Clinical Rheumatology (2020) 39:3223–3235
https://doi.org/10.1007/s10067-020-05376-x

REVIEW ARTICLE

The potential similarities of COVID-19 and autoimmune disease pathogenesis and therapeutic options: new insights approach

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Received: 13 July 2020 / Revised: 23 August 2020 / Accepted: 27 August 2020 / Published online: 3 September 2020

Abstract

Cytokine pathways and their signaling disorders can be the cause of onset and pathogenesis of many diseases such as autoimmune diseases and COVID-19 infection. Autoimmune patients may be at higher risk of developing infection due to the impaired immune responses, the use of immunosuppressive drugs, and damage to various organs. Increased secretion of inflammatory cytokines and intolerance of the patient's immune system to COVID-19 infection are the leading causes of hospitalization of these patients. The content used in this paper has been taken from English language articles (2005–2020) retrieved from the PubMed database and Google Scholar search engine using "COVID-19," "Autoimmune disease," "Therapeutic," "Pathogenesis," and "Pathway" keywords. The emergence of COVID-19 and its association with autoimmune disorders is a major challenge in the management of these diseases. The results showed that the use of corticosteroids in the treatment of autoimmune diseases can make diagnosis and treatment of COVID-19 more challenging by preventing the fever. Due to the common pathogenesis of COVID-19 and autoimmune diseases, the use of autoimmune drugs as a possible treatment option could help control the virus.

Key Points

- *Inflammatory cytokines play an essential role in the pathogenesis of COVID-19*
- *ACE2 dysfunctions are related to the with COVID-19 and autoimmune diseases*
- *The use autoimmune diseases drugs can be useful in treating COVID-19*

Keywords Autoimmune disease · COVID-19 · Pathogenesis · Pathway · Therapeutic

Introduction

Coronavirus disease 2019 (COVID-19) belongs to the Coronaviridae family, amid the outbreak of the virus in Wuhan, China, in late December 2019, which quickly became pandemic in many countries [1, 2]. The virus targets the human respiratory system, leading to severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS), which has a relatively high mortality rate [3]. Infection with the virus alters leukocyte counts, impairs liver

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enzyme function, and increases plasma inflammatory cytokines [4]. Cytokines are the primary regulators of the immune system, and increased production of inflammatory cytokines leads to the deregulation of the immune system and immunopathology. The cytokine storm syndrome in people with COVID-19 can lead to other disorders including autoimmune diseases (ADs) [5]. ADs are a set of chronic diseases that inadvertently activate the immune system against self-antigens and various organs of the body, leading to inflammation and tissue damage in patients [6]. Continuous production of cytokines leads to the loss of tolerance to self-antigens, which causes ADs and worsens the condition in ADs patients [7, 8]. Due to the undeniable role of inflammatory cytokines in patients with ADs, COVID-19 can be cured through a treatment plan aiming to inhibit the over-activation of the immune system and control of cytokine production [9]. In this paper, we review the pathogenesis and therapeutic similarities of COVID-19 patients and several autoimmune diseases including multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and diabetes mellitus (DM). We have also evaluated the therapeutic challenges associated with autoimmune diseases and their use in controlling the clinical condition of COVID-19 patients. This study uses recently published articles on the COVID-19 research as well as articles on the treatment options for patients with autoimmune diseases.

Systemic lupus erythematosus (SLE)

The similarity of pathogenesis with COVID-19

SLE is a chronic autoimmune disease that can affect many organs, especially the skin, joints, kidneys, and CNS [10]. Infection is one of the leading causes of death in SLE patients [11]. Approximately 30% of deaths in SLE are associated with infections, of which respiratory infections are the most common [12, 13]. SLE patients with higher levels of IL-17, IFN-γ, and IL-23 are more likely to develop severe clinical conditions [14]. As a key factor in the pathogenesis of SLE, Th17 is not only a source of IFN-γ secretion but also by producing IL-23 and IL-17 leads to kidney problems in people with the disease [15]. According to studies, kidney problems have been observed not only in SLE patients but also in people with COVID-19. These complications can be caused by an increase in inflammatory cytokines. It has been shown that the rate of inflammatory cytokines in COVID-19 patients admitted to the ICU to be higher than in patients with better clinical status [16, 17].

Th2, Th17 and follicular helper T (Tfh) are subgroups of $CD4^+$ Th. The increase in $CD4^+$ T cells is associated with an increase in Th17 and memory B cells in SLE patients [18]. These findings suggest that Th17 and Tfh may be involved in the pathogenesis of autoimmune diseases. The Tfh is a new class of Th cells that helps B cells to generate a germinal center and produce high-affinity B cells [19]. Recently, Tfh cells have been shown to increase in SLE patients, but no increase in Th17 has been observed. Also, autoimmune patients show changes in the circulating Tfh (cTfh) phenotype. cTfh2 and cTfh17 which are shown to be elevated in SLE patients are characterized by the secretion of interleukin-21 (IL-21) [20, 21]. IL-21 promotes differentiation of Th17 and induction of inflammatory conditions, thereby inducing B cell production. Tfh2 and Tfh17 are thought to be involved in the production of autoantibodies from germinal center B cells [22]. According to this finding, the examination of these cells in COVID 19 patients can be useful in identifying the pathogenesis of this disease.

IL-17 mediates kidney tissue damage by inducing G-CSF, which is responsible for granulopoiesis and neutrophil production. Also, IL-21 produced by Th17 induces Th17 differentiation in a STAT3-dependent manner, and IL-22 secreted by the same cells plays a key role in the pathogenesis of COVID-19 and SLE by regulating anti-apoptotic proteins, serum amyloid A (SAA) level, and fibrinogen production [23, 24]. SAA, which is an acute phase marker, increases in the serum due to inflammation and infection and is shown to be moderately increased in viral infections and SLE patients [25, 26]. It has recently been identified that SAA activity and signaling are regulated through TLR2 signaling. IL-22 activates STAT3 by binding to its receptor on the surface of hepatocytes and directly leads to the production of SAA. On the other hand, it can indirectly lead to the production of SAA by inducing the expression of various cytokines [27]. The accumulation of nuclear antigens and the production of antibodies against them lead to vascular damage in SLE patients. Also, it is shown that SAA plays a key role in developing vascular damage [28, 29]. One study found that the serum SAA level was higher than average in patients with COVID-19, and the use of anti-SAA drugs may be beneficial to the patients [30]. Findings confirmed SAA as an important prognostic and diagnostic marker in inflammation and autoimmune diseases [31], and its pharmacological inhibition may improve the clinical condition in COVID-19 patients.

Procoagulant changes, such as changes in serum fibrinogen levels, have been reported in SLE and COVID-19 patients [32]. Inflammation in COVID-19 patients, in addition to increased inflammatory cytokines, is also due to an increase in fibrinogen levels [33]. In one study, fibrinogen levels in unsurvived COVID-19 patients decreased; however, in another study, serum fibrinogen and IL6 levels were higher in patients than in healthy subjects [34]. IL-6 is the primary regulator of fibrinogen synthesis and the increase of which is associated with an increase in the fibrinogen level in the serum. In essence, inflammation and coagulation are related [35, 36], and abnormal coagulation tests have been observed in SLE and COVID-19 patients. From this point of view, monitoring of COVID-19 patients can be useful in the disease prognosis.

Angiotensin-converting enzyme 2 (ACE2) is a COVID-19 receptor on the surface of endothelial cells, which is also expressed in many organs such as the kidneys and lungs. Viral infection with this receptor infects the tissue and increases cell death in the area [37, 38]. It has recently been reported that SLE patients with higher levels of ACE2 are more susceptible to COVID-19 infection [39]. Viral particles present in the endothelial cells can induce apoptosis by accumulating inflammatory cells in that area. One of the critical factors in SLE patients is the improper function of the apoptosis mechanism. Many factors associated with SLE pathogenesis, such as infections and toxins, can lead to increased apoptosis of infected cells. During apoptosis, nuclear antigens become available to the immune system and lead to increased production of antibodies and cytokines. These cytokines cause cell death by accumulating in the cell [40–44]. One study found that lymphopenia in COVID-19 patients could be due to the induction of apoptosis and the P53 signaling pathway. Interestingly, in another study, the TP53 gene, an important factor in apoptosis, was increased in two patients with COVID-19 [45]. COVID-19 can prevent apoptosis by reducing TGF-β signaling, which plays a key role in apoptosis and cell differentiation, leading to differentiation of fibroblasts and lung damage [46, 47]. Cytokine storms through T cell apoptosis mediated by IFN-I (Type I interferon) dampen the immune system and cause lymphopenia (reducing CD8 and CD4 T cells) [48]. IFN-γ stimulation also reduces ATP in T cells and induces T cell apoptosis [49].

The onset of cytokine storms is associated with increased apoptosis in the lung and kidney in people with COVID-19. It has been shown that receptors that detect nucleic acids also detect viral pathogens [41], and the over-availability of nucleic acids due to apoptosis reduces the effectiveness of virus recognition by these receptors. In general, these findings indicate the key role of cytokines and apoptosis mechanisms in renal and pulmonary lesions in COVID-19 and SLE patients, and it is possible to improve the clinical conditions of these patients by blocking the cell cytokine receptors of the target organ and controlling cytokine-producing cells.

Common therapeutic pathway

While a vaccine against COVID-19 takes time to develop, it is possible to use drugs intended to use in diseases with similar pathogenesis or clinical signs. For example, anti-IL-17 or anti-IL17R can inhibit Th17 cell function and its effects, or RORγt inhibitors can block Th17 cell differentiation [23]. STAT3 plays a role in Th17 cell differentiation, and IL-6 and IL-23 activate this transcription factor through JAK2 and JAK1. Regulating JAK2, which is a bridge to differentiation and function of Th17 cells, can have a positive effect on the clinical condition of SLE and COVID-19 patients [50]. Fedratinib is a JAK2-specific inhibitor that inhibits the production of cytokines by Th17. Interestingly, this drug does not jeopardize the function of B cells and the secretion of its cytokines. JAK2 is also involved in the activation of GM-CSF signaling and can limit its function [23].

ACE2 inhibitors can be beneficial to autoimmune patients who are more susceptible to infection by preventing organ damage [38]. As inflammatory cytokines, such as IFN-I, have been implicated in the apoptosis of T cells, this process is associated with a decreased level of cyclic-adenosine monophosphate (c-AMP) in these cells. Decreased ATP level makes the cell more vulnerable to harmful agents and can impair the immune system [51–53]. Increased c-AMP with effect on P38/JNK/ATF-2 signaling pathway enhances IFN secretion against COVID-19 [54]. The JAK/STAT signaling pathway plays a key role in the regulation of the immune system. When IFN-I binds to its receptor, JAK, as an ATP-dependent enzyme, activates STAT through phosphorylation [55]. So low levels of ATP can reduce the immune responses, especially in defense against viruses, by increasing the apoptosis of T cells. IFN-I receptor inhibition prevents abnormal immune responses in lupus patients [56]. Anifrolumab is a monoclonal antibody that inhibits IFN-I signaling by binding to the IFN-I receptor [57]. A study has shown that the use of anifrolumab is practical and useful in controlling the complications of SLE (Table 1) [58]. Unlike corticosteroids, anifrolumab can be beneficial to the patient's immune system by protecting patients against viral infections and retaining the strength of the immune responses. We hypothesize that the use of anifrolumab in COVID-19 patients can prevent further damage to the patient's internal organs, especially the lungs, by controlling the inflammatory condition.

Studies have shown that the drug chloroquine (CQ) can interfere with the glycosylation of the ACE2 by binding to the virus and inhibiting respiratory syndrome in COVID-19 patients. Hydroxychloroquine (HCQ) is an anti-malarial drug commonly used for the treatment of skin inflammation in SLE patients. HCQ regulates the immune system and its anti-thrombotic and anti-inflammatory properties in SLE patients [59–61]. HCQ has fewer side effects and more clinical benefits than CQ, and it can act against COVID-19 in in vitro conditions. It is shown that HCQ could not protect SLE patients from COVID-19 infection [62, 63]. There is no evidence that SLE patients develop a more severe phenotype of COVID-19, and also the therapeutic effect of HCQ in eliminating COVID-19 has not been confirmed. However, epigenetic changes, such as an increase in ACE2 expression, may increase the risk of COVID-19 in SLE patients. Modulating the secretion and effects of inflammatory cytokines by drugs used in the treatment of SLE, as well as examining the course of apoptosis, could be a way to treat patients with COVID-19 in the future.

Table 1 The effect of some autoimmune disease drugs on the clinical course of patients with COVID-19

Autoimmune diseases	medicines	Drug function	Response in autoimmune patients	Possible response in COVID-19 patients	Ref.
Multiple sclerosis	Ocrelizumab and rituximab	Anti-CD20 in B cells	Good	Good (due to the reduction of interleukins produced by B cells)	[154–156]
	Alemtuzumab	Anti-CD52 in T and NK cells	Good	cannot be good (due to the removal of T cells, which are a defense barrier against the virus)	[138, 140]
	Tocilizumab	IL-6 receptor blocker	Good	Good (due to the reduced risk of cytokine storms)	[141]
	IFN-β and glatiramer acetate	Anti-inflammatory mechanism and increased production of cytokine by TH2	Good	It can be both good and bad)due to the antiviral properties and induction of IL10 secretion, stimulation of the immune system and)	[131, 146]
	Etanercept	Connect to TNFα	Cannot be good	Good (due to the reduced risk of cytokine storms)	[150]
	Natalizumab	Antibody against CD49d on the surface of leukocytes	Good	Good (due to the restriction of binding and transfer of leukocytes)	[157]
Systemic lupus erythematosus	Fedratinib	JAK2 dedicated inhibitor	Good	Good (due to the reduced risk of cytokine storms)	[23, 158]
	Anifrolumab	Antibody against IFN-α receptor	Good	Good (due to the reduced risk of cytokine storms)	[57, 58]
	Chloroquine and hydroxychloroquine	Connecting to malaria DNA and interfering with protein production	Good	Good (interference with glycosylation of the ACE2 and reduced risk of cytokine storms)	[159]
	Belimumab	Antibody against soluble B lymphocyte stimulator	Good	Good (prevents the production of inflammatory cytokines from B cell)	[39, 160]
Rheumatoid arthritis	Tocilizumab and sarilumab	Anti-IL-6 receptor antibody	Good	Good (inhibits the binding of IL-6 to its receptors and reduces the cytokines pro-inflammatory activity)	[161, 162]
	Quinapril and ramipril	By inhibiting NF-κB activity, it leads to inhibition of ACE	Good	Good (due to the prevention of angiotensin II production and its inflammatory effects)	[89, 163]
Diabetes mellitus	Thiazolinediones (rosiglitazone and pioglitazone)	By activating the PPAR-γ without increasing the secretion of endogenous insulin, it amplifies insulin receptors	Good	Cannot be good (because of the stimulus ACE2)	[164, 165]
	Metformin	Activates AMPK by phosphorylation	Good	Good (by phosphorylation of ACE2 can reduce the binding of the virus to it)	[166]
	Liraglutide	It is an agonist of the GLP1 receptor and leads to insulin secretion	Good	Cannot be good (because it leads to increased expression of ACE2 and viral load in the cell)	[167, 168]

PPAR-γ peroxisome proliferator-activated receptor gamma, *AMPK* AMP-activated protein kinase, *GLP1* glucagon-like peptide-1, *NK* natural killer cell, *IFN-β* interferon-beta, *TNFα* tumor necrosis factor-alpha, *ACE2* angiotensin-converting enzyme 2, *NF-kB* nuclear factor-kappa B, *JAK2* Janus kinase 2

Rheumatoid *arthritis (RA)*

The similarity of pathogenesis with COVID-19

RA patients are at a higher risk of infection with the COVID-19 virus than healthy subjects are. RA is an immune system disorder, in which patients received immunosuppressive agents that increase the risk of developing viral infections [64]. The migration of white blood cells to the synovium causes pain, inflammation, dryness, and decreased joint function in RA patients [65]. Scientists have not yet found the cause of immune system dysfunction in RA; however, factors including genetic factors, environmental factors such as viral and bacterial infections (especially in genetically susceptible individuals), and hormonal factors play roles in causing impaired immune responses [66, 67]. Genetic predisposition is responsible for 60% of the RA incidence [65]. ACE2 converts angiotensin II (an effective peptide associated with vascular and inflammatory biology) to angiotensin-1-7 [68]. Angiotensin II uses JAK to initiate activity through the Ras/Raf/MAPK signaling pathway [69]. In inflammatory conditions, angiotensin II stimulates the production of prostaglandins and vascular endothelial cell growth factor (VEGF), thereby triggering inflammatory responses and vascular permeability [70]. This inflammatory mediator activates transcription factor nuclear factor-κB (NF-κB) and increases the infiltration of inflammatory cells in damaged tissues [71]. Angiotensin II enhances the expression of TNF-α and IL-6 genes in endothelial cells, macrophages, and cardiac fibroblasts and increases C-reactive protein (CRP) [72, 73]. Patients with the flu virus have been shown to have increased angiotensin II levels [74]. In a study using ACE2−/− mice, it is shown that ACE2 can prevent acute lung damage by converting angiotensin II to angiotensin-1-7 and reducing inflammatory effects [75]. The use of recombinant ACE2 can also be useful in preventing lung damage associated with SARS-COV2 [75, 76]. SARS-COV2 increases the production of angiotensin II, decreases vascular permeability, and increases lung damage by downregulation of ACE2 expression. Decreasing ACE2 and the persistence of angiotensin II increases the risk of further lung damage in ARDS patients, and the use of ACE2 inhibitors may increase the severity of COVID-19 clinical conditions in RA patients.

ACE converts angiotensin I to angiotensin II [68]. Inflammatory mechanisms in synovial RA patients may involve endothelial cells and the development of atherosclerotic lesions, in which the use of ACE inhibitors in these patients can improve vascular endothelial function due to the lack of angiotensin II production. [73, 77, 78]. Given the role of ACE2 and ACE in the pathogenesis of RA and COVID-19, further genetic research on these two important inflammatory mediators can provide more information about their biological roles in COVID-19 pathogenesis. The study of ACE2 in virus-infected patients shows that reducing this receptor is not beneficial because it enhanced angiotensin II effects, but decreased ACE can be effective in improving the clinical conditions in RA patients by reducing angiotensin II. An important point to clarify is the role of genetic factors in increasing the risk of COVID-19 in RA patients. ACE2 gene polymorphisms may play a role in worsening the condition of patients infected with the virus [79]. In general, polymorphisms in the ACE2 gene may be present in COVID-19 patients with severe clinical conditions. Therefore ACE2 gene polymorphism can be considered as a prognostic factor.

Common therapeutic pathway

In patients with arthritis, infection is a major concern that can ignite the development of the disease [80]. Although corticosteroids are effective in suppressing inflammation in RA, their side effects and increased incidence of infection are common [81, 82]. One study found that the rate of infection was higher in RA patients treated with corticosteroids [83]. Corticosteroids act by suppressing the host's immune responses and regulating the inflammatory conditions caused by the cytokine storm that triggers viral infections of the respiratory tract and develops ARDS [84]. In general, there is no evidence why corticosteroids may be beneficial to COVID-19 patients, and the use of corticosteroids is still controversial [64].

Given that ACE activity is higher in RA patients and ACE2 is the main receptor for COVID-19 [77], ACE inhibitors can inhibit the production of inflammatory cytokines by monocytes and dendritic cells by inhibiting NF-κB activity [85, 86]. Angiotensin II is produced in monocytes and macrophages by expressing ACE [87]. Quinapril is an ACE inhibitor used in cardiovascular diseases to prevent elevated angiotensin II levels and inflammatory reactions. It can also inhibit the production of TNFα from monocytes [88–90] (Table 1). Based on the anti-inflammatory function of this drug and the important role of ACE2 in COVID-19 pathogenesis, it can be hypothesized that the use of quinapril in these patients could be a new treatment strategy. Also, the use of angiotensin II receptor antagonists or other cytokine inflammatory receptors can help control cytokine release syndrome.

Diabetes mellitus (DM)

The similarity of pathogenesis with COVID-19

DM is divided into two types: insulin-dependent diabetes mellitus (IDDM, type 1) and non-insulin-dependent diabetes mellitus (NIDDM, type 2), which, in most cases, both have an autoimmune origin [91–93]. DM is the most common type of diabetes, and the pathogenesis of this disease is complicated because many factors have roles in developing this disorder.

For example, the production of antibodies against pancreatic islet cells causes these cells to function abnormally and increases blood sugar levels [94]. On the other hand, abnormalities in organs such as the liver, adipose tissue, and skeletal muscle are also responsible for developing DM. Impaired insulin secretion, decreased sensitivity of target tissues, and increased liver glucose production are three metabolic abnormalities in DM [95]. In this disease, the functions of neutrophils and Th1 cells, chemotaxis, phagocytosis, and intracellular killing are impaired, and a defect in the immune responses is observed [96]. Due to these abnormalities, patients with diabetes are at higher risk of infections, especially respiratory infections, in which glycemic control can reduce the risk of infection [97]. DM patients are more prone to SARS-COV2 infection, and clearance of this virus appears to be difficult in infected patients [98]. A study of COVID-19 patients in Wuhan found that 42.3% of the 26 deaths were in diabetic patients [99].

Dietary fats activate toll-like receptor signaling 2 and 4 (TLR2 ad TLR4) and trigger endoplasmic reticulum stress (ERS). TLR signaling increases the secretion of inflammatory cytokines by inducing transcription of inflammatory genes. On the other hand, TLR2 and TLR4 increase the activity of the intracellular serine tyrosine kinase, which inhibits insulin signaling through this mechanism [100–102]. As a result, obesity is a major cause of insulin resistance, which induces ERS to activate inflammatory mediators and disrupt insulin production from pancreatic islet cells [102, 103]. Plasma glucose levels increase with insulin production. Decreased tissue sensitivity to insulin leads to a compensatory rise in insulin secretion from pancreatic islet cells, but due to the resistance of target tissues to this hormone, blood sugar remains high. This process leads to hyperinsulinemia and hyperglycemia in DM patients [104, 105]. The risk of COVID-19 infection and DM is higher in obese patients and people on a high-fat diet due to continuous inflammatory activity, inappropriate activation of the immune system, and involvement of macrophages and TNF-α in these conditions [106, 107]. Obesity is considered a risk factor in COVID-19 patients due to its detrimental effects on the clinical condition of patients and its complications, such as pulmonary dysfunction [108]. Modulating blood sugar levels in obese people can be a way to reduce their risk of developing DM and COVID-19 infection.

Common therapeutic pathway

ACE2 expression is increased in diabetes, and this increased expression can enhance the risk of COVID-19 infection. It is also hypothesized that the treatment of diabetes with ACE2 stimulants such as thiazolidinediones could increase the risk of COVID-19 (Table 1). Proof of this hypothesis requires further research because, as mentioned, ACE2 reduces inflammation by converting angiotensin II and has recently been proposed as a new treatment for inflammatory diseases of the lungs, diabetes, and cancer [79]. ACE2 is elevated in the lungs, heart, and kidneys of all DM patients, and insulin injection reduces its expression [109, 110]. ADAM metallopeptidase domain 17 (ADAM17) increases ACE2 in the urine of diabetic mice; however, insulin and rosiglitazone inhibit its expression [111–113]. Also, a diet high in sodium lowers ACE activity and thus reduces its inflammatory effects [114]. In a study of the H1N1 virus, it was shown that zinc nanoparticles reduce viral load [115]. The use of this method may also be effective in reducing the side effects of COVID-19. Elimination or inhibition of ACE2 activity leads to renal impairment and increased inflammatory cytokines [116–120]. The mechanism of reduction of ACE2 by COVID-19 is not known, but following this reduction, the inflammatory complications of angiotensin II can damage various organs of the patient. Ibuprofen causes excessive expression of ACE2 in diabetic mice, which may play a role in worsening the clinical conditions of COVID-19 patients [121]. Due to hyperinsulinemia in DM, it can be stated that the same increase in insulin and decrease in ACE2 can lead to an increase in angiotensin II and worsen the inflammatory conditions. On the other hand, increased expression of angiotensin II reduces the expression of the COVID-19 receptors, leading to the proper control of the virus. In general, ACE, angiotensin I and II blockers can be considered an appropriate treatment for diabetic patients by modulating (RAS) renin-angiotensin system [122, 123].

Multiple sclerosis (MS)

The similarity of pathogenesis with COVID-19

MS is a chronic and often progressive inflammatory disease of the central nervous system (CNS) that results in the loss of myelin sheath due to autoimmune reactions [124]. Pathogenesis of the disease has not yet been elucidated, but studies show that immune and inflammatory reactions lead to damage to the nervous system. In principle, the migration of lymphocytes across the blood-brain barrier causes inflammation in the CNS and lymphopenia in the peripheral blood [125]. Also, a significant increase in inflammatory cytokine levels such as IFN-γ, IL-12, TNF-α, and IL-17 in serum and cerebrospinal fluid (CSF) of MS patients has been reported. The increased levels of these cytokines are associated with the migration of lymphocytes from lymphoid tissues, especially T helper cells, Th1, and Th17, which produce various inflammatory cytokines [126]. IL-6 and TGF-β induce IL-17 and IL-21 secretion by stimulating the differentiation of Th17 cells through signal transducer and activator of transcription 3 (STAT3) activation [127, 128]. On the other hand, IL-21 through the activation of the STAT3 pathway induces IL-17 secretion from Th17 cells which acts in an autocrine feedback

loop [129, 130]. IL-17 and osteopontin play important roles in MS pathogenesis [131]. Osteopontin induces IFN-γ and IL-12 secretion from macrophages [132, 133]. Recent studies have shown that serum levels of osteopontin have increased in patients with MS [134, 135]. Also, the elevated levels of IFN-γ and IL-12 in CSF were associated with an increase in Th1 cells in these patients [136]. In COVID-19 patients, as in MS patients, the rate of inflammatory cytokines increases, leading to shortness of the breathe [17]. Elevation of Th17 in COVID-19 patients, which promotes the differentiation of immune cells and the regulation of inflammatory conditions by producing IL6 and IL23, indicates the vital role of this cell in the development of cytokine storm [137].

Common therapeutic pathway

It is not yet known whether people with MS are at higher risk of COVID-19 infection than healthy people, or if they develop more acute conditions after it. Sometimes a specific infection can make clinical symptoms worse in MS patients, thereby making treatment decisions of these patients challenging [138]. Corticosteroids, which are used as a therapeutic option in MS patients, suppress the immune system and result in many infections in these patients. Therefore, MS patients should be screened for COVID-19 before receiving corticosteroids. However, there is a theory that suppression of the immune system may play a protective role against COVID-19 infection; in fact, the weakened immune system can prevent the production of inflammatory cytokines and inhibit the onset of respiratory complications in these patients [139]. One study found that an MS patient with COVID-19 responded favorably to ocrelizumab (a type of anti-CD20 drug in B cells). Following the reduction of B cells, the cytokines produced by this cell such as IL6 reduced. Because of the severe lymphopenia in MS patients, the use of anti-CD20 drugs does not have much effect on T cells, but drugs such as alemtuzumab, whose mechanism of action is linked to CD52, which is a T cell and Natural Killer (NK) cell marker, may worsen MS conditions in people with COVID-19. In other words, the loss of T cells, which are the crucial defense barrier against viruses, causes an impaired immune response against the viruses (Table 1) [140]. Tocilizumab, as an immunosuppressant, inhibits the activity of IL-6 by blocking its receptor. Due to the beneficial effects of this drug, it can be used to control the acute conditions of COVID-19 patients [141]. One study found that clinical symptoms and hypoxemia were found to have improved in patients with severe COVID-19 treated with tocilizumab [142]. Another study reported that the use of tocilizumab reduced the acute phase of the disease in patients undergoing treatment and stabilized their clinical condition [143]. A cohort study also found that tocilizumab could significantly reduce mortality and acute respiratory conditions in COVID-19 patients [144]. A study has shown that the use of tocilizumab in two patients with COVID-19 has led to the development of secondary hemophagocytic lymphohistiocytosis and viral myocarditis [145]. These findings support the need for further investigations of this challenging drug and its effects on COVID-19 patients.

It is reported that the long-term use of corticosteroids increases the risk of infections, while short-term use can cause infection virus, such as the herpes virus [146]. One study found that patients treated with corticosteroids showed severe clinical symptoms and inflammation [147]. Contrary to the results of this study, another study reported that taking corticosteroids for more than 10 days reduced the severity of clinical symptoms in COVID-19 patients [148]. The inconsistent results related to the effect of corticosteroids require further investigation of this drug in COVID-19 patients. Differences in clinical symptoms in patients may also be referred to as differences in drug response.

Today, patients with MS are at higher risk for COVID-19 infection, and using drugs such as interferon β (IFN-β) and glatiramer acetate and TNF-α blockers have faced challenges and problems [138]. TNF-α is a T cell activator [149], and reports suggest that the use of TNF-α receptor blocker, etanercept, may worsen MS by increasing gadolinium-enhancing lesions [150]. TNF-α is also elevated in the lungs of COVID-19 patients and injecting TNF-α receptor blockers or TNF-α receptor itself may prevent cytokine storms in COVID-19 patients [151]. IFN-β, which is administered in MS patients to improve the condition in these patients, is found to have anti-viral properties. IFN-β triggers the production of Th2 cytokines by an anti-inflammatory mechanism, inhibits the IL-21 secretion, and prevents the production of osteopontin by T cells [131]. It can be useful in COVID-19 patients by preventing the migration of T cells and inducing IL-10 secretion [152]. It is hypothesized that using these drugs could worsen the respiratory problems of MS patients with COVID-19 by producing Th2 cytokines and stimulating the immune system [138]. In one study, SARS-CoV-2 proteins disrupt the type I interferons mechanism of action by disrupting STAT1 phosphorylation, which could lead to complications in the treatment of MS patients infected with COVID-19 [153]. A study found that the prevalence of infection in MS patients who received ocrelizumab was higher than in patients taking IFN-β [154]. Anti-viral immune responses are generated by lymphocytes; therefore modulation of the immune system in MS patients who suffer from severe lymphopenia becomes more challenging following the outbreak of COVID-19. According to these studies, we have hypothesized that modulating the T cells counting and the secretion of cytokines produced in response to the administration of corticosteroid in MS patients (infected with COVID-19) cannot be beneficial to these patients.

Conclusion

COVID-19 is a global threat, so finding an effective treatment for the virus is critical. The association of COVID-19 with autoimmune diseases is undeniable. Also, there is no reason to rule out a high risk of getting infected with the virus in patients with autoimmune disorders. The similarity of the pathogenesis of COVID-19 and autoimmune diseases can help to better understand the virus and discover its therapeutic options. Due to the increased activity of ACE and ACE2 in ARDS patients and the critical role of inflammatory mediators, especially angiotensin II in autoimmune diseases and COVID-19, further studies on these factors can be beneficial in detecting the therapeutic pathway. Genetic testing for the risk of developing SARS-COV2, which may be due to ACE2 polymorphisms, could also be a solution in prognosis and diagnosis of infected patients. The use of ACE2 inhibitors is still challenging, and corticosteroid administrationin autoimmune diseases can make it more difficult to diagnose and treat COVID-19 because ACE2 inhibitors prevent fever during the course of the disease. However, further examination of the lymphocyte signaling and cytokines in COVID-19 patients and the testing of autoimmune disease drugs in infected patients make it easier to find better therapeutic options.

Acknowledgments We wish to thank all our colleagues in Golestan Hospital and Allied Health Sciences School, Ahvaz Jundishapur University of Medical Sciences.

Compliance with ethical standards

Disclosures None.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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