-species barriers. Over 200 novel coronaviruses have been identified in bats, 35% of the bat virome sequenced to date is composed of coronaviruses, in addition to snakes, pangolins, and bamboo rats [26].

Obstacles impair discovering of specific therapy for COVID19

Despite the discovering of coronavirus was in the 1930s and the time of first coronavirus pandemic was in 2002, the global disability for discovering specific therapies till now, the ongoing COVID19 pandemic, makes the only opportunity now to rescue the humanity is the drug repositioned [9, 10]. Of course, the first step to discover

specific vaccines or new specific therapies requires the understanding of the viral life cycle and identifying the cellular factors participate in viral infection. As virus entry is the first step in the viral life cycle, and inhibition of this vital procedure is an attractive tactic to block viral infection. The first obstacle of studying viral entry directly is the low amounts of virus particles, thus current methods usually assess post-entry parameters, such as replication or the expression of a reporter gene, rather than measuring entry per se [27]. The second one is the non-specific symptoms which are discovered continuously since the beginning of the COVID19 pandemic, including myocarditis, encephalitis, glomerulonephritis as well as the recent finding of Kwasaki syndrome increase the complexity of the disease and the difficulties of specifying therapies [22]. Also, SARS-CoV-2 can evade from the immune system as well as enhance the cytokines production causing aggressive cytokines storm that is the leading cause of severe illness and high mortality rate [20].

Dysregulation of Myeloid lineage in viral infection Monocytes, Neutrophiles, Eosinophils

The role of myeloid cells in the regulation of both immune responses and returning to homeostasis during viral infections involves suppressive receptors, specialized cellular subsets, and cytokines [28]. Monocytes, a key source of serum ferritin, are poorer reservoirs of iron than intracellular ferritin. Serum ferritin is a well-known acute-phase reactant, with levels that mirror to inflammation associated with infection [29]. Regulation of ferritin synthesis is cytokine responsive at both the transcriptional and translational levels in a diversity of cells including hepatocytes, mesenchymal cells, monocytes, and macrophages [30]. Ferritin synthesis is regulated by various oxidant and antioxidant stimuli such as glutathione (GSH), nitric oxide (NO), and other reactive oxygen species (ROS) [31]. Also, macrophages act as a major iron sink by directly phagocytizing senescent red blood cells [32]. Neutrophils have pro- and anti-inflammatory roles. They reduce lung injury during influenza virus infections and help in clearing an inflamed area by removing killed infected cells. Also, they can return to the quiescence state (de-prime) via the degradation of a superoxide anion response [33]. Despite lack of neutrophil leads to increase inflammation and viremic spread [34], the elevation of neutrophils enhances the inflammation via increasing angiogenesis and formation of NETs that function via serine proteases to degrade excess cytokines in areas with high densities of neutrophils [35, 36].

Eosinophils link the viral infection with the exacerbation of lung inflammation via secretion of cationic proteins such as epoxidase (EPO), eosinophil-derived neurotoxin (EDN), and RNase [37]. EPO exerts their action via oxidation of chloride, thiocyanate, hypochlorous, and hypothiocyanate. Particularly, RNase participates in the anti-viral actions of eosinophils, rather anti-bacterial or antihelminthic [38]. The neurocytotoxicity of EDN is attributed to its ability to enhance the formation of blood clots. EPO reduces the anticoagulant effects of heparin and shortens the coagulation time of normal plasma via inhibiting the thrombomodulin and activating the Factor XII-dependent pathway [39]. Generally, the neurotoxin action of Coronaviruses was documented where they can cross the brain barrier causing an inflammation in CNS, subsequently, resulting in nervous manifestations such as psychiatric symptoms including depression PTSD, panic disorder, and obsessive-compulsive disorder for months after survive [40]. The same was reported recently in COVID19 patients including stroke and alterations in consciousness in positively tested patients and different psychological distress in either symptomatic (mild, moderate, and severe) patients or asymptomatic persons [41].

Dysregulation of lymphoid lineage in viral infection Th1, Th2, Th17, and Treg

Th1 and Th2 were long described as the main mediators in auto-immune diseases (AID). These conditions increase the Th1/Th2 ratio accompanied by increasing Th17 cells. Th1 overrepresentation and reaction against self-antigens cause tissue destruction, which plays a dynamic role in AID, while Th2 cells were suggested to protect against Th1 and Th17-related AID [42]. Recent data highlight the role of assessment of the lymphocytes ratios to monocytes, neutrophils, and platelets as well as their pro-inflammatory cytokines and markers such as Il-6, CRP, D-dimer and ferritin to manage the severity of COVID19 [43, 44]. Tregs', a subpopulation of CD4+ T cells, secretes IL-10 and TGFβ to maintain the balance of immune responses, self-tolerance, prevent autoimmunity, and limiting chronic inflammatory diseases via down-regulation of dendritic cells (DCs), CTLs, macrophages, T, and B lymphocytes [45]. Transcription factor forkhead box protein 3 (FOXP3) and its downstream EBV-induced gene 3 (EBI3) are significant transcription factors for the development and function of Treg cells [46]. Patients with mutations in Foxp3 and EBI3 suffer from massive autoimmune reactions [47]. Although the data from many investigations differ in the evaluation of the role of EBI3 whether their down-regulation was associated with suppression of Treg cell activity or not, a Chinese study demonstrated that SNP EBI3 rs428253 (CG/CC) has a protective effect against arthritis rhinitis (CG/CC) while the diplotype rs3761548-rs4824747 with ‘‘AG’’ and IVS9+459 T/C (rs2280883) may increase the risk of developing AR in Han Chinese subjects [48]. SNP of FOXP3 gene-2383 C/T and T allele of IVS9+459 T/C were associated with the risk of lung cancer in Iranian population [49, 50], idiopathic infertility

in a Brazilian population (C allele), and primary biliary cirrhosis (PBC) in an American population (T allele) [51]. It was revealed that females homozygous for the rare FOXP3 rs3761548 allele (A/A) are protected against AR; otherwise, females who are either wild types (C/C) or heterozygote carriers (C/A) of the rare allele are more susceptible to AR in European and Chinese not in Sub-Saharan Africans [52].

Implication of cytokines storm in COVID19 severity

Since 1975 when interferon (IFN) was discovered [53], more than 90 inflammatory cytokines and their corresponding receptors have been identified. Of these, 40 ILs are mainly regulating the immune cell proliferation, growth, differentiation, survival, activation, and functions [54], thus they are crucial for maintaining the immune response including the balance between pro- and anti-inflammatory effectors [55]. Many years ago, interferon-γ (IFNγ) was utilized for treatment against several pathological diseases; however, it is also a major cytokine that participates in the pathogenesis of several autoimmune diseases [56, 57]. In the current pandemic, it is clearly observed that COVID19 induced systemic inflammatory response syndrome (SIRS) that leads to organ failure and death. This is attracted the attention for more researches about the effectiveness of immunotherapies in this case. The immunotherapies modulate the aggressive immune response. Turning on most cytokine genes in response to infection is a great challenge with death among patients infected with COVID19 [21]. This directs us to throw light about the crucial role of cytokine storm in response to COVID19 and its application in discovering and/or reposition therapies. In support, a previous study revealed that the treatment protocol for viral infections must be included both anti-viral therapy together with immunotherapy that was dedicated to increase and adjust the immune system [58]. Herein, the innate immune response that is nothing more than a cytokine storm, as in current COVID19 disease, can be considered as a key determinant in its virulence and the clinical outcomes where innate immune elements have privilege on adaptive in that, they participate in both sensing and response to influenza viruses [59]. Besides, the initial IFN-mediated antiviral response, human epithelial cells of alveoli secrete various cytokines and chemokines such as IL-6, TNF-α, IL-8, and several chemoattractants to lessen the viral infection [60]. IL-6 is generated in an infectious lesion and sends out a warning signal to the entire body. TNF-α and IL-1β activate the transcription factors to create IL-6. Together, they promote leukocyte recruitment, the activation of T cells, and the elaboration of other pro-inflammatory molecules such as serum amyloid A and C-reactive protein [61, 62]. Also, many pro-inflammatory interleukins such as IL-2, IL-4, IL-10, and Il-17 participate in the IL-6 signal pathway. Collectively, their overexpression is associated with cytokine storm that is the hallmark of lung dysfunction that worsens ARDS and can lead to MOD associated with the high mortality rate in patients infected with COVID19 [63, 64].

The implications of cytokines inhibitors in the treatment of cytokines storm-induced inflammation

Despite the variable effects of cytokines in autoimmune diseases, cancers, and infectious diseases, not all of them are effective or promising targets for the treatment of these diseases [65]. Beginning in the recent century, cytokines that are produced by innate immune cells represented an attractive target for therapeutic intervention. Targeting these cytokines using either specific or non-specific inhibitors showed successful achievement in the treatment of many inflammatory diseases including autoimmune diseases and cancers. Despite their applications in infectious diseases are very rare, successful data support our hypothesis about the importance of this class of therapy to be involved in treatment protocols for infectious disease-induced cytokine storm. In this aspect, the downregulation of systemic inflammation might be conceptually beneficial in controlling systemic responses to pathogens [66]. This is due to the limited perspective of their inhibitory effects, rather than their regulatory role. A great deal of effort has been devoted to targeting the host response with a diversity of anti-inflammatory drugs and adjunct tactics in a range of acute severe infections, including treatment with monoclonal antibodies (MAbs), corticosteroids, anti-cytokine and anti-chemokine agents, aspirin, plasma exchange, and statins. Despite these efforts, none has been verified to be efficient [67], however, some have worsened the outcome [68]. Also, strong evidence demonstrated that antiviral treatment was less effective alone than in combination with immunomodulatory therapies that suppressed inflammation. Of note, combination with micronutrients may improve and regulate the immune response and response to therapies. Particularly, deficiency of important micronutrients such as Zinc was reported in elderly patients [69]. Many aspects must be taken in considerations to improve the clinical outcomes in response to immunomodulatory therapies in infectious diseases: 1) Doses and time of intervention in infectious diseases that are completely different from that in auto-immune diseases; 2) Timely assessment of the target cytokines help in monitoring the clinical outcomes; 3) Genetic variations among populations such as SNP determine the target population for therapy; 4) Whether virus induces epigenetic alterations. This helps in understanding the time course of infection, subsequently, timely delivery and efficacious care must be balanced to limit the progression of the disease to the fatal condition

[70]. Further researches would answer an important question that is whether SARS-CoV-2 triggers epigenetic alterations in the gene expression of cytokines. The answer will help in directing specific interleukin inhibitor to its specific target. For example, CMV triggers epigenetic alterations resulting in overexpression of IL-1,-2, STAT-1,-4 that mediate the chromatin remodeling in NK and reach the peak within one week [71]. Wide varieties of cytokines and their different roles in immune response open the field to apply more immune-modulatory therapies in the treatment of infectious diseases especially as the urgent needing for treatment of COVID19 patients who attack all populations worldwide with different symptoms and different degree of severity. Of note, variations in gene expression of cytokines among populations due to single nucleotide polymorphism (SNP) cause variations in the immune response to immunotherapy as shown in table (1). Subsequently, dysregulation of ILs is known to be involved in the pathogenesis of human inflammatory and autoimmune diseases [72]. Collectively, resolving the inflammation and maintenance of the homeostasis is as important as the immune response to pathogens. Failure of their maintenance results in immunopathology as shown in severe illness in COVID19 patients.

Interferon-γ (IFN-γ), which is produced by T helper 1 (Th1) lymphocytes, plays a major role in both innate and adaptive immune response. It enhances Th1 responses by activating NK cells and macrophages, promotes innate immune responses by activating macrophages, disrupts several anti-inflammatory feedback loops, up-regulates various pro-inflammatory mediators, and promotes the specific cytotoxic immunity via T cell and APC interaction [73]. A recent Chinese study revealed that the treatment of patients with COVID19 with IFN-α2b accelerated viral clearance from the upper respiratory tract as well as reduced the levels of the pro-inflammatory marker in the blood such as IL-6 and CRP [74]. However, it was found that IFN-g-induced downregulation of Secretory leukoprotease inhibitor (SLPI), an anti-inflammatory protein, present in airway epithelial cells results in improved airway hyperresponsiveness and steroid resistance [75]. This may be explained as the genetic variation among the population, affecting the response to therapy. It was revealed that A allele of SNP IFN-γ (874A/T) (rs2430561) is correlated with low expression and is associated with many autoimmune diseases and infectious diseases such as tuberculosis susceptibility in China [76]. On the contrary, T allele is a major allele in Caucasian, Latin American, and Middle Eastern populations [77].

Tumor necrosis factor-alpha (TNF-α)

Wang et al. demonstrated that a surface viral protein from the SARS virus directly stimulated the production of tumor necrosis factor-alpha (TNF-α) by alveolar macrophage [78] and is associated with SARS-induced severity of the disease. The same is reported in COVID19 related to severe illness [79]. Meta-analysis indicated a potential association between SNPs of TNF-α −308G/A (rs1800629) and the risk of and severity of Osteoarthritis (OA) among Asians and Caucasians [80]. Earlier, Etanercept was verified by the FDA for the treatment of rheumatoid arthritis having a high level of TNF-α [81]. Five TNF inhibitors were accepted for the treatment of Psoriasis, Rheumatoid arthritis, and other autoimmune diseases. Infliximab, adalimumab, and golimumab are fully human bivalent IgG monoclonal antibodies that neutralize the biological function of TNF. Certolizumab is the Fab' fragment of a recombinant, humanized antibody against both solTNF and tmTNF. Etanercept is a genetically engineered fusion protein binds with high affinity to both soluble and transmembrane types of TNF [82].

Transforming growth factor-β (TGF-β) is a potent immunosuppressive profibrogenic cytokine that severely influences the function of NK cells, innate lymphocytes able to recognize and kill virus-infected. TGF-β has a prominent role in both innate and adaptive immune responses. It regulates the IFN-γ production by NK cells, the differentiation of pro-inflammatory macrophage (M1), and the anti-inflammatory type (M2) [83]. Interstitial lung disease (ILD) is one of the principal causes of death in patients with systemic sclerosis (SSc). A recent systematic review revealed that although SSc is a rare disease, ILD constitutes one of the most common types of direct pulmonary involvement in SSc patients in the European and North American populations especially, aging women [84]. The sarcoidosis, an inflammatory multisystem disease predominant in the lung, was associated with many autoimmune diseases including systemic sclerosis (SSc), Hashimoto's thyroiditis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) in addition to high risk of infection [85]. The typical treatment of symptomatic sarcoidosis usually includes systemic immunosuppressants such as cyclophosphamide and corticosteroids, however, recent clinical trials on the basis of the anti-fibrotic effect of TGF-β inhibitor, galunisertibis underway as a monotherapy or in combination with anti-cancer therapy for the treatment of cancers and autoimmune diseases [86]. A previous study demonstrated a strong association between SNP TGF-β3 (rs3917200) while G carriers in TGF-β2 (rs1891467) might be protected from emerging chronic lung fibrosis in sarcoidosis patients in the German population. Likewise, fresolimumab, an engineered human monoclonal Ig that neutralizes the 3 major isoforms of TGF-β, namely, β1, β2, and β3, was developed reverse fibrosis [87].

Interleukin-10 (IL-10), an immunosuppressive cytokine, is released by innate and adaptive immune cells to fine-tune the action of pro-inflammatory cytokines [88]. Polymorphisms implicated to influence IL-10 transcription and secretion include rs1800872 (− 592 C > A), rs1800896 (− 1082 A > G), and rs1800871 (− 819 C > T) [89]. Interestingly, the IL-10 − 819 T allele was also significantly related to T2DM among African but not in European and Asian subjects. However, the IL-10 − 1082 G allele was meaningfully related to T2DM in total subjects, mainly in European and Asian but not in African subjects. Recombinant human (rh) IL-10 (ilodecakin/Tenovil) was verified to treat Psorioticpatients with IL-10 deficiency. Also, the high efficiency ofAM0010, a pegylated recombinant IL-10 in the treatment of cancer patients was noted [90-92].

Interleukin 1β (IL-1β) is a prominent cytokine that is generated in the early stage of microbial infections by the cleavage action of caspase-1 on pro-IL-1β in inflammasomes. Binding of IL-1β to its receptor triggers the signal cascade. This results in the induction of various proinflammatory cytokines, activation of lymphocytes, as well as, viral persistence and pathogenesis [93]. IL-1β is a key cytokine driving proinflammatory activity in bronchoalveolar lavage fluid of patients with lung injury. IL-1α −899C/T was related to the enhanced risk of cerebral infarction in the Asian population [94]. Anakinra, a recombinant IL-1 receptor antagonist, revealed efficacious data in the treatment of macrophage activation syndrome (MAS) and indicated effectiveness in disease remission with normalization of lab abnormalities and fever [95].

Interleukin-4 (IL-4) is secreted mostly by activated T cells and monocytes, basophilic granulocyte, and mast cells. IL-4 promotes the incidence and development of inflammatory reactions characterized by Th2, the producers of IL-4, IL-5, and IL-13 [96]. It has been demonstrated that the high prevalence of T allele of -33C>TIL4 and A allele of 576Q>RIL4RA results in increasing the IL-4 level that was related asthma in South European populations [97]. Dupilumab includes fully human non-cytotoxic monoclonal antibodies to IL-4Ra that blocks the IL-4 pathway and reduces tissue eosinophilia. It meaningfully decreases exacerbation frequency and lessens oral corticosteroid utilization in patients with severe asthma [98].

Interleukin-17A (IL-17A), a family consists of six members IL-17A-F, is a proinflammatory cytokine expressed mostly by Th17 along with macrophages, mast cells, neutrophils, natural killer cells, dendritic cells, gamma-delta T cells in addition to non-immune cells. They play significant roles in host defense against microbial organisms and the development of inflammatory illnesses. IL-17A levels were enhanced in Ischemic stroke (IS), the first common cause of death worldwide, mainly, in the USA and China. Individuals carrying G and T carriers of SNP of IL-17 (rs2275913) and (rs8193036) present higher serum IL-17A levels compared with those A carriers and C carriers in Chinese patients with ischemic stroke and ARDS, respectively [99]. Recently, SNP of IL-17 (rs4819554) G/A is meaningfully related to a high level of IL-17 and psoriasis in the Egyptian population [100].

Interleukin 6 (IL-6) is the protagonist in the pathogenesis of the cytokines storm. It has double actions; pro- and anti-inflammatory effects because of its ability to promote some immune cells (B lymphocytes) and inhibit others. IL-6 increases during inflammatory diseases, infections, autoimmune disorders, and CRS, as well as in the acute phase sera in Taiwan SARS patients causing a high mortality rate [101]. Also, it plays a significant role in thermoregulation as well as maintenance of bone and the central nervous system. Furthermore, it induces the overexpression of CD26 and ACE-2, two receptors of SARS-CoV-2 [102, 103]. It promotes the differentiation of fibroblasts into myofibroblast cells in patients with pulmonary fibrosis [104]. Several studies proved the benefits of blocking IL-6 pathway in inflammatory diseases. SNP of IL-6 -634C/G is common in the Chinese population, and is related to high circulating levels of IL-6 and C-reactive protein. IL-6 −572C/G, −174G/C, and IL-10 −1082A/G polymorphisms were associated with increased cerebral infarction risk in Asians [105, 106]. Also, SNP of IL-6 (rs1800795) −174G/C was related to RA in Egypt [107]. Tocilizumab (Actemra), a monoclonal antibody targeting the IL-6 receptor, may mitigate the effects of cytokines released in response to the virus and limit lung damage in COVID19 patients with severe ailment [108].

From previous, it is observed that polymorphic variations add complexity to deal with the immune system with immunomodulatory therapies among different populations. This may explain the debate about the variations in response to therapies among the populations in different countries.

Micronutrients Supplements

In the lack of a specific treatment for SARS, the importance of non-specific influences of vitamins on severe viral respiratory tract infections should be considered. For optimizing the therapeutic use of interleukin inhibitors, combination with micronutrients such as Zn, Selenium, and vitamin C is very important [109, 110].

Zinc

Zinc is a nutritionally fundamental trace element and is the second most abundant trace metal in the human body after iron. The impact of zinc on human health was first

detected and defined by Prasad et al. in the 1960s [111]. Zinc deficiency modifies both innate and adaptive immune responses. Initially, its deficiency enhances the fabrication of proinflammatory cytokines, such as interleukins IL-1β, IL-6, and tumor necrosis factor (TNF)-α. Recognition of MHC class I by NK cells and the lytic activity of NK cells is affected by zinc depletion. Secondly, its influence on the adaptive immune response is attributed to thymic atrophy and subsequent T-cell lymphopenia as well as a decrease of premature and immature B cells, and thus, antibody production is also lessened [112]. Exacerbated inflammation may result in mucosal injury which further contributes to intestinal and lung ailment. The prophylactic benefits of Zinc were reported, where its supplementation during sepsis may provide pathogens Zinc microenvironment that is more favorable for pathogen growth. Besides, zinc is considered a structural component in numerous proteins, and its participation in numerous cellular functions is nowadays well-established. Such functions include, but are not restricted to, cell proliferation and differentiation of RNA and DNA, as well as cell structures and cell membrane stabilization [113]. Zinc plays a crucial role in: 1) reducing infections and necrosis in addition to preserve and restore membrane function and structure in lung epithelium [114]; 2) maintaining the membrane barrier structure and function for lung and intestine, subsequently protect them against the myriad of pathogens [115]; 3) increasing the antiviral activity of IFN-α 10-fold against rhinovirus by interfering with rhinovirus polyprotein processing [116]; 4) reinforcing the shared IFN signaling cascade by inhibiting protein tyrosine phosphatase enzymatic activity since dephosphorylating of such key signaling molecules (STAT), several phosphatases have been shown to “put the brakes” on IFN signaling [117].

