



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 million worldwide. 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-CoV-2, 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 Kawasaki 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, Neutrophils, 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 TGF β 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 (IFN γ) 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-1 β 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 autoimmune 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 need 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- α 2b 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- β 3 (rs3917200) while G carriers in TGF- β 2 (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, β 1, β 2, and β 3, 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 Psoriatic patients with IL-10 deficiency. Also, the high efficiency of AM0010, a pegylated recombinant IL-10 in the treatment of cancer patients was noted [90-92].

Interleukin 1 β (IL-1 β) is a prominent cytokine that is generated in the early stage of microbial infections by the cleavage action of caspase-1 on pro-IL-1 β in inflammasomes. Binding of IL-1 β 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-1 β is a key cytokine driving proinflammatory activity in bronchoalveolar lavage fluid of patients with lung injury. IL-1 α -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-1 β , 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 C in 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 C reduces 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 C in: 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-1 β , 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 Tocilizumab plus 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, and 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.

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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- α 2b	[73-77]
		T allele	Tuberculosis	Caucasian, Latin American, and Middle Eastern		
		A allele	low expression of IFN- γ COVID19	Chinese		
TNF- α	rs1800629		alveolar macrophage and severity in SARS, COVID19	Chinese	Certolizumab, Etanercept	[78-82]
		-308G/A	Osteoarthritis	Asians and Caucasians		
TGF- β 3	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		African but not in European and Asian subjects		
	rs1800871	- 819 C > T				
	polymorphic microsatellite markers in the human IL-10 promoter IL10.G and IL10.R		Deficiency of IL-10, Psoriasis			
IL-1 β		-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>RIL4R A	increasing the IL-4 level in asthma	South European	Dupilumab	[97, 98]
IL-6	rs1800795	-572C/G and -174G/C	increased the cerebral infarction risk	Asians] Tocilizumab (Actemra)	[104]
		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 Psoriasis	Egypt		[106]