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The Crosstalk between Covid-19 and Autoimmune Diseases: An Overview

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ABSTRACT

The COVID-19 pandemic has created significant public health challenges, and one of the major concerns is its potential association with pre-existing medical conditions. Our comprehensive review aims to provide the latest information on the relationship between COVID-19 and autoimmune diseases, shedding light on current knowledge, emerging concepts, and underlying mechanisms that may exacerbate viral infections and even trigger autoimmunity. We delve into the complex interplay between the immune system and the virus, exploring how COVID-19 impacts individuals with autoimmune diseases and the potential implications for disease severity, clinical outcomes, and management strategies. Additionally, we investigate the potential impact of autoimmune therapy on COVID-19 prognosis, discussing the latest findings and insights on the benefits and risks of immunosuppressive and immunomodulatory agents in COVID-19 patients with underlying autoimmune diseases.

Keywords: Sars-Cov2; Covid-19; Autoimmunity; Autoimmune Diseases; Immune Tolerance; Coronavirus

Abbreviations: SARS: Severe Acute Respiratory Syndrome; ACE2: Angiotensin-Converting Enzyme 2; sHLH: Secondary Hemophagocytic Lymphohistiocytosis; PAMP: Pathogen-Associated Molecular Pattern; RAAS: Renin-Aldosterone-Angiotensin System; SIRS: Systemic Inflammatory Response Syndrome; ARDS: Acute Respiratory Distress Syndrome; COPD: Chronic Obstructive Pulmonary Disease; MHC: Major Histocompatibility Complexes; CTL: Cytotoxic T Lymphocytes; SLE: Systemic Lupus Erythematosus; TFH: T Follicular Helper Cells; PRRs: Pattern Recognition Receptors; MAVS: Mitochondrial Antiviral Signaling Proteins; CRP: C-Reactive Protein; GR: Glucocorticoid Receptor; TCZ: Concluded That Tocilizumab; ARDS: Acute Respiratory Distress Syndrome; NIV: Noninvasive Ventilation; ICU: Intensive Care Unit; HLH: Hemophagocyte Lymphohistiocytosis; GFR: Glomerular Filtration Rate; GBS: Guillain Barre Syndrome

Introduction

The ongoing pandemic of coronavirus disease 2019 (COVID-19) have promoted a significant change in twenty-first-century medicine. In this scenario, comorbidities have gained an extreme significance as they may be associated with increased risks of hospitalization and death in the wake of COVID-19 pandemic. In addition, COVID-19 has also demonstrated to trigger other permanent diseases, such as autoimmune diseases. Although the exact etiology of many autoimmune diseases is still unknown, it is known that viral infection is one of the main responsible for tolerance loss to autoantigen and consequent autoimmunity development [1]. Such observations led researchers to question the role of COVID-19 in the development of autoimmunity, as well as the implications of pre-stablished autoimmune diseases during COVID-19. This review collated the fragmented literature information and current knowledge on COVID-19, autoimmunity, and their relationship.

Covid-19: History, Disease, and Epidemiology

A cluster of patients presenting an atypical pneumonia were first described in December 2019 in Wuhan City, Hubei Province, in China. The outcomes of the epidemiologic and etiologic investigation detected a novel coronavirus, which through RNA isolation, evidenced similarities to the bat SARS-like CoV genome with distinctions from the SARS-CoV and MERS-CoV. The new virus belonging to the subgenus sarbecovirus (Coronaviridae family) was first called 2019-nCoV [2]. Using a genomic study, it was elucidated that the novel coronavirus presented about 88% identity to bat-SL-CkVZ45 and bat-SL-CoVZXC21, two coronavirus related to bat severe acute respiratory syndrome, while SARS-CoV and MERS-CoV showed about 79% and 50% genome sequences similarities, respectively, presuming that the animals sold at the Wuhan seafood center contained an intermediate animal that could possibly be the primary host of the virus [3]. The term "coronavirus" is derived from an electron microscopy observation in 1968 by a group of virologists, in which the virus showed to have the solar corona appearance [4]. Coronavirus (CoV) is an RNA virus, represented by a single stranded RNA and positive sense. It can also be classified in four genera: α-CoV, β-CoV (SARS-CoV-2 classification), γ-CoV, and δ-CoV [5]. Birds and mammals are the main infected species by α-CoVs and β-CoVs, although humans are also included. Coronavirus-derived symptoms can be similar to a simple flu, affecting manly the superior respiratory tract, or can course to a severe symptomatology, by harming the inferior respiratory tract, causing a severe acute respiratory syndrome (SARS), which include the SARS-CoV-2, MERS-CoV, and SARS-CoV [6,7]. Consonant its phylogeny and taxonomy, and considering that the novel coronavirus is related to the bat and human severe acute respiratory syndrome, the International Committee on Taxonomy of Viruses decided that the previously 2019-nCoV should be named SARS-CoV-2 and the disease caused by it COVID-19 [8]. The pandemic caused by SARS-CoV-2 is reported as the fifth pandemic after the Spanish flu in 1918 and it is still believed that this novel coronavirus will be circulating in the populations in the future [9]. It is presumed that the first spread of the virus occurred as an animal-to-human transmission due to the association to the environment where it was first found, a wholesale seafood center in Wuhan [10]. The principles of the SARS-CoV-2 transmissibility were also pointed in association to an intermediate host animal or to the wild animal consumption, despite the fact that this theory remains questionable [6]. Furthermore, nowadays it is known that human-to-human transmission is the main way of spreading SARS-CoV-2 by symptomatic patients, despite studies have shown that it can also be spread by asymptomatic people before the first symptoms appear [10]. A study of a familial cluster corroborates that person-to-person transmission of the novel coronavirus is consistent, either in the same environment or at hospitals or different geographic locations due to travels [11].

