REVIEW ARTICLE

Mystery Behind COVID-19 and Autoimmune Diseases

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ABSTRACT

Background: *Viruses cause autoimmunity using several mechanisms such as molecular mimicry, bystander activation of T cells, transient immunosuppression, and inflammation.* ***Objective:*** *To understand the link between Coronavirus disease 2019 (COVID-19), autoimmunity and hyperstimulation of the immune system which is still an unknown mystery.* ***Methodology:*** *We reviewed many research articles about the mechanisms used by SARS-CoV-2 to induce autoimmunity. We tried to explain in detail these mechanisms including molecular mimicry, the role of innate immunity, the role of adaptive immunity and autoantibodies detected in patients with COVID-19. Also, giving insights into similarities in immunopathogenesis of COVID-19 and autoimmune diseases, listing autoimmune diseases associated with COVID-19, clarifying the impact of covid-19 on pre-existing autoimmune diseases and finally presenting some therapeutic strategies & future prospectives for this disease.* ***Conclusion:*** *Autoimmune diseases are serious complications induced by SARS-CoV-2, which need more understanding by researchers to help develop appropriate treatment.*

Virology: Human coronaviruses (HCoVs)

Human coronaviruses belong to the family Coronaviridae, subfamily Orthocoronavirinae which contains four genera designated alpha, beta, gamma, and delta CoVs. These viruses can affect both the upper and lower respiratory tract. Serious lower respiratory tract infections (LRTIs) are currently caused by three coronaviruses: MERS-CoV (Betacoronavirus subgenus, Merbecovirus), SARS-CoV, and SARS-CoV-2 (Betacoronavirus subgenus, Sarbecovirus) [1].

Animal origin of coronaviruses

The origin of the SARS-CoV-2 genome has been linked to bats like the SARS-CoV-1 and MERS-CoV viruses. The receptor binding domain (RBD) of the S gene showed 93.1% similarity to Bat-CoVRaTG13. The RBD of the human SARS-CoV-2 and the closely related bat virus is assumed to have been obtained by a recombination event from a pangolin virus suggesting that pangolins could be a possible intermediate host of SARS-CoV-2 [2,3].

SARS-CoV-2 Cell receptor

SARS-CoV-2 is using angiotensin-converting enzyme-2 (ACE-2) and the transmembrane serine protease-2 (TMPRSS2) as receptors, which are expressed on type 2 pneumocytes and many other cell types, to fuse the envelope with the cell membrane and penetrates the cells. ACE-2 is also widely expressed on endothelial cells maintaining vascular homeostasis. SARS-CoV-2 also inhibits ACE-2 in the cells it targets, resulting in an overproduction of angiotensin II, an active metabolite that stimulates inflammation, vasoconstriction, cell division, vascular leakage, and ultimately pulmonary fibrosis. These characteristics of SARS-CoV-2 aid in the development of lung failure-causing acute respiratory distress syndrome (ARDS) [4].

Mechanisms of COVID- 19 induced autoimmunity

1. **Molecular mimicry between SARS-CoV-2 and humans**

Recent findings pointed out a homology of primary sequence between humans and components of SARS-CoV-2. Molecular mimicry readily leads to the generation of autoantibodies that may lead to the new beginning of an autoimmune disease (AID) since the acquired immune system generates antibodies that cross-react with common molecules across pathogens and self-components [5]. Table 1 lists 34 human proteins with high pathogenic potential whose linear sequences are shared by SARS-CoV-2 and the human proteome [6].

Table 1: Human proteins sharing heptapeptides with SARS-CoV-2; Quated from [6]

List and short description of 34 human proteins that share heptapeptides with SARS-CoV-2.