Vitamin C

Also, it was suggested that vitamin C supplementation is urgently impeded in the treatment protocol of patients with viral infection because they suffer from vitamin C deficiency due to high metabolic consumption [118]. A recent study mentions the effectiveness of vitamin Cin counteracting the cytokines storm in cases with COVID19 [119]. Particularly, infection with the Influenza virus results in vitamin C deficiency accompanied by oxidative stress. Together, they aggravate lung dysfunction. Many clinical trials reported that supplementation with vitamin Creduces the severity and fatality of asthma especially that related to a viral infection which impairs both the immune system and the metabolism of iron and folate [120]. Strong evidence highlight the role of vitamin Cin: 1) improving the immune system via enhancing phagocytic activity, accelerating Lymphocyte proliferation and regulate gene expression of pro-inflammatory cytokines [121]; 2) detoxifying histamine which is associated with deleterious inflammation in asthmatic patients, triggering airway hyperresponsiveness and remodeling [122]; 3) reducing the duration and severity of common cold episodes as well as prevention of pneumonia in viral infectious diseases by reducing the viral load [123].

Glutathione (GSH)is the most abundant antioxidant in the airway epithelial lining fluid, and acts as a vital intra- and extracellular antioxidant, protecting against oxidative stress, helping to decrease pro-inflammatory processes in the lungs [124]. Counteracting of oxidative stress induced-inflammation in patients with pneumonia reduce lung injury. A recent study revealed that the administration of N-acetylcysteine a cysteine pro-drug is an effective therapy in relieving the severity of pneumonia [125].

1.7.d. Vitamin D in combination with non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme 2 (ACE2) inhibitor, Angiotensin II receptor blockers (ARB) or thiazolidinediones improves the immune system in fighting SARS-CoV-2 [126].

The global ongoing clinical trials

Most ongoing clinical trials based on the drug repositioned that were already approved for the treatment of various types of viruses, bacteria, and parasites such as lopinavir, ritonavir, interferon-1β, RNA polymerase inhibitor remedies, and chloroquine as the only possible opportunity to rescue patients infected with SARS-CoV-2. Also, depending on inhibitors that target angiotensin-converting enzyme 2 (ACE2) and renin-angiotensin because SARS-CoV-2 receptor binding site has a strong affinity with this system may have a role in treating severe respiratory disease [127]. The usual approved antibiotic Azithromycin was widely used in the treatment of influenza viral infection. However, there is a debate about the efficacy of Chloroquine, a lysosomotropic base to disrupt intracellular trafficking and viral fusion events that prevent viral replication [128]. For five months all health organizations highlight and support the role of Chloroquine and its derivatives in the treatment of patients with COVID19, however, a few days ago, some prevented their applications [129]. The high prevalence of COVID19 and related mortality was reported in Europe, the USA, and China. One possible explanation is the genetic variations related to the susceptibility to the virus such as SNP in ACE2.

Also, failure of Glucocorticoid therapies in the treatment of numerous COVID19 patients insists on the importance of integration of new therapies line in treatment of COVID19 including immunotherapies. Particularly, it is well established that both Glucocorticoids and COVID19 induce osteoporosis via increased urinary calcium excretion [130, 131]. Thus, further studies will be needed to explain whether it is a consequence of SARS-CoV-2

infection or Glucocorticoid therapies. Meanwhile, many researchers are trying to develop new therapeutic approaches, based on the effectiveness of various immunotherapies such as IL-6 inhibitor (Tocilizumab) to improve the clinical outcomes in patients with COVID-19 who display elements of cytokine storm [132]. Also, supplementation with multi-vitamins and composed formula containing Selenium, Zinc, Magnesium, vitamin C, in addition to antioxidants such as acetylcysteine and lactoferrin improve the clinical outcomes in COVID19 patients since they participate in hundreds of biological reactions especially in immune response [119, 133].

Our ongoing clinical trials

1. Monitoring the response of COVID19 patients to Tocilizumabplus phytotherapy on a wide scale.
2. Assessment of IL-17 in blood samples of COVID19 patients as a first step to get the approval of Cosentyx in the treatment protocol of COVID19 patients.
3. The epigenetic alteration accompanied by SARS-CoV-2 infection.

CONCLUSION

Combination therapy of immunotherapies plus micronutrients including Zinc, Selenium, vitamin C, Dand cysteine prodrug may improve the lung function in COVID19 via maintenance of the immune balance.

Competing interests

The authors declare no competing interest.

Author contributions

H. F. wrote the manuscript, M.A. revised the manuscript.

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Implications: A combination therapy of immunotherapies plus micronutrients including Zinc, vitamin C, and Glutathione may provide a new trend in the treatment of COVID19-induced pneumonia via not only counteracting the cytokine storm but also maintain the delicate balance of the immune system.

REFERENCES

[1] Eltayeb LB. An update about Coronaviruses with Emphasis on Newly Emerged COVID 19. J Biochem Technol. 2020;11(3):14-20.

[2] Alshammari E. Implementing eOSCE During COVID-19 Lockdown. J. Adv. Pharm. Educ. Res. 2020;10(1):174-80.

[3] https://covid19.who.int/?gclid=EAIaIQobChMI0yIoaLc6gIVgvhRCh3ZMAc9EAAYASAAEgK-B_D_BwE

[4] Lestari K, Sitorus T, Instiaty SM, Levita J. Molecular Docking of Quinine, Chloroquine and Hydroxychloroquine to Angiotensin Converting Enzyme 2 (ACE2) Receptor for Discovering New Potential COVID-19 Antidote. J. Adv. Pharm. Educ. Res. 2020;10(2):1-4.

[5] Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B, von Bergwelt-Baildon MS. Cytokine release syndrome. Journal for immunotherapy of cancer. 2018 Dec;6(1):56.

[6] Shomali Ahmadabadi M, Royat Z, Aghaei Meybodi F, Hashemian F. Investigating The Effect of Worries about Controlling Thought and Anxiety about Corona Disease In Predicting Learning Anxiety among High School Students In Mahshahr. Journal of Organizational Behavior Research. 2020;5(2):1-7.

[7] Klatt NR, Chomont N, Douek DC, Deeks SG. Immune activation and HIV persistence: implications for curative approaches to HIV infection. Immunological reviews. 2013 Jul;254(1):326-42.

[8] Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine & Growth Factor Reviews. 2020 May 11.

[9] Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clinical Rheumatology. 2020 May 30:1.

[10] Hudson CB, Beaudette FR. Infection of the cloaca with the virus of infectious bronchitis. Science. 1932 Jul 8;76(1958):34-.

[11] Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiology and molecular biology reviews. 2005 Dec 1;69(4):635-64.

[12] Tse H, To KK, Wen X, Chen H, Chan KH, Tsoi HW, Li IW, Yuen KY. Clinical and virological factors associated with viremia in pandemic influenza A/H1N1/2009 virus infection. PloS one. 2011 Sep 27;6(9):e22534.

[13] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020 Feb 15;395(10223):497-506.

[14] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA neurology. 2020 Jun 1;77(6):683-90.

[15] Miller MR. Spirometry in primary care. Primary care respiratory journal: journal of the General Practice Airways Group. 2009 Dec;18(4):239.

[16] Yu B, Li X, Chen J, Ouyang M, Zhang H, Zhao X, Tang L, Luo Q, Xu M, Yang L, Huang G. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. Journal of Thrombosis and Thrombolysis. 2020 Jun 10:1-0.

[17] Ehsani AH, Nasimi M, Bigdelo Z. Pityriasis rosea as a cutaneous manifestation of COVID-19 infection. Journal of the European Academy of Dermatology and Venereology. 2020 May 2.

[18] Valkenburg SA, Rutigliano JA, Ellebedy AH, Doherty PC, Thomas PG, Kedzierska K. Immunity to seasonal and pandemic influenza A viruses. Microbes and infection. 2011 May 1;13(5):489-501.

[19] Taubenberger JK, Morens DM. The pathology of influenza virus infections. Annu. Rev. Pathol. Mech. Dis.. 2008 Feb 28;3:499-522.

[20] Malavolta M, Giacconi R, Brunetti D, Provinciali M, Maggi F. Exploring the relevance of senotherapeutics for the current SARS-CoV-2 emergency and similar future global health threats. Cells. 2020 Apr;9(4):909.

[21] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV).

[22] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). InStatpearls [internet] 2020 Mar 8. StatPearls Publishing.

[23] Denison MR, Graham RL, Donaldson EF, Eckerle LD, Baric RS. Coronaviruses: an RNA proofreading machine regulates replication fidelity and diversity. RNA biology. 2011 Mar 1;8(2):270-9.

[24] Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le HQ, Nguyen TT, Cao TM, Pham QD. Importation and human-to-human transmission of a novel coronavirus in Vietnam. New England Journal of Medicine. 2020 Feb 27;382(9):872-4.

[25] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD. A pneumonia outbreak associated with a new coronavirus of probable bat origin. nature. 2020 Mar;579(7798):270-3.

[26] Lam TT, Shum MH, Zhu HC, Tong YG, Ni XB, Liao YS, Wei W, Cheung WY, Li WJ, Li LF, Leung GM. Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China. BioRxiv. 2020 Jan 1.

[27] Caffrey M. HIV envelope: challenges and opportunities for development of entry inhibitors. Trends in microbiology. 2011 Apr 1;19(4):191-7.

[28] Stegelmeier AA, van Vloten JP, Mould RC, Klafuric EM, Minott JA, Wootton SK, Bridle BW, Karimi K. Myeloid cells during viral infections and inflammation. Viruses. 2019 Feb;11(2):168.

[29] Cohen LA, Gutierrez L, Weiss A, Leichtmann-Bardoogo Y, Zhang DL, Crooks DR, Sougrat R, Morgenstern A, Galy B, Hentze MW, Lazaro FJ. Serum ferritin is derived primarily from macrophages through a nonclassical secretory pathway. Blood, The Journal of the American Society of Hematology. 2010 Sep 2;116(9):1574-84.

[30] Leimberg MJ, Prus E, Konijn AM, Fibach E. Macrophages function as a ferritin iron source for cultured human erythroid precursors. Journal of cellular biochemistry. 2008 Mar 1;103(4):1211-8.

[31] Torti FM, Torti SV. Regulation of ferritin genes and protein. Blood, The Journal of the American Society of Hematology. 2002 May 15;99(10):3505-16.

[32] Korolnek T, Hamza I. Macrophages and iron trafficking at the birth and death of red cells. Blood, The Journal of the American Society of Hematology. 2015 May 7;125(19):2893-7.

[33] Summers C, Singh NR, White JF, Mackenzie IM, Johnston A, Solanki C, Balan KK, Peters AM, Chilvers ER. Pulmonary retention of primed neutrophils: a novel protective host response, which is impaired in the acute respiratory distress syndrome. Thorax. 2014 Jul 1;69(7):623-9.

[34] Tate MD, Deng YM, Jones JE, Anderson GP, Brooks AG, Reading PC. Neutrophils ameliorate lung injury and the development of severe disease during influenza infection. The Journal of Immunology. 2009 Dec 1;183(11):7441-50.

[35] Li RH, Tablin F. A comparative review of neutrophil extracellular traps in sepsis. Frontiers in veterinary science. 2018 Nov 28;5:291.

[36] Naess A, Nilssen SS, Mo R, Eide GE, Sjursen H. Role of neutrophil to lymphocyte and monocyte to lymphocyte ratios in the diagnosis of bacterial infection in patients with fever. Infection. 2017 Jun 1;45(3):299-307.

[37] Månsson A, Cardell LO. Role of atopic status in Toll-like receptor (TLR) 7-and TLR9-mediated activation of human eosinophils. Journal of leukocyte biology. 2009 Apr;85(4):719-27.

[38] Hogan SP, Rosenberg HF, Moqbel R, Phipps S, Foster PS, Lacy P, Kay AB, Rothenberg ME. Eosinophils: biological properties and role in health and disease. Clinical & Experimental Allergy. 2008 May;38(5):709-50.

[39] Swaminathan GJ, Weaver AJ, Loegering DA, Checkel JL, Leonidas DD, Gleich GJ, Acharya KR. Crystal Structure of the Eosinophil Major Basic Protein at 1.8 Å AN ATYPICAL LECTIN WITH A PARADIGM SHIFT IN SPECIFICITY. Journal of Biological Chemistry. 2001 Jul 13;276(28):26197-203.

[40] Lam MH, Wing YK, Yu MW, Leung CM, Ma RC, Kong AP, So WY, Fong SY, Lam SP. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. Archives of internal medicine. 2009 Dec 14;169(22):2142-7.

[41] Ferrando SJ, Klepacz L, Lynch S, Tavakkoli M, Dornbush R, Baharani R, Smolin Y, Bartell A. COVID-19 Psychosis: A potential new neuropsychiatric condition triggered by novel coronavirus infection and the inflammatory response?. Psychosomatics. 2020 May 19.

[42] Crane IJ, Forrester JV. Th1 and Th2 lymphocytes in autoimmune disease. Critical Reviews™ in Immunology. 2005;25(2).

[43] Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19–A systematic review. Life Sciences. 2020 May 13:117788.

[44] Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nature Reviews Immunology. 2013 Apr;13(4):227-42.

[45] van Hamburg JP, Asmawidjaja PS, Davelaar N, Mus AM, Colin EM, Hazes JM, Dolhain RJ, Lubberts E. Th17 cells, but not Th1 cells, from patients with early rheumatoid arthritis are potent inducers of matrix metalloproteinases and proinflammatory cytokines upon synovial fibroblast interaction, including autocrine interleukin-17A production. Arthritis & Rheumatism. 2011 Jan;63(1):73-83.

[46] Yagi H, Nomura T, Nakamura K, Yamazaki S, Kitawaki T, Hori S, Maeda M, Onodera M, Uchiyama T, Fujii S, Sakaguchi S. Crucial role of FOXP3 in the development and function of human CD25+ CD4+ regulatory T cells. International immunology. 2004 Nov 1;16(11):1643-56.

[47] Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nature genetics. 2001 Jan;27(1):20-1.

[48] Zhang Y, Duan S, Wei X, Zhao Y, Zhao L, Zhang L. Association between polymorphisms in FOXP3 and EBI3 genes and the risk for development of allergic rhinitis in Chinese subjects. Human immunology. 2012 Sep 1;73(9):939-45.

[49] Haghighi MF, Ghayumi MA, Behzadnia F, Erfani N. Investigation of FOXP3 genetic variations at positions-2383 C/T and IVS9+ 459 T/C in southern Iranian patients with lung carcinoma. Iranian journal of basic medical sciences. 2015 May;18(5):465.

[50] André GM, Barbosa CP, Teles JS, Vilarino FL, Christofolini DM, Bianco B. Analysis of FOXP3 polymorphisms in infertile women with and without endometriosis. Fertility and sterility. 2011 Jun 1;95(7):2223-7.

[51] Park O, Grishina I, Leung PS, Gershwin ME, Prindiville T. Analysis of the Foxp3/scurfin gene in Crohn's disease. Annals of the New York Academy of Sciences. 2005 Jun;1051(1):218-28.

[52] Fodor E, Garaczi E, Polyánka H, Koreck A, Kemény L, Széll M. The rs3761548 polymorphism of FOXP3 is a protective genetic factor against allergic rhinitis in the Hungarian female population. Human immunology. 2011 Oct 1;72(10):926-9.

[53] Isaacs A, Lindenmann J. Virus interference. I. The interferon. Proceedings of the Royal Society of London. Series B-Biological Sciences. 1957 Sep 12;147(927):258-67.

[54] Catalan-Dibene J, McIntyre LL, Zlotnik A. Interleukin 30 to interleukin 40. Journal of Interferon & Cytokine Research. 2018 Oct 1;38(10):423-39.

[55] Fietta P, Costa E, Delsante G. Interleukins (ILs), a fascinating family of cytokines. Part I: ILs from IL-1 to IL-19. InTheoretical biology forum 2014 Jan 1 (Vol. 107, No. 1-2, pp. 13-45).

[56] Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. New England Journal of Medicine. 2006 Sep 7;355(10):1018-28.

[57] Choubey D, Moudgil KD. Interferons in autoimmune and inflammatory diseases: regulation and roles. Journal of Interferon & Cytokine Research. 2011 Dec 1;31(12):857-65.

[58] Iwasaki A, Pillai PS. Innate immunity to influenza virus infection. Nature Reviews Immunology. 2014 May;14(5):315-28.

[59] Vareille M, Kieninger E, Edwards MR, Regamey N. The airway epithelium: soldier in the fight against respiratory viruses. Clinical microbiology reviews. 2011 Jan 1;24(1):210-29.

[60] Gabay C. Interleukin-6 and chronic inflammation. Arthritis research & therapy. 2006 Jul 1;8(S2):S3.

[61] Pulendran B, Maddur MS. Innate immune sensing and response to influenza. InInfluenza Pathogenesis and Control-Volume II 2014 (pp. 23-71). Springer, Cham.

[62] Bryant-Hudson KM, Gurung HR, Zheng M, Carr DJ. Tumor necrosis factor alpha and interleukin-6 facilitate corneal lymphangiogenesis in response to herpes simplex virus 1 infection. Journal of virology. 2014 Dec 15;88(24):14451-7.

[63] Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harbor perspectives in biology. 2014 Oct 1;6(10):a016295.

[64] Ingraham NE, Lotfi-Emran S, Thielen BK, Techar K, Morris RS, Holtan SG, Dudley RA, Tignanelli CJ. Immunomodulation in COVID-19. The Lancet Respiratory Medicine. 2020 May 4.

[65] Lai Y, Dong C. Therapeutic antibodies that target inflammatory cytokines in autoimmune diseases. International immunology. 2016 Apr 1;28(4):181-8.

[66] Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiology and Molecular Biology Reviews. 2012 Mar 1;76(1):16-32.

[67] Meijvis SC, Hardeman H, Remmelts HH, Heijligenberg R, Rijkers GT, van Velzen-Blad H, Voorn GP, van de Garde EM, Endeman H, Grutters JC, Bos WJ. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. The Lancet. 2011 Jun 11;377(9782):2023-30.

[68] Brun-Buisson C, Richard JC, Mercat A, Thiébaut AC, Brochard L. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. American journal of respiratory and critical care medicine. 2011 May 1;183(9):1200-6.

[69] Kitabayashi C, Fukada T, Kanamoto M, Ohashi W, Hojyo S, Atsumi T, Ueda N, Azuma I, Hirota H, Murakami M, Hirano T. Zinc suppresses Th17 development via inhibition of STAT3 activation. International immunology. 2010 May 1;22(5):375-86.

[70] Khosravani H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (COVID-19) pandemic. Stroke. 2020 Jun;51(6):1891-5.

[71] Lau CM, Adams NM, Geary CD, Weizman OE, Rapp M, Pritykin Y, Leslie CS, Sun JC. Epigenetic control of innate and adaptive immune memory. Nature immunology. 2018 Sep;19(9):963-72.

[72] Zharkova O, Celhar T, Cravens PD, Satterthwaite AB, Fairhurst AM, Davis LS. Pathways leading to an immunological disease: systemic lupus erythematosus. Rheumatology. 2017 Apr 1;56(suppl_1):i55-66.

[73] Gessani S, Conti L, Del Cornò M, Belardelli F. Type I interferons as regulators of human antigen presenting cell functions. Toxins. 2014 Jun;6(6):1696-723.

[74] Zhou Q, Chen V, Shannon CP, Wei XS, Xiang X, Wang X, Wang ZH, Tebbutt SJ, Kollmann TR, Fish EN. Interferon-α2b Treatment for COVID-19. Frontiers in Immunology. 2020 May 15;11:1061.

[75] Raundhal M, Morse C, Khare A, Oriss TB, Milosevic J, Trudeau J, Huff R, Pilewski J, Holguin F, Kolls J, Wenzel S. High IFN-γ and low SLPI mark severe asthma in mice and humans. The Journal of clinical investigation. 2015 Aug 3;125(8):3037-50.

[76] Lee SW, Chuang TY, Huang HH, Lee KF, Chen TT, Kao YH, Wu LS. Interferon gamma polymorphisms associated with susceptibility to tuberculosis in a Han Taiwanese population. Journal of Microbiology, Immunology and Infection. 2015 Aug 1;48(4):376-80.

[77] Sallakcı N, Coskun M, Berber Z, Gürkan F, Kocamaz H, Uysal G, Bhuju S, Yavuzer U, Singh M, Yeğin O. Interferon-γ gene+ 874T–A polymorphism is associated with tuberculosis and gamma interferon response. Tuberculosis. 2007 May 1;87(3):225-30.

[78] Wang W, Ye L, Ye L, Li B, Gao B, Zeng Y, Kong L, Fang X, Zheng H, Wu Z, She Y. Up-regulation of IL-6 and TNF-α induced by SARS-coronavirus spike protein in murine macrophages via NF-κB pathway. Virus research. 2007 Sep 1;128(1-2):1-8.

[79] Girija AS, Shankar EM, Larsson M. Could SARS-CoV-2-Induced Hyperinflammation Magnify the Severity of Coronavirus Disease (CoViD-19) Leading to Acute Respiratory Distress Syndrome?. Frontiers in Immunology. 2020 May 27;11:1206.

[80] Chen J, Wu Y, Yu J, Shen J. Association between tumor necrosis factor alpha rs1800629 polymorphism and risk of osteoarthritis in a Chinese population. Brazilian Journal of Medical and Biological Research. 2018;51(8).

[81] Meroni PL, Valentini G, Ayala F, Cattaneo A, Valesini G. New strategies to address the pharmacodynamics and pharmacokinetics of tumor necrosis factor (TNF) inhibitors: A systematic analysis. Autoimmunity reviews. 2015 Sep 1;14(9):812-29.

[82] Malaviya R, Laskin JD, Laskin DL. Anti-TNFα therapy in inflammatory lung diseases. Pharmacology & therapeutics. 2017 Dec 1;180:90-8.

[83] Atri C, Guerfali FZ, Laouini D. Role of human macrophage polarization in inflammation during infectious diseases. International journal of molecular sciences. 2018 Jun;19(6):1801.

[84] Bergamasco A, Hartmann N, Wallace L, Verpillat P. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. Clinical epidemiology. 2019;11:257.

[85] Yu M, Sandhu VK, Lezcano SD, Maken K, Kirk S, Torralba KD. Sarcoidosis and systemic sclerosis: strange bedfellows. Case reports in rheumatology. 2017 Oct;2017.

[86] Luangmonkong T, Suriguga S, Bigaeva E, Boersema M, Oosterhuis D, de Jong KP, Schuppan D, Mutsaers HA, Olinga P. Evaluating the antifibrotic potency of galunisertib in a human ex vivo model of liver fibrosis. British journal of pharmacology. 2017 Sep;174(18):3107-17.

[87] Pabst S, Fränken T, Schönau J, Stier S, Nickenig G, Meyer R, Skowasch D, Grohé C. Transforming

growth factor-β gene polymorphisms in different phenotypes of sarcoidosis. European Respiratory Journal. 2011 Jul 1;38(1):169-75.

[88] Vincenti F, Fervenza FC, Campbell KN, Diaz M, Gesualdo L, Nelson P, Praga M, Radhakrishnan J, Sellin L, Singh A, Thornley-Brown D. A phase 2, double-blind, placebo-controlled, randomized study of fresolimumab in patients with steroid-resistant primary focal segmental glomerulosclerosis. Kidney international reports. 2017 Sep 1;2(5):800-10.

[89] O'Garra A, Vieira P. TH 1 cells control themselves by producing interleukin-10. Nature Reviews Immunology. 2007 Jun;7(6):425-8.

[90] Li J, Wu S, Wang MR, Wang TT, Zhu JM. Association of the interleukin-10− 592A/C,− 1082G/A and− 819T/C gene polymorphisms with type 2 diabetes: A meta-analysis. Gene. 2013 Jun 1;521(2):211-6.

[91] Tarabay M, Elshazli R, Settin A. African vs. Caucasian and Asian difference for the association of interleukin-10 promotor polymorphisms with type 2 diabetes mellitus (a meta-analysis study). Meta gene. 2016 Sep 1;9:10-7.

[92] Asadullah K, Sterry W, Volk HD. Interleukin-10 therapy—review of a new approach. Pharmacological reviews. 2003 Jun 1;55(2):241-69.

[93] Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood, The Journal of the American Society of Hematology. 2011 Apr 7;117(14):3720-32.

[94] Pugin J, Ricou B, Steinberg KP, Suter PM, Martin TR. Proinflammatory activity in bronchoalveolar lavage fluids from patients with ARDS, a prominent role for interleukin-1. American journal of respiratory and critical care medicine. 1996 Jun;153(6):1850-6.

[95] Sönmez HE, Demir S, Bilginer Y, Özen S. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. Clinical Rheumatology. 2018 Dec 1;37(12):3329-35.

[96] Silfverswärd CJ, Penno H, Frost A, Nilsson O, Ljunggren Ö. Expression of markers of activity in cultured human osteoblasts: effects of interleukin-4 and interleukin-13. Scandinavian journal of clinical and laboratory investigation. 2010 Sep 1;70(5):338-42.

[97] Isidoro-García M, Dávila I, Laffond E, Moreno E, Lorente F, González-Sarmiento R. Interleukin-4 (IL4) and Interleukin-4 receptor (IL4RA) polymorphisms in asthma: a case control study. Clinical and Molecular Allergy. 2005 Dec 1;3(1):15.

[98] Castro M, Rabe KF, Corren J, Pavord ID, Katelaris CH, Tohda Y, Zhang B, Rice MS, Maroni J, Rowe P, Pirozzi G. Dupilumab improves lung function in patients with uncontrolled, moderate-to-severe asthma. ERJ open research. 2020 Jan 1;6(1).

[99] Huang HT, Lu YL, Wang R, Qin HM, Wang CF, Wang JL, Xiang Y, Guo J, Lan Y, Wei YS. The association of IL-17A polymorphisms with IL-17A serum levels and risk of ischemic stroke. Oncotarget. 2017 Nov 28;8(61):103499.

[100] Sabry D, Aboraia N, Samir M. A potential association between psoriasin to rs4819554 of IL-17RA gene polymorphism in psoriasis Egyptian patients. Archives of Dermatological Research. 2019 Nov 19:1-9.

[101] Huang KJ, Su IJ, Theron M, Wu YC, Lai SK, Liu CC, Lei HY. An interferon-γ-related cytokine storm in SARS patients. Journal of medical virology. 2005 Feb;75(2):185-94.

[102] Vankadari N. Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking the trimerization of viral spike glycoprotein?. International Journal of Antimicrobial Agents. 2020 Apr 28:105998.

[103] Ozsvari B, Nuttall JR, Sotgia F, Lisanti MP. Azithromycin and Roxithromycin define a new family of "senolytic" drugs that target senescent human fibroblasts. Aging (Albany NY). 2018 Nov;10(11):3294.

[104] Li F, Xu J, Zheng J, Sokolove J, Zhu K, Zhang Y, Sun H, Evangelou E, Pan Z. Association between interleukin-6 gene polymorphisms and rheumatoid arthritis in Chinese Han population: a case-control study and a meta-analysis. Scientific reports. 2014 Jul 17;4:5714.

[105] Wang J, Fan N, Deng Y, Zhu J, Mei J, Chen Y, Yang H. Association between genetic polymorphisms of interleukins and cerebral infarction risk: a meta-analysis. Bioscience reports. 2016 Dec 1;36(6).

[106] Amr K, El-Awady R, Raslan H. Assessment of the− 174G/C (rs1800795) and− 572G/C (rs1800796) interleukin 6 gene polymorphisms in Egyptian patients with rheumatoid arthritis. Open access Macedonian journal of medical sciences. 2016 Dec 15;4(4):574.

[107] Settin A, Zedan M, Farag M, El Regal ME, Osman E. Gene polymorphisms of IL-6− 174 G/C and IL-1Ra VNTR in asthmatic children. The Indian Journal of Pediatrics. 2008 Oct 1;75(10):1019-23.

[108] Michot JM, Albiges L, Chaput N, Saada V, Pommeret F, Griscelli F, Balleyguier C, Besse B, Marabelle A, Netzer F, Merad M. Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. Annals of Oncology. 2020 Apr 2.

[109]Hemilä H. Vitamin C and SARS coronavirus. Journal of Antimicrobial Chemotherapy. 2003 Dec 1;52(6):1049-50.

[110]Prasad AS, Miale Jr A, Farid Z, Sandstead HH, Schulert AR. Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypogonadism. Journal of Laboratory and Clinical Medicine. 1963;61(4):537-49.

[111]Aydemir TB, Chang SM, Guthrie GJ, Maki AB, Ryu MS, Karabiyik A, Cousins RJ. Zinc transporter ZIP14 functions in hepatic zinc, iron and glucose homeostasis during the innate immune response (endotoxemia). PloS one. 2012 Oct 24;7(10):e48679.

[112]Naing A, Kyriakos P et al " Safety, Antitumor Activity, and Immune Activation of Pegylated Recombinant Human Interleukin-10 (AM0010) in Patients With Advanced Solid Tumors" J Clin Oncol, 2016, 34(29): 3562-3569 .

[113]Haase H, Rink L" Multiple impacts of zinc on immune function" Metall. Integr. Biometal Sci, 2014, 6:1175–1180 .

[114]Lazzerini M, Wanzira H " Oral zinc for treating diarrhoea in children" Cochrane Database Syst. Rev, 2016,12(12):CD005436.

[115]Gammoh NZ, Rink L " Zinc in Infection and Inflammation" Nutrients, 2017,9(6):624.

[116]Berg K, Bolt G et al " Zinc potentiates the antiviral action of human IFN-α tenfold" J Interferon Cytokine Res, 2001, 21(7):471–4.

[117]Xiong Y, Luo DJ, et al " Zinc binds to and directly inhibits protein phosphatase 2A in vitro" Neurosci Bull, 2015,31:331–7.

[118]Marik PE " Vitamin C for the treatment of sepsis: the scientific rationale" Pharmacol. Therapeut, 2018, 189:63–70.

[119]Boretti A, Banik BK " Intravenous Vitamin C for reduction of cytokines storm in Acute Respiratory Distress Syndrome" PharmaNutrition, 2020,12:100190.

[120]Maggini S, Pierre A et al, " Immune Function and Micronutrient Requirements Change over the Life Course" Nutrients, 2018, 10(10):1531.

[121]Tsurikisawa N, Oshikata C, et al " Bronchial reactivity to histamine is correlated with airway remodeling in adults with moderate to severe asthma" J Asthma, 2010,47(8):841-848.

[122]Hemilä H, Chalker E "17,000 mg/day vitamin C given intravenously shortened intensive care unit stay by 44%" Nutrients, 2019,11(4):708

[123]Dey S, Bishayi B" Killing of S. aureus in murine peritoneal macrophages by ascorbic acid along with antibiotics chloramphenicol or ofloxacin: correlation with inflammation" Microb. Pathog, 2018,115:239–250.

[124]Oskresenska N, Voicehovska J et al " Glutathione level in community-acquired pneumonia patients" Eur. Respir. J, 2017,50

[125]Zhang Q, Ju Y, Ma Y, Wang T. N-acetylcysteine improves oxidative stress and inflammatory response in patients with community-acquired pneumonia: A randomized controlled trial. Medicine (Baltimore). 2018,97(45):e13087.

[126]Glinsky GV " Tripartite Combination of Candidate Pandemic Mitigation Agents: Vitamin D, Quercetin, and Estradiol Manifest Properties of Medicinal Agents for Targeted Mitigation of the COVID-19 Pandemic Defined by Genomics-Guided Tracing of SARS-CoV-2 Targets in Human Cells" Biomedicines, 2020, 8(5):129.

[127]Sun L, Shen L, et al " Clinical features of patients with coronavirus disease 2019 from a designated hospital in Beijing" China J Med Virol, 2020,10.

[128]Colson P, Rolain JM et al " Chloroquine for the 2019 novel coronavirus SARS-CoV-2" Int J Antimicrob Agents, 2020,55(3):105923.

[129]Touret F, de Lamballerie X " Of chloroquine and COVID-19" Antiviral Res, 2020, 177:104762.

[130]Canalis E, Mazziotti G et al "Glucortiocid-induced osteoporosis: pathophysiology and therapy" Osteoporos Int, 2007,18:1319–28.

[131]Di Filippo L, Formenti AM et al "Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19" Endocrine, 2020, 68(3):475-478.

[132]Tocilizumab in COVID-19 Pneumonia (TOCIVID-19).Clinical Trials. gov identifier: NCT04317092. https://www.clinicaltrials.gov/ct2/show/NCT04317092. Updated March 20,2020. Accessed March 21, 2020.

[133]Horowitz RI, Freeman PR et al "Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases" Respir Med Case Rep, 2020, 30: 101063.

Table 1. Different cytokines polymorphisms and their effects on different populations' health with suggesting therapies

Cytokines	SNP	Allele	Effect, disease		Suggesting Immunomodulatory therapy	References
IFN	rs2430561	874A/T	low expression, autoimmune diseases and infectious disease (TB)	Chinese	IFN-α2b	[73-77]
		T allele	Tuberculosis	Caucasian, Latin American, and Middle Eastern		
		A allele	low expression of IFN-γ COVID19	Chinese		
TNF-α			alveolar macrophage and severity in SARS, COVID19	Chinese	Certolizumab, Etanercept	[78-82]
	rs1800629	−308G/A	Osteoarthritis	Asians and Caucasians		
TGF-β3	rs3917200 rs1891467	G carrier	lung fibrosis in sarcoidosis patients	German	Fresolimumab	[87, 88]
IL-10	rs1800872	− 592 C > A	IL-10 transcription and secretion, chronic kidney disease, T2DM	Asians and Caucasians	AM0010, a pegylated recombinant IL-10 recombinant human & (ilodecakin/Tenovil)	[92,93]
	rs1800896	− 1082 A > G				
	rs1800871	− 819 C > T		African but not in European and Asian subjects		
	polymorphic microsatellite markers in the human IL-10 promoter IL10.G and IL10.R		Deficiency of IL-10, Psoriosis			
IL-1β		−899C/T	increased the risk of cerebral infarction	Asian population	Anakinra	[95]
IL-4		high prevalence of T allele of -33C>TIL4 and the A allele of 576Q>RIL4RA	increasing the IL-4 level in asthma	South European	Dupilumab	[97, 98]
IL-6		−572C/G and −174G/C	increased the cerebral infarction risk	Asians	] Tocilizumab (Actemra)	[104]
	rs1800795	*IL6–174G/C* guanine (G) to cytosine (C) at positions −174 at promotor	C allele increases risk of rheumatoid arthritis, asthma	Egyptian		[107, 108]
IL-17A	rs2275913 and rs8193036	G and T carriers	Ischemic stroke and acute respiratory distress syndrome	USA and China	Cosentyx	[105]
	rs4819554	- 947 A/G	A carriers have high IL-17 Psoriosis	Egypt		[106]