Studies have shown that the transmission of COVID-19 can be carried out in different ways, such as face-to-face exposure to symptomatic patients, by which droplets from sneezing, coughing, or talking could be easily spread in the air. Moreover, it has been documented the virus transmission via fomites, but the viral load and the type of material may interfere to the transmission effectiveness; however, face-to-face remains the main way of transmissibility [12]. Researches have also elucidated that SARS-CoV-2 could be found in places such as the gastrointestinal tract, feces, tears, and conjunctival secretions [13-15]. The period of 3 to 7 days is considered the COVID-19 incubation stage. The infection can course into 3 different features, in which about 80% of the cases are asymptomatic or mild, 15% courses progress to a severe phase, and 5% evolve to a complex case [16]. The main documented clinical presentation of SARS-CoV-2 in hospitalized patients are cough and fever, followed by fatigue, dyspnea, and shortness of breath [16-19]. Besides the systemic involvement, nonclassical manifestations, such as gastrointestinal and taste and olfactory disorders have also been reported: vomiting, diarrhea, and abdominal pain, as well as ageusia and anosmia [17,20-22].

For patients presenting asymptomatic or mild COVID-19 disease, the presence of Neutralizing Antibodies (Nabs) has shown an important key for COVID-19 recovery even though its titers vary on age. Some patients may recover without developing SARS-CoV-2 specific Nabs. A study with 175 COVID-19 patients showed that elderly (60-85 years old) and middle-age (40-59 years old) patients presented high levels of Nabs, which is crucial for the recovery for this age by clearing the virus, compared to young patients [23]. The mechanism of COVID-19 infection starts when the virus binds to angiotensin-converting enzyme 2 (ACE2) receptor in the bronchial and lung epithelium through its S (Spike) protein. This effectiveness is followed by TMPRSS22 activity, a serine protease that primes the S protein of SARS-CoV-2, allowing the virus to enter the host cell [24]. To eradicate

infections, the immune system reacts using inflammatory responses. Under normal conditions, pathogens are recognized by the immune system and trigger an inflammatory response, leading to pathogen elimination, tissue repair, and finally homeostasis. Nevertheless, SARS-CoV-2 provokes an extensive cytokine/chemokine response in some patients, also called cytokine storm (Figure 1). This cytokine storm has been exposed as a critical mechanism for bad prognosis, by increasing the chances of the disease to progress to acute respiratory distress syndrome and leading to organ failure [25]. Patients with a serious case of infection may present secondary hemophagocytic lymphohistiocytosis (sHLH), a pulmonary and extrapulmonary inflammation caused by hyperactivity of the immune system due to the overproduction of pro-inflammatory cytokines as a result of an improper macrophages suppression activated by NK cells and T lymphocytes [26,27]. Studies in China have also reported the cytokine storm, showing the increase of different immune mediators such as IL-2, IL-7, IL-10, TNF-α, IP-10, G-CSF, MCP-1, and MIP-1A [28,29].