Shared 7-mer	Human proteins sharing heptapeptides with SARS-CoV-2*
SSRSSSR	Abl interactor 2
ALALLLL	Insulin-like growth factor-binding protein complex acid labile subunit
ALALLLL	Cerebellin-2
LLSAGIF	UPF0600 protein C5orf51
SSRSSSR	CLK4-associating serine/arginine rich protein
RGQGVPI	Putative uncharacterized protein encoded by the long intergenic non-protein coding RNA 346
ALALLLL	Cytochrome P450 2S1
ALALLLL	Delta and Notch-like epidermal growth factor-related receptor
GLTVLPP	FH1/FH2 domain-containing protein 3
LDKYFKN	Follistatin-related protein 1
RQLLFVV	Guanosine triphosphate-binding protein 10
IGAGICA	Hepatitis A virus cellular receptor 2
SSRSSSR	Hornerin
LFAAETL	Tyrosine-protein kinase ITK/TSK
LASFSAS	Maltase-glucoamylase, intestinal
LIRAAEI	Unconventional myosin-XVIIIa
QRMLLEK	Unconventional myosin-Vc
TGRLQSL	Neuron navigator 3
LIMLIIF	Sodium/potassium/calcium exchanger 2
IIFWFSL	Olfactory receptor 7D4
SLLSVLL	Orosomucoid 1-like protein 2
SSRSSSR	Oxysterol-binding protein-related protein 10
SSRSSSR	Pleckstrin homology domain-containing family G member 2
SRGGSQA	Ras-associating and dilute domain-containing protein
SSRSSSR	Solute carrier family 12 member 6
VLQLPQG	Prestin
AEGSRGG	snRNA-activating protein complex subunit 3
ALALLLL	Translocon-associated protein subunit delta
IVDTVSA	Alanine-tRNA ligase, mitochondrial
NASVVNI	Thyroid adenoma-associated protein
ALALLLL	Thrombospondin-3
LDDFVEI	Wolframin
SSRSSSR	Zinc finger CCCH domain-containing protein 18
SSRSSSR	Zinc finger Ran-binding domain-containing protein 2

* Human proteins sharing heptapeptides with SARS-CoV-2 are given by Uni-Prot name. Details on function/ associated diseases, and references at www.uniprot.org.

2. Hyper-stimulation of the immune system by the SARS-CoV-2

Viruses can trigger or exacerbate autoimmunity in genetically predisposed individuals, likely by activating immune pathways involving either innate or adaptive immunity. The innate and adaptive immune systems fight the virus in a COVID-19 infection, but it also activates immunological and non-immune cells, causing an overreaction [7].

An overactive cytokine storm, also known as "cytokine release syndrome," occurs in some patients with mild to severe COVID-19. This condition is characterized by the release of cytokines from monocytes, dendritic cells, and macrophages, including ferritin, tumor necrosis factor alpha (TNF-α), tumor necrosis factor beta (TNF-β), and interleukin 1 (IL1) and interleukin 6 [8,9]. Low levels of eosinophils, CD8+ T cells, natural killer (NK) cells, and naive T-helper cells are characteristics of eosinopenia and lymphocytopenia brought on by the presence of these cytokines, while simultaneously activating naive B-cells, increasing T-helper cell 17 (Th17) lymphocyte differentiation, and stimulating monocyte and neutrophil recruitment. An acute respiratory distress syndrome (ARDS) results from a generalized, nonspecific hyperinflammatory response in the lungs with consequent activation of nonspecific inflammatory response in the circulatory system and other organs, leading to multiorgan failure, leaky vasculature, coagulopathies, or strokes [10,11].

2.1. The role of innate immunity in triggering an autoimmune response in SARS-CoV-2 infections

a. Toll-like receptors (TLR)

Many TLRs including TLR2, TLR3, TLR4, TLR6, TLR7, TLR8, and TLR9 are involved in COVID-19 infection. When it comes to COVID-19 infection, these receptors have both positive and negative consequences. TLRs may help manage the infection in the early stages of the illness, but they can also cause tissue damage and chronic inflammation, which can be harmful to the host[12].

COVID-19 infection activates the TLRs, leading to the production of pro-inflammatory cytokines, such as IL-1β and type 1 IFN [13]. Many autoimmune diseases, such as systemic lupus erythematosus (SLE), primary Sjogren's syndrome (SS), Kawasaki syndrome, and behcet's disease are characterized by hyper-production of IFN (mainly type I), which may be linked to primitive viral infections [14].

b. The inflammasome pathway

After the inflammasome system in monocyte-macrophage cells is activated, viral proteins and nucleic acids can produce IL-1 and IL-18, which have systemic pro-inflammatory effects in addition to the IFN response. Pro-inflammatory cytokines like IL-1 and IL-18 are produced as a result of RNA viruses, such as SARS-CoV-2, activating pyrin-containing NOD receptor 3 (NLRP3), which causes nuclear factor kB (NF-kB) to translocate intranuclearly, pro-IL-1 and pro-IL-18 genes to be transcriptionally transcribed, and inflammasome-driven caspases to transform these precursors into active cytokines [15].

c. Neutrophil extracellular traps (NETs)

Increased neutrophil counts have been described as an indicator of severe respiratory symptoms in COVID-19. NETs are networks of extracellular fibers composed of DNA containing histones and granule derived enzymes, such as myeloperoxidase (MPO) and elastase. The process of NET formation by neutrophils, called NETosis. When NETs produce a variety of active chemicals, such as histones, enzymes, and danger associated molecular patterns (DAMPs), they accelerate inflammatory processes by inducing further inflammatory responses in the extracellular environment[16].

SARS-CoV-2 induces healthy neutrophils to release NETs, which is mediated by the ACE2–serine protease axis and virus replication. Finally, NETs promote lung epithelial apoptosis. NETs may, therefore, serve as an additional source of autoantigens against which autoantibodies may be directed by a wide range of autoimmune diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), psoriasis, and gout. The over-production of NET by CVID-19 can lead to autoimmune diseases in genetically predisposed people. Therefore, the inhibition of NET release or actions could represent a potential therapeutic target for COVID-19 [17].

d. The complement system

Complement activation has a significant role in the pathophysiology and severity of SARS-CoV-2, resulting in negative consequences such as inflammation and fibrosis in the musculoskeletal system. Either a direct (cytolysis of infected cells) or indirect (immune complex-mediated) viral clearance can occur when the glycoprotein S of SARS-CoV-2 binds to mannose binding lectin and starts the complement cascade. Among the pathogenic processes that exacerbate the severe situations of patients in need of intensive care are the overactive complement system, cytokine release syndrome, and the disseminated thrombotic phenomena[18]. The highly pathogenic coronavirus N protein aggregated the lung injury caused by SARS-CoV-2 by binding to mannan-binding lectin-associated protease (MASP-2), a serine protease that directly activates the complement cascade [19]. Dysregulation of the complement system can generate an imbalance between host defense and inflammatory response that leads to autoimmunity. Autoantibodies and immunological complexes via the classical pathway cause the complement system cascade to become hyperactive, just like in SLE [20].

2.2. The role of adaptive immunity in triggering an autoimmune response in SARS-CoV-2 infections

a. Cellular immunity

Epitopes present on SARS-CoV-2 envelope proteins, including S, E and M can trigger an adaptive immune response once dendritic cells recognize them. CD4+ T cell responses to SARS-CoV-2 are more prominent than CD8+ T cell responses. type 1 helper T cells (Th1) recognize the peptides of SARS COV-2 and produces inflammatory cytokines, including MCP1, IFNγ, IL-1B, IL-8, andIL-17. Also, Th1 produces large amounts of IFNγ, which activates macrophages, resulting in delayed hypersensitivity [21].

Furthermore, there is mounting evidence that Th17 cells contribute significantly to the pathophysiology of COVID-19, not only by triggering the cytokine cascade but also by triggering Th2 responses, preventing Th1 differentiation, and suppressing Treg cells. Autoimmunity reactions can also result from T helper 17 cells (Th17) recruiting neutrophils. Increased serum IL-17, IFNγ, and multinucleated giant cells in COVID-19 lung specimens from patients are suggestive of an active Th1 and Th17 response[22].

b. Humoral immunity

SARS-CoV-2 virus has a critical effect on human immunity, and its ability to trigger autoimmune diseases in genetically predisposed individuals is based on certain clues as the reported inflammatory and autoimmune symptoms, the presence of circulating autoantibodies, and the diagnosis of defined

autoimmune diseases in a subgroup of SARS-CoV-2-infected patients [23,24].

Autoantibodies in SARS-CoV-2-infected patients

Pascolini *et al.* [24] found that 33 consecutive COVID-19 patients had antinuclear antibodies (ANA), anti-cytoplasmic neutrophil antibodies (ANCA), and anti-antiphospholipid (APL) antibodies. Patients with positive autoantibodies tended to have a substantially higher respiratory rate at admission and a worse prognosis.

One of the dangerous side effects of SARS-CoV-2 infection is coagulopathy. In contrast to controls who tested negative for COVID-19 reverse transcriptase–PCR, the researchers discovered that patients with COVID-19 had a higher rate of lupus anticoagulant positive. Additionally, the rate of thrombosis was higher in COVID-19 individuals who tested positive for lupus anticoagulant [25].

Amezcua-Guerra *et al.* [26] additionally showed that individuals with severe and critical COVID-19 had a greater prevalence of APL antibodies, and that the presence of APL antibodies appears to be linked to pulmonary thromboembolism and a hyperinflammatory state with abnormally high ferritin, C reactive protein, and IL-6 levels. The findings suggest that SARS-CoV-2 can trigger autoimmune reactions and may help to explain the hypercoagulable state seen in severe and critical COVID-19 cases.

Case studies have demonstrated the presence of autoantibodies against contactin-associated protein 2 (anti-Caspr2), ganglioside GD1b (anti-GD1b), and myelin oligodendrocyte glycoprotein (anti-MOG) in COVID-19 patients exhibiting neurological symptoms or retrospective studies [27&28]. However, the clinical significance of these antibodies remains unclear. Autoantibodies detected in COVID-19 patients are presented in **Table 2**[29].

Table 2: Autoantibodies detected in patients with COVID-19; Quated from [29]

Autoantibodies	Clinical significance	Refs.
ANA	Poor prognosis and a significant higher respiratory rate	[14]
APL	Poor prognosis and a significant higher respiratory rate Possible association with a hyperinflammatory state and thrombosis and thromboembolism	[14,52▪]
Lupus anticoagulant	A higher rate of thrombosis	[51▪]
Cold agglutinins	Haemolytic anaemia. Complicating laboratory assessment and renal replacement therapy	[55,58]
Anti-Ro/SSA antibodies	Possible association with severe pneumonia	[56]
Anti-Caspr2 antibody	Unclear	[54▪]
Anti-GD1b antibody	Unclear	[54▪]
Anti-MOG antibody	Unclear	[53]
Red cell bound antibodies	Associated with the severity of anaemia	[57]

Similarities in immunopathogenesis of COVID-19 and autoimmune diseases

Autoimmune diseases are characterized by the existence of autoantibodies and perpetuated inflammatory reactions due to the loss of immune tolerance and dysregulated immune system, leading to target organ damage and malfunction These immune-mediated injuries also exist in COVID-19 [29].

In clinical laboratory tests, lymphopenia is associated with severe illness in COVID-19 patients and might be a prognostic factor for disease severity and mortality. Another notable haemocytological change is neutrophilia and associated excessive neutrophil extracellular traps, which paralleled lung injury in severe COVID-19 patients [30].

As observed in autoimmune diseases; in COVID-19 patients, pro-inflammatory cytokines and chemokines, including interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10 and CCL2, increased significantly and the expression levels of some of these cytokines, such as IL-1, IL-6, IL-10 and IL-18, have been demonstrated to be associated with disease severity. Activation and infiltration of immune cells participate in the pathogenesis of organ injury in patients with COVID-19. Macrophage activation syndrome (MAS) could be a continuum of cytokine storm syndrome leading to life-threatening complications in COVID-19. In this condition, activated macrophages will produce excessive proinflammatory cytokines, polarize into the inflammatory M1 phenotype and exhibit cytotoxic dysfunction [31&32]. Recently, **Conti *et al.*** [33] suggested

that histamine released by SARS-CoV-2 activated mast cells could raise IL-1 levels, start a cytokine storm, and worsen lung damage.

Woodruff *et al.* [34] found extrafollicular B cell activation in critically ill patients with COVID-19, as in autoimmunity. Further, extrafollicular B cell activation correlated strongly with the production of high concentrations of SARS-CoV specific neutralizing antibodies and poor disease outcome. Peripheral blood B-cell subpopulations are altered during COVID-19. In COVID-19 patients, atypical memory β-cells expanded significantly, while classical memory β-cells were significantly reduced. Analysis of immune profiles of severe COVID-19 patients revealed an increased proportion of mature natural killer (NK) cells and decreased proportion of T-cell numbers.

Neutrophil activation and neutrophil extracellular trap production (NETosis) appear to have a pathogenic role in COVID-19 like some autoimmune and immune-mediated thromboinflammatory diseases, including lupus, antiphospholipid syndrome, and ANCA-associated vasculitis [29]. **Zuo *et al.*** [35] reported increased markers of NETs in sera from patients with COVID-19, and significantly more in patients requiring mechanical ventilation. Similarities in immunopathogenesis of COVID-19 and autoimmune diseases are summarized in **Table 3** [30].

Table 3: Similarities in immunopathogenesis of COVID-19 and autoimmune diseases; Quated from [29]

Items	COVID-19 immunological features similar to autoimmune diseases	Refs.
Innate immune cells	Overactivation of monocytes, macrophages, mast cells and neutrophils. Increased proportion of mature natural killer (NK) cells.	[12,27,29,32,33▪]
Adaptive immune cells	Decreased T-cell numbers, altered B-cell subsets, dysregulation of T cells and B cells.	[17,30,31]
Cytokines and chemokines	Increased levels of IL-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10, CCL2.	[22–24]
Autoantibodies	ANA, APL, lupus anticoagulant, cold agglutinins, anti-Ro/SSA antibodies, anti-Caspr2 antibody, anti GD1b antibody, anti-MOG antibody	[14,51▪,52▪,53,54▪,55–58]
Clinical conditions	Immune-mediated haemolysis, decreased white blood cell counts, cytokine storm syndrome, macrophage activation syndrome, procoagulant condition	[25,28,57,74]
Other immunopathogenesis	Increased levels of DAMPs, molecular mimicry	[26,46]

Autoimmune diseases (AIDs) associated with COVID-19

There is evidence that SARS-CoV-2 can cause the immune system to become hyperstimulated, which can result in the production of autoantibodies. Additionally, there is evidence that patients infected with the virus may get AIDS for the first time.

1. **Post-SARS-CoV-2 Guillain–Barre´ syndrome (GBS):**

It had been suggested that COVID-19 has an association with the immune-mediated neuropathy GBS. About 31 confirmed cases of GBS following a SARS-CoV-2 infection were announced in August 2020; since then, additional cases of the illness have been made public. Damage to the peripheral nerve cells' myelin sheath is a hallmark of GBS. Similarly, rare variations of GBS, Miller Fisher syndrome (MFS) and Polyneuritis cranialis (PNC), were also reported to occur in COVID-19 individuals with acute onset [36,37].

2. **Post-SARS-CoV-2 Graves' disease (GD):**

Concerning autoimmune endocrine diseases, A recent study that included 191 individuals with COVID-19- infection had shown abnormalities in thyroid function of 13.1%. Furthermore, case reports of Graves' disease after COVID-19 infection had been described, as well as atypical thyroiditis with characteristic features of autoimmune thyroiditis [38,39].

3. **Kawasaki disease (KD):**

There is new evidence of autoimmune diseases in children brought on by COVID-19: For example, KD is an immunologic reaction that primarily affects children under the age of five and manifests as acute, self-limited vasculitis. A total of 320 children were reported in 36 distinct studies detailing cases of SARS-CoV-2 infection followed by an acute onset of KD [40].

4. **Autoimmune hemolytic anemia (AIHA):**

Autoantibodies that target erythrocytes and cause hemolysis are the hallmarks of this rather uncommon disorder. The probability that antibodies against SARS-CoV-2 were also functioning as AIHA autoantibodies to a particular protein on the surface of erythrocytes was increased by the publication of articles detailing the development of AIHA following SARS-CoV-2 infection with both warm and cold IgG [41,42].

5. **Post-SARS-CoV-2 Idiopathic thrombocytopenic purpura (ITP):**

It is a hematological disorder affecting the total number of blood platelets and thrombocytopenia (platelet count < 100 × 109 /L, normal range 150–450 × 109 /L). Infections that cause autoantibodies to cross-react to glycoproteins IIb-IIIa or Ib on platelets and megakaryocytes can be the secondary cause of two-thirds of ITP cases, which can result in decreased platelet production and a shorter lifespan of circulating platelets[43]. In a study of case series, **Bomhof *et al.*** [44] showed that the ITP occurred not only during active COVID-19 infection but also up to 10 days after the reduction of the clinical symptoms of COVID-19. Thrombocytopenia in a moderate form is reported in about 36% of admitted COVID-19 patients.

6. **Post-SARS-CoV-2 multiple sclerosis (MS):**

Although the precise mechanism of MS has been remaining unclear, activation of Toll-like receptors (TLRs) on microglia/macrophages and dendritic cells by viral particles can disrupt self-tolerance and promote auto-immunity. For example, infection with the Epstein-Barr virus is considered a significant risk factor for MS development and viral respiratory infections may also exacerbate MS [45].

7. **Post-SARS-CoV-2 myasthenia gravis (MG):**

It is an autoimmune disorder characterized by fluctuating fatigability and muscle weakness. Thymic impairment and peripheral self-tolerance mechanisms followed by different factors such as viral infection promote CD4+ T cell-mediated B cell activation and synthesis of pathogenic high-affinity autoantibodies. The autoantibodies bind to the acetylcholine receptor (AchR) and lead to impaired neuromuscular transmission and clinical manifestation of the disease. According to many studies, MG can be a particular complication of Covid-19 patients [46,47].

8. **Post-SARS-CoV-2 systemic lupus erythematosus (SLE):**

Systemic lupus erythematosus pathogenesis comprises the inherent and adaptive immune systems, autoantibody formation, complement system activation, cytokine dysregulation (especially interferons of type I) and disrupted apoptotic clearance. Literature correlated COVID-19 with SLE as they demonstrated the onset of SLE with the development of antiphospholipid antibodies, anti-nuclear antibodies (ANAs) and anti-double-stranded DNA antibodies (anti-dsDNA) by serologic testing [48,49].

The impact of covid-19 on pre-existing autoimmune diseases

Remarkably, pharmacologically immunosuppressed individuals with rheumatic disease were found to have comparable COVID-19 incidence, prevalence, morbidity, and mortality rates to the general population[50,51].

Risk factors for a more severe disease in rheumatic patients are the same as those reported for the general population and include male gender, older age, cardiovascular disease, diabetes mellitus, obesity, lymphopenia, and increased serum level of IL-6, C-reactive protein (CRP) and lactate dehydrogenase (LDH). The American College of Rheumatology recently proposed a panel of therapeutic recommendations to guide physicians' decisions in treating ascertained COVID-19 rheumatic patients. In these cases, the discontinuation of conventional, synthetic, and biologic disease modifying anti-rheumatic drugs (DMARDs) and immunosuppressive drugs is advised, while non-steroidal anti-inflammatory drugs (NSAIDs), low doses of glucocorticoids, anti-malarials and anti-IL-6 inhibitors may be maintained [52].

Therapeutic strategies & Future prospectives

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

COVID-19 and autoimmune diseases share a common pathogenesis, making autoimmune drugs a possible treatment option. Chloroquine (CQ) can interfere with the glycosylation of the ACE2 by binding to the virus and inhibiting respiratory syndrome in COVID-19 patients. Rheumatoid arthritis patients may benefit from Baricitinib, a reversible oral inhibitor of the Janus kinases JAK1 and JAK2. This drug interrupts the signaling of multiple cytokines implicated in COVID-19 immunopathology [53].

Tocilizumab, an IL-6 receptor blocker that helps lessen cytokine storm and immune system hyperactivity, is another useful medication that is frequently used in conjunction with COVID-19 and multiple sclerosis. Actually, COVID-19 patients with increased inflammation might benefit from interleukin-6 inhibition [54].

Application of monoclonal antibodies targeting IL-6 and IL-6R

Tocilizumab (Actemra)

By blocking IL-6 signaling, the recombinant humanized anti-IL-6R monoclonal antibody tocilizumab (TCZ) can prevent cytokine storms. Rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, neuromyelitis optica, and giant cell arteritis are among the inflammatory illnesses that TCZ has shown promise in treating [55].

Sarilumab (Kevzara)

Sarilumab is a recombinant human IL-6Rα antagonist that blocks both classical and trans-signaling pathways by attaching to both soluble and mbIL-6R. In addition to treating rheumatoid arthritis, it has lately been given to a number of patients with respiratory failure and severe COVID-19 [56].

Siltuximab

A chimeric monoclonal antibody called siltuximab inhibits IL-6 signaling pathways by attaching to soluble

IL-6 and preventing it from attaching to the appropriate receptors [57].

Antagonist of the IL-1 receptor

Anakinra

As a recombinant antagonist of the interleukin-1 receptor, Anakinra inhibits the signaling pathways of IL-1α and IL-1β. This immunomodulatory drug is authorized for the treatment of autoinflammatory diseases and rheumatoid arthritis when administered subcutaneously at a dose of 100 mg per day [58].

Application of monoclonal antibodies targeting IL-1β

Canakinumab

Canakinumab is a human monoclonal antibody that targets IL-1β with high affinity. Canakinumab has recently been shown to have positive effects on patients with severe COVID-19. Canakinumab does not react with other IL-1 members and selectively inhibits IL-1 β[59].

Application of monoclonal antibodies targeting IL-17

The monoclonal IgG1 antibodies ixekizumab and secukinumab both have a similar mode of action and selectively target IL-17A. The lymphocyte count was much lower in individuals with severe COVID-19, indicating that these two antagonists are appropriate treatments for COVID-19 patients. Anti-IL-17 receptor A (IL-17RA) is the target of the recombinant human monoclonal antibody brodalumab. This treatment choice has the ability to totally block Th-17-mediated pathways [60].

Application of monoclonal antibodies targeting TNF-α

At first, five TNF inhibitors—infiximab, adalimumab, golimumab, certolizumab, and etanercept were authorized for use in clinical settings. Members of the lymphotoxin (LT) family are bound by the TNF antagonist etanercept. These antagonists work by attaching to sTNF or tmTNF, and for etanercept, by attaching to LTα3 and LTα2β and preventing subsequent cascades as presented in **Table 4** [61].

Table 4: Anti TNF agents; Quated from [61]

	Structure	Cognate ligands	Half life	Dosing	Frequency
Infliximab (Remicade®)	Chimeric (mouse and human)/ whole mAB against TNF	sTNF, tmTNF	8–10	Intravenous	Very 8 weeks following loading at 0, 2 and 6 weeks
Adalimumab (Humira®)	Human whole mAb against TNF	sTNF, tmTNF	10–14	Subcutaneous	Every 2 weeks following initial loading
Golimumab (Simponi®)	Human whole mAb against TNF	sTNF, tmTNF	12 ± 3	Subcutaneous	Monthly following initial loading
Certolizumab	Humanized PEGylated Fab fragment of a mAb against TNF	sTNF, tmTNF	3	Subcutaneous	Every 2 weeks following initial loading
Etanercept# (Enbrel®)	TNFR2 fused to IgG1 Fc	sTNF, tmTNF, LTα3	14	Subcutaneous	Weekly/twice Weekly

LTα3 trimeric lymphotoxin α, *sTNF* soluble TNF, *tmTNF* transmembrane TNF, *mAb* monoclonal antibody

CONCLUSION

We present a review of the association between COVID-19 and autoimmune diseases, trying to explain in detail the mechanisms which may be used by SARS-CoV-2 to induce autoimmunity; These mechanisms include molecular mimicry, the role of innate immunity, the role of adaptive immunity and autoantibodies detected in patients with COVID-19. Also, giving insights into similarities in immunopathogenesis of COVID-19 and autoimmune diseases, Autoimmune diseases associated with COVID-19, the impact of covid-19 on pre-existing autoimmune diseases and finally therapeutic strategies & future prospectives for this disease.

Conflict of interest:

There is no conflict of interest

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