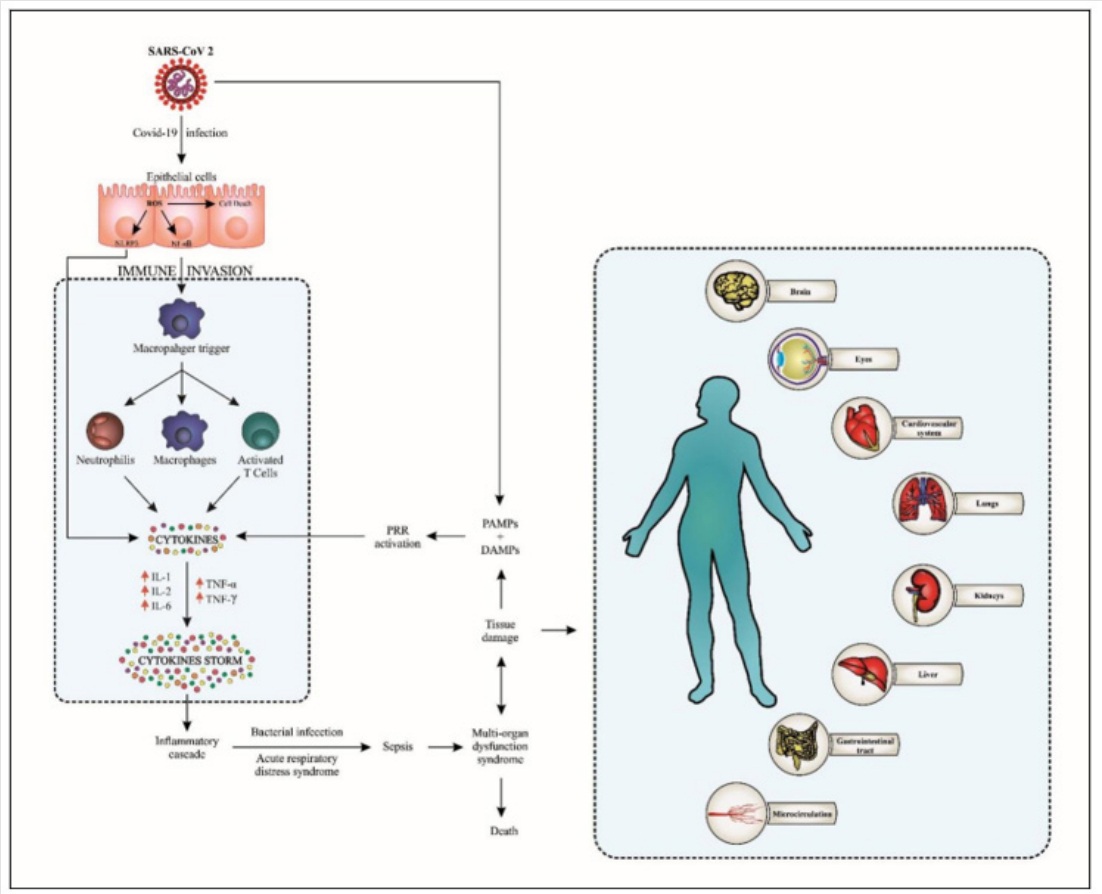

Figure 1: Cytokine storm caused by SARS-CoV-2.

Infection with SARS-CoV-2 can stimulate a hyperinflammatory immune response wherein epithelial-cell-mediated production of reactive oxygen species (ROS) can cause cell death. ROS can also stimulate the synthesis of NLRP3 and NF-κB increasing the cytokine levels, resulting in cytokine storm. This essentially causes immune invasion which can lead to clinically relevant conditions such as ARDS, sepsis, MODS, and death. ROS, reactive oxygen species; NLRP3, (NOD)-like receptor protein 3 inflammasome; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PRR, pattern recognition receptors; ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome. Cytokine storm is known to be a serious condition of hyper-inflammation that can result in multi-organ failure and even death, caused by cytokine excess in the organism [30]. Despite the fact the cytokine storm is shown in different diseases, such as rheumatologic disease and sepsis, there is a concern over this inflammatory condition due

to its appearance in severe COVID-19 [31,32]. A study portrayed an increase of cytokine levels (IL-2, IL-7, IL-10, IP10, G-CSF, MCP1, TNF-α and MIP-1alpha) in patients admitted to the intensive care unit (ICU) compared to those who did not require ICU treatment [33] as well as an increase of IL-6 levels in patients who died of COVID-19, which shows the relevance of cytokine storm in disease [34].

Ultimately, cytokine storm has also been described as an ineffective response of the immune system to the virus removal, characterized by a delay release of type I and III IFNs, which is a momentary immune-deficient state, followed by a later stage, portrayed as the excessive pro-inflammatory cytokine secretion because of type I and III IFN release failure [27,35,36]. Another important issue to be considered is that cytokine storm has a key pathogenic cytokine, which may differ depending on the underlying disease [37]. Lymphopenia showed to be associated with the severity of the cytokine storm. In addition, it is believed that it comes from an effective immune reaction outcome against infections to efficiently leading immune cells to secondary lymphoid organs [34]. As an immunologic feature, in severe cases of COVID-19, T lymphocytes are in low number, including CD4, CD8, NK cells and regulatory T cells [38-40]. Lung immunopathogenic injury is reported as a cause of cytokine storm production, with a Th1/Th17 specific response [16,30,31]. Thus, SARS-CoV-2 can activate innate and adaptative responses. Viral genomic ssRNA is recognized as a pathogen-associated molecular pattern (PAMP), and it is responsible for the innate immune system recognition by TLR7 and TLR8 receptors, the cytosolic receptors RIG (retinoid-inducible gene), and MDA5 (melanoma differentiation-associated gene 5) [41-43]. The main cytokines produced in response to this activation are TNF-α,which is involved in the coagulation process, neutrophilic activation, and fever; and INF-γ, responsible for macrophage activation [28,38,44-47]. High levels of IL-6 and TNF-α are products of activation of TLR4 receptors, which are involved in the cardiometabolic diseases to be risk factors for COVID-19 [48,49]. Under controlled conditions, the immune system fights to SARS-CoV-2 by producing antibodies (IgG), anti-inflammatory cytokines, such as IL-10, and pro-inflammatory cytokines, such as INF-γ and TNF-α in a balanced environment [38,47,48].

T cell response studies reveled that there is no necessary association of T cell response with symptom severity in COVID-19 individuals. Furthermore, IFN-γ and IL-2 secretion by T cells in asymptomatic patients was higher than symptomatic SARS-CoV-2 patients, exhibiting a more organized generation of pro-inflammatory cytokines. Fundamentally, antiviral cellular immunity is more competent in asymptomatic patients [50]. In contrast, in the convalescent period, functional T cell response presents a different association with frequency and disease severity, showing a more robust in mild symptoms individuals who precociously had a viral clearance compared to those with severe case [51]. A meta-analysis study detailed the comorbidities associated with COVID-19, especially among severe and fatal cases, and it was found that hypertension showed to have high prevalence both in the severe and fatal COVID-19 disease. In addition, considering fatal cases, diabetes and respiratory diseases when associated to the COVID-19 showed to have high dominance in the fatal cases [52]. Hypertension has been associated to a bad prognosis due to dysregulation of renin-aldosterone-angiotensin system (RAAS). It is reported that SARS-CoV-2 enters the cell through ACE2, an enzyme involved in the RAAS, and using angiotensin-converting enzyme inhibitors could, experimentally, increase the expression of ACE2 [53,54]. Nevertheless, there is no evidence that expression of ACE2 increases by using angiotensin-converting enzyme inhibitors [53].

Moreover, an immune system alteration is related to hypertension, notably a CD8+ T lymphocyte increase, that may lead to decrease of viral infection combat and cytokines dysregulations [55], which could have a crucial role in the systemic inflammatory response syndrome (SIRS) and the acute respiratory distress syndrome (ARDS), observed in severe COVID-19 cases [52]. Meanwhile, it is observed that diabetic patients are prone to be infected by SARS-CoV-2 due many factors, such as the phagocytosis disturb caused by their compromised innate immunity [56,57], dysregulated expression of cytokines that leads to cytokine storm [57], and a downregulated amount of ACE2, that may be present in these patients [58]. As ACE2 is reduced in diabetic patients and it is postulated that ACE2 has a crucial role in anti-inflammatory and anti-oxidation response, patients with severe COVID-19 infections may present a decrease of angiotensin [1-7], an important peptide responsible for antioxidant and anti-inflammatory response, and an increase of angiotensin II levels, which leads to a pro-inflammatory response [59,60]. Indeed, deregulation of ACE2 contributes to the lethal disease [52] and increase the risk of severe lung injury and ARDS in COVID-19 infected patients [57]. Another event is the high furin expression, a molecule present in high levels in diabetic patients that is involved with the entry of the virus in the host cell since it activates the attachment of SARS-CoV-2 spike protein to the ACE-2 receptor [61]. Finally, chronic obstructive pulmonary disease (COPD) has shown to increase the number of ACE2 receptors, which contribute to the onset of critical symptoms, lungs damage, and mucous overproduction [62].

Regarding gender, there are some differences in susceptibilities of having a severe prognosis in COVID-19. Even though men and women have the same prevalence of COVID-19, a Chinese study showed that men are considered more prone to death, regardless of age, which means that gender can be considered a risk factor for bad clinical severities and mortality [63]. Other studies, using a group of 1482 hospitalized patients, have pointed that men (54%) are framed at a higher rate of infection compared to women (46%) [64]. It was also reported in a South Korean study that the virus shedding shows different aspects between the genders, since men are more favorable than women (54 deceased COVID-19 patients by which 61% were

male), besides presenting more viral load (18.2 days for male compared to 15.2 for female) [65].

On the other hand, immunosenescence implicates into susceptibility to any infection, such as by the influenza virus [66,67]. Indeed, COVID-19 occurs more commonly in older adults then in children [68]. Therefore, another branch exploited by SARS-CoV-2 infection is age. When considering the severity of SARS-CoV-2 and its poor prognosis, evidence suggest that age is a risk factor. Studies from different countries show that the case fatality ratio (CFR) increases with age, as it occurred in China, where CFR of 14.8% was observed for people in their 80s, compared to 3.6% in their 60s, and 0.4% for those in their 40s or younger [2,69]. In Italy, a 20.2% CFR of COVID-19 was observed for those in their 80s, compared to 3.5% in their 60s, and 0.4% for those in their 40s or younger [70]. Until 24 March 2023, there have been more than 763 million confirmed cases (763,740,140) of COVID-19 all over the world, including more than 6,9 million deaths reported to World Health Organization (WHO) (6,908,554) and more than 13 billion vaccine doses (24 March 2023) have been administered (13,321,463,740 vaccine doses). The countries that have the highest number of cases are Australia (11,178,368), Vietnam (11,531,072), Spain (13,813,830), Turkey (17,004,677), Russian Federation (22,776,383), United Kingdom (24,555,629), Italy (25,737,170), Republic of Korea (30,994,088), Japan (33,580,723), Brazil (37,358,092), Germany (38,385,526), France (38,843,098), India (44,834,859), China (99,240,488) and United States of America (102,977,396) [71].

An Overview of Autoimmune Diseases

Autoimmunity is defined as an inadequate immunological response targeted to self-antigens as a consequence to a loss of immunological tolerance, leading to pathological occurrences [72]. Nonetheless, the loss of immunological tolerance may occurs in various degrees, which might or not result in clinical manifestations [73]. Whenever the loss of immunological tolerance evolves to a clinical manifestation, it is then classified as an autoimmune disease. The mechanism of immunological tolerance is developed during the selection and maturation on naïve lymphocytes, by a myriad of ligands and proteins whose function is to recognize the presented antigen and develop a proper response in two scenarios:

i) A self-antigen is presented to the naïve lymphocyte, which must not react to it or produce cytokines, suffering apoptosis.

ii) A non-self-antigen is presented to the naïve lymphocyte, therefore producing cytokines accordingly to the characteristics of the antigen, resulting in a proper immunological response [74,75].

As a matter of fact, there are many factors involved in providing immunological tolerance to self-antigens, one of them being the proteins from the autoimmune regulation (Aire) group, responsible by the aforementioned negative selection on lymphocytes, previously described by the mechanism (I), which is the core of the tolerance principle, whether occurring to central lymphocytes (on the bone marrow and thyme mediated by Aire proteins or forehead box proteins such as Foxp3) or on peripheral lymphocytes by active suppression and apoptosis induced by T Regulators lymphocytes on the peripheric system such as lymph nodes and conjunctive tissue. Indeed, the thymic maturation and induction of tolerance holds such a place of importance due to its presentation of a wide array of self-antigen repertoire, including antigens restricted to specific tissues regardless of their concentration, as is the case of abundant molecules like albumin, or those that may not reach the systemic circulation such as thyroid peroxidase [76-79].

It is known that a naïve cell, with proper stimulation of the T-cell receptor and the MHC-II and under the adequate array of interleukins and cytokines can undergo differentiation into a variety of T-helper cells, which are more prominent in certain scenarios such as Th1 (focused on intracellular reaction), Th2 (focused on extracellular pathogens), Th9, Th17 (more reactive to fungi and bacteria), T Regulatory, Follicular Helper T and many more [80-83]. Nevertheless, the mechanism that effectively led to the loss of tolerance to self-antigens (therefore leading to autoimmune diseases) or to previously innocuous antigens (therefore leading to atopic patterns of immunological manifestation, i.e., allergy) are not completely understand. Allergies and atopic responses are explored in the field of peripheric immunological responses and are characterized by an exacerbated reaction due to the lack of previous exposures or immature regulation of the immune system (as proposed by the hygiene hypothesis) [81]. On the other hand, autoimmune events possess another set of hypothesis and possible mechanisms. There are several studies showing that failures on the previously mentioned Aire and suppressor genes (e.g., Foxp3) may be involved, besides mutations that lead to decrease on the quality of the self-antigens presented by the thymus during lymphocyte positive/negative selections. In addition, modifications/mutation on the Major Histocompatibility Complexes (MHC) are described as an important factor leading to the development of autoimmune diseases [76,77,79,84,85].

In addition, modifications/mutations on the Major Histocompatibility Complexes (MHC), which are also known as Human Leukocyte Antigen (HLA), derived from the short arm of chromosome 6, are described as an important factor leading to the development of autoimmune diseases. The HLA is divided into three classes of regions and two classes of molecules. Regions I and II are responsible for encoding the chains and subregions for binding and immunological ligands, meanwhile region III encodes subcomponents, necrosis factors, and other cytokines. Class I molecules are present in virtually all nucleated cells, whereas Class II molecules exclusive to B-cells, antigen presenting cells and activated T-cells responsible for interaction with TCD4+ and TCD8+ respectively, being a product

of genetical polymorph and reorganization, uneven on distribution at a level on the surface of cells, it makes easier to understand the precision demanded on the cell-line selection and maturation and how mistakes can lead to autoreactivity [69,76,77,84-86]. It is known that the roles of B lymphocytes and CD4+ T lymphocytes in autoimmune diseases are well recognized, however evidence suggests that CD8+ T cells, in particular, are fundamental in the induction, progression, pathogenesis and protection of immune diseases [87]. The increase in CD8+ T cells, or cytotoxic T lymphocytes (CTL), had a potential role in different autoimmune diseases, such as systemic sclerosis, which contributed to skin fibrosis, in type I diabetes, these cells induced the death of β cells and in systemic lupus erythematosus (SLE), it triggered not only the appearance of antibodies but also organ damage [88].

The abnormal expression of regulatory T cells, derived from CD4+ T cells, promotes the differentiation of B cells that produce autoantibodies and, consequently, the appearance of several autoimmune diseases [88]. In Systemic Sclerosis, for example, the activation of T cells and the Th1/Th2, Th17 or T regulatory cytokine response play a fundamental role in the pathogenesis of this disease, especially the Th2 response, characterized by the production of IL-4, IL-10 and TGF -β, which lead to tissue fibrosis in these patients [89]. In psoriasis, Th1 cells play a key role. These cells secrete IFN-γ and IL-2 and are produced in the skin of most psoriatic lesions, demonstrating the role of Th1. Th17 cytokines, especially IL-17A, have been shown to influence the maintenance of inflammation in psoriatic plaques [88]. Similarly, in SLE, CD4+ T cell dysfunction has been reported, especially a subset of T helper cells, T follicular helper cells (Tfh), which are increased in SLE patients and may become differentiate into plasma cells, increasing self-reactive B cell clones leading to autoimmunity [90]. In Inflammatory Bowel Disease, which includes Crohn's Disease, CD4+ T cells are considered to be the main factor in IBD and therefore blocking or depleting CD4+ T cells is effective in these patients [88]. Apparently, the increase in Th17 cells in the synovial fluid of patients with rheumatoid arthritis suggests its association with the destruction of bone and cartilage in these patients [91]. Therefore, the importance of B and T cells in the pathogenesis of different autoimmune diseases is evident.

Autoimmune diseases are the result of inadequate immunological responses targeted to self-antigens in consequence to a complex interaction of genetic predisposition and environmental influence, such as cross-reactions to diverse antigens [81,92], resulting in a gamut of pathophysiologic pathways [93,94]. Considering common points or characteristics of the inadequate response, it is possible to group the autoimmune diseases either accordingly to the well-known pathophysiology or to the clinical presentation [95]. For instance, a great example of the aforementioned classification are the autoimmune diseases of the connective tissue, which can be characterized as:

i) Leucocyte activation and infiltration (e.g., Sjogren syndrome, autoimmune myopathies, and rheumatic polymyalgia).

ii) Inadequate tissue regeneration (e.g., scleroderma and mixed connective tissue disease); and

iii) Diseases triggered by immunocomplexes (e.g., antiphospholipid antibody syndrome and erythematous systemic lupus).

It is important to note that SLE is a disease of broad spectrum of manifestation and dynamic clinical occurrence, being able to present most of the fundamental characteristics of the collagenous diseases [73,74,96-101]. However, since the autoimmune diseases are mostly a multifactorial event, being the results of genetic predisposition, environmental influence, genetic mutation, and in different degrees, it is a hard mission to classify them or to pinpoint a single causative agent, if any [81,102]. A better comprehension on the profile of occurrence on autoimmune diseases by epidemiological study is not an easy task since there are described more than one hundred well-known autoimmune diseases so far; nonetheless, the Global Health Metrics and Global Health Data Exchange (http://ghdx.healthdata.org) have been struggling to provide the society an outlook on epidemiological data throughout the world [103,104]. Amongst the studied diseases available on Global Health Data Exchange are the rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, type 1 diabetes, alopecia areata, and rheumatic heart disease.

Association between Covid-19 and Autoimmune Diseases

Although the exact etiology of many autoimmune diseases is still unknown, it is known that viral infection is one of the main responsible for tolerance loss to autoantigen and consequent autoimmunity development [106]. Since 2019, SARS-CoV-2 became the most remarkable disease in the world, grabbing the attention of researchers that searched for the mechanism by which the immune system can be useful or harmful during COVID-19 pathogenesis [107]. In parallel, studies have been reported of patients that developed autoimmune disease concurrently or post COVID-19 infection. Such observations led researchers to question if autoimmune diseases have influence on the infection or severity of COVID-19 and vice-versa (Figure 2). In this section different autoimmune diseases and their relation to COVID-19 will be explored.

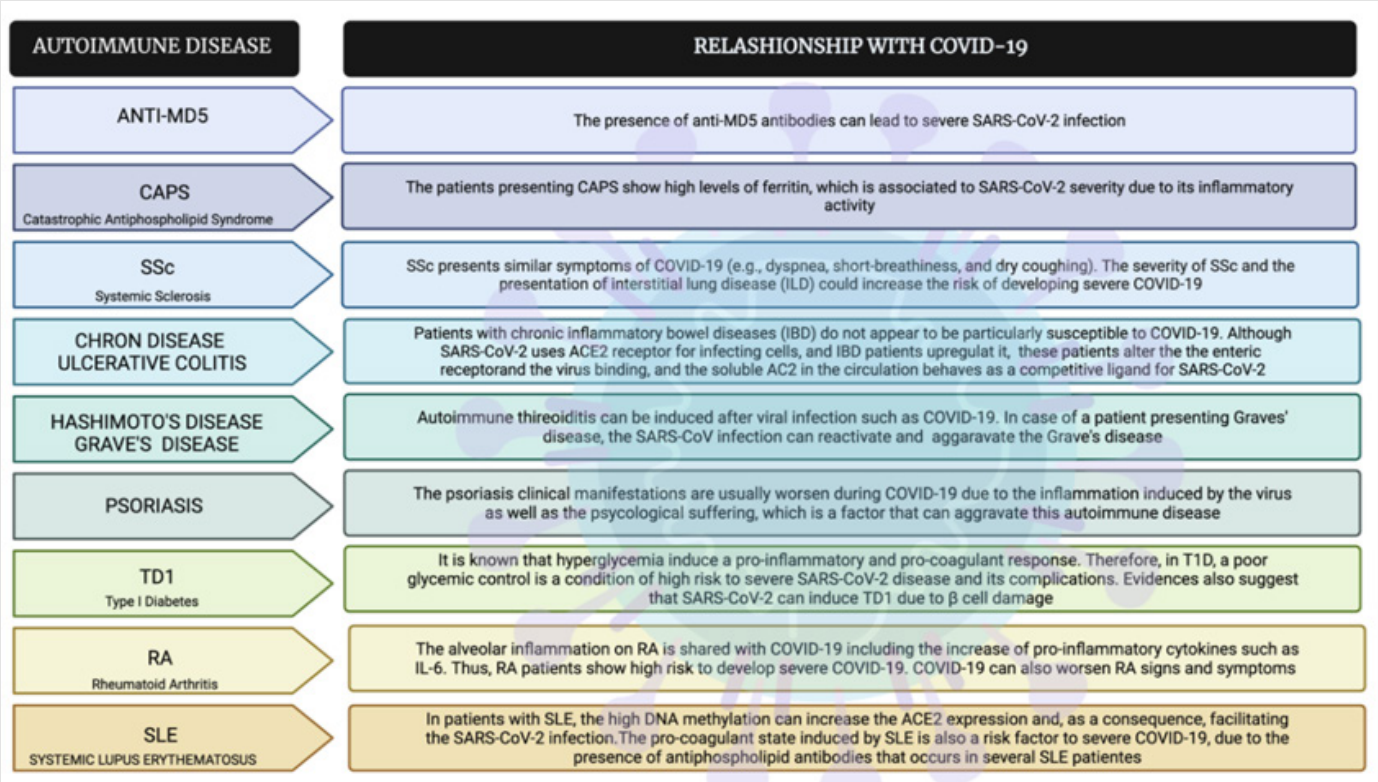

Figure 2: The crosstalk of Autoimmune diseases and COVID-19.

Influence of Specific Autoimmune Diseases on Covid-19

- Antimelanoma Differentiation-Associated Gene 5 (Anti-Mda5)

The anti-MDA5 is a rare autoimmune disease developed in patients presenting a variant of dermatomyositis (DM), which usually evolve to interstitial lung disease (ILD) [108]. The MDA5 is a receptor from the innate immunity that recognizes intracellular viruses resulting in the production of type I Interferons (i.e., a cytokine that suppresses the replication of viral particles). The hypothesis is that viral infection may be the initial event for the pathogenesis of DM. After the MDA5 cell pattern recognition receptors (PRRs) recognize the viral RNA, the sensor (MDA5) is activated and interacts with mitochondrial antiviral signaling proteins (MAVS), which activates the expression of interferon type I (IFN-I) genes. IFN-I proteins are exported outside the cell, and initiate an IFN signaling sequence when they bind to their receptors in neighboring cells, which results in the production of more IFN-I [109]. Self-tolerance, in turn, can be broken when occurs a release of damaged cells [110], which can expose privileged antigens (e.g., MDA5) and generate critical epitopes, developing a self-perpetuating autoimmune cycle [111]. About 3-58% of dermatomyositis patients evolve to interstitial lung disease (ILD), resulting in symptoms like the SARS-COV-2-induced manifestations, being the severe acute respiratory syndrome the main cause of lethality on ILD patients. Similar to COVID-19 infection, ILD does not have an established treatment [112], but it is known that ILD presents a good response to glucocorticoids, immunosuppressants, and anti-cytokine therapy, which also seems to benefit from agents antifibrotics and plasmapheresis. In COVID-19, glucocorticoids, anti-cytokine therapy, and plasmapheresis represent possible benefits in the treatment [108], suggesting that therapy for ILD may be an option for the treatment of COVID-19. Studies have reported that the presence of anti-MDA5 antibody in patients infected with SARS-CoV2 (about 48.2%) were prone to have a more severe disease course (a longer period of the disease, respiratory failure, shock, and others organic dysfunctions). It was also observed a high amount of anti-MDA5 antibodies in patients who progressed to death [113]. However, to the best of our knowledge, only one case of anti-MDA5 juvenile dermatomyositis have been reported in a pediatric patient who had their condition aggravated by SARS-CoV2. This patient had severe hypoxemic respiratory failure and progressed to ILD [114].

- Catastrophic Antiphospholipid Syndrome (CAPS)

CAPS is a serious manifestation of antiphospholipid syndrome, an autoimmune disease due to cardinal manifestations of thrombosis. CAPS is characterized by simultaneous multiple organ thrombosis. In

the classic form, the pathogenesis of the disease occurs by the presence of antiphospholipid antibodies targeting lipid binding proteins, such as β2 GPI, and thus activate endothelial cells, platelets, monocytes, trophoblastic cells, and neutrophils. In addition to acting directly on cells, antiphospholipid antibodies can also interrupt anti and procoagulant regulators, such as annexin V, protein C, prothrombin, and tissue factor [115]. The clinical manifestations of CAPS include the Systemic Inflammatory Response Syndrome, with an excessive release of cytokines similar of the observed in severe COVID-19 patients [116]. Moreover, it is known that one of the characteristics of CAPS is the high level of ferritin, an acute-phase protein [117], and in a study of 39 patients with SARS-CoV-2, the serum levels of this protein were directly associated with the severity of the infection. This can be explained because ferritin, in addition to its immunomodulatory activity, also plays pro-inflammatory functions, which culminate in the expression of several inflammatory mediators, including IL-1β [118]. Despite being a physiological metabolite, ferritin high levels alter due to inflammatory process, impairing its iron binding capacity and a reduction of functionality, due to cell destruction, especially hepatocytes. Such alterations lead to elevation of free iron levels, which increase the inflammatory reaction and induce oxidative stress by favoring the creation of hydroxyl radicals, leading to the formation of denser and easier-formed clots.

The coagulopathy is one of the most important complications that might happen in a patient with SARS-CoV-2, being the reason for the higher occurrence of encephalic vascular accident and, in some cases, disseminated intravascular coagulation, which are also complications during CAPS [118]. In addition, the third stage of COVID-19 infection is markedly characterized by a cytokine storm (see Section 1), including, but not limited to, the increasing of 1L-β, 1RA, IL-7, IL-8, IL-9, IL- 10, with most severe cases also showing high levels of IL-2, IL-6, granulocyte colony stimulating factor, INF-γ, TNF-α, and MCP-1. The same cytokines are also high expressed in CAPS' patients and it is well known that this cytokine storm can lead to multiple organ failure [119-121]. Despite the clinical similarities between CAPS and COVID-19, there was no case report of a patient presenting CAPS that was infected with SARS-CoV-2. On the other hand, it is speculated that the SARS-CoV-2 virus could induce CAPS, since few COVID-19 patients demonstrated to develop anti-phospholipid antibodies [122,123]. This is because infections, especially those caused by respiratory organisms as SARS-CoV-2, are considered one of the main risk factors for CAPS development. It seems that, through molecular mimicry, some infectious agents lead to non-pathogenic antiphospholipid antibodies and anti-β2-GPI. It is known that, in mice, there is an association between the Complement System and COVID-19 that supports CAPS pathogenesis [123].

- Systemic Sclerosis (SSc)

SSc is an autoimmune disease defined by vascular damage and lung fibrosis in 80% of the patients. Nearly 30% of the cases progress to ILD, which present radiological similarities to SARS-CoV-2, where the bilateral interstitial and subpleural affection are added to ground-glass opacities with or without consolidations. Moreover, the clinical manifestation of dyspnea, short-breathiness, and dry coughing is common to both diseases. The Computed Tomography (CT) on both diseases is of hard distinction, therefore a quick laboratorial trial is needed to determine the best therapeutic approach [124,125]. There is no proven evidence on the increased susceptibility of COVID-19 infection in patients with SSc; however, it is possible that patients treated with immunosuppressive drugs and/or severe ILD are at higher risk for developing a severe and progressive SARS-CoV-2 infection, which will largely depend on the severity of ILD due to SSc and lung function [126]. On the other hand, evidences support the fact the COVID-19 infection may cause SSc, via molecular mimicry or Aberrant NETosis, a way that, in normal conditions, microorganisms are trapped during an infection and causing autoimmunity [127-129].

- Chron's Disease (CD) and Ulcerative Colitis (UC)

CD and UC are chronic inflammatory bowel diseases (IBD) that affect millions of individuals and whose pathogenesis suggests an interaction between environmental factors and genetic susceptibility [130]. Inflammatory bowel diseases are often in need of immunosuppressive and immunomodulatory therapy and therefore present risks for opportunistic viral and bacterial infections [131]. It is known that the ACE2 receptor plays a central mechanism in the pathogenesis of COVID-19 and is found in abundance in the gastrointestinal tract, being highly expressed in the terminal ileum and colon, regions frequently affected by IBD. In addition to the transmembrane ACE2 receptor, a soluble form of ACE2 is present in the circulation in high concentrations in IBD. However, according to studies, enteric inflammation alters the expression of ACE2 receptors and host cell surface proteases, such as the transmembrane serine protease 2 protease (TMPRSS2), which hinders the adhesion and entry of SARS-CoV-2. It is also suggested that the soluble form of ACE2, which is positively regulated in IBD, behaves as a competitive ligand for SARS-CoV-2 by sequestering virus particles and thus preventing its binding to the cellular ACE2 protein, which is the gateway to the virus in the body. It should also be considered that the drugs used in IBD were able to decrease the expression of ACE2 in inflammatory cells. Therefore, patients with IBD do not appear to be particularly susceptible to COVID-19. Even though, it is prudent to consider the replacement, gradual reduction, or delay of systemic steroids in patients with IBD that are infected with COVID-19, considering their immunosuppressive character [131].

- Hashimoto Thyroiditis and Graves' Disease

The expression of ACE2 receptor for SARS-CoV-2 is notable in different endocrine organs, as the thyroid gland. In May 2020, it was evidenced the first report of acute thyroiditis in patients who

had COVID-19, which indicated a possible interaction between both. From then on, cohorts have been describing the relation between COVID-19 and thyroid dysfunction [132]. In a cohort study of 191 patients with moderate or mild COVID-19, a 13.1% rate of abnormal thyroid function test in patients was evidenced [132]. Two groups were identified, one consisting of 10 patients with low TSH (probably indicating thyroiditis) and the other with 10 patients with low free T3 (suggesting a non-thyroid syndrome). In this same study, the incidence of thyroid abnormalities suggested that thyroiditis was a manifestation presented in patients with severe COVID-19. This fact may suggest a potential viral effect on the thyroid gland, if confirmed by quantitative RT PCR test, which can measure SARS-CoV-2 viral load. The study also highlighted that a high level of C-reactive protein (CRP) was independently associated with free T3, and demonstrated that there is a decrease in free T3 levels when there is a worsening of the disease, and even associated with adverse effects including clinical worsening, need for dexamethasone and/or supplemental oxygen, and prolonged hospital stay. Most thyroid diseases are autoimmune in origin, such as Hashimoto's thyroiditis and Graves' disease [133], which can be either induced by viral infections or by molecular mimicry.

According to a study review, a pre-existing thyroid autoimmune disease may not make adults vulnerable to COVID-19, despite some studies have shown recurrence of Grave´s disease or Grave´s disease diagnosed about one month after SARS-CoV-2 infection [134]. There is a study that analyzed two cases involving patients diagnosed with Graves and COVID-19. One is a female patient who had Graves (12 years diagnosed with the disease) and 2 episodes of hyperthyroidism (2008 and 2015). In March 2020 this patient was presenting a normal thyroid function, but in May 2020 she was diagnosed with bilateral pneumonia, and it was evidenced infection by SARS-CoV-2. This patient presented a thyroid gland hypervascularization and symptoms as palpitation and nervousness. The other patient, female, 61 years old, with DG relapse in 2014, was presenting a normal thyroid gland function since 2016. When diagnosed with COVID-19 in March 2020, the patient had to be hospitalized. This patient also presented thyroid hypervascularization and symptoms as palpitations. Therefore, patients presenting prior GD presented those finding probably due to SARS-CoV-2 infection. Furthermore, studies have shown that infection by SARS-CoV-2 can lead to a thyroid autoimmune disease worsening due to modulation of the immune system, that leads to cytokine storm and consequently GD reactivation [134].

- Psoriasis

With the increase of COVID-19, a concern was also directed to patients with psoriasis due to the possibility that the immunosuppressive therapy used in patients could be a risk factor for SARS-CoV-2 infection [135]. This chronic immunoinflammatory disease of the skin affects about 2-3% of the world population, and it seems that the status caused by COVID-19 can alter the course of this disease. Authors conclude that psoriasis patients may be more vulnerable to COVID-19 and that psoriasis is possibly more aggravated due to COVID-19, as the hyperinflammation caused by SARS-CoV-2 can exacerbate dermatopathy [136]. In addition, the feeling of fear caused by COVID-19 can lead to excessive psychological suffering, which further aggravates the disease [135]. Indeed, a case report with a male psoriasis patient, 73 years old, who was following a diary treatment with cyclosporine (100mg) and a weekly treatment with methotrexate (7.5 mg), presented a psoriasis outbreak after stopping the psoriasis treatment during COVID-19 infection. This patient also had scaly plaques that evolved to an erythroderma. Indeed, authors suggest that the hyperinflammation state generated by COVID-19 can exacerbate the psoriasis condition. It is important to consider that the psoriasis treatment with the use of cyclosporine, which has as a side effect kidney dysfunction and hypertension could potentiate severe COVID-19 cases (138). Finally, it must be considered that the use of hydroxychloroquine, as a therapeutic alternative to COVID-19, can lead to an increase of IL-17, resulting in an increase in the growth of keratinocytes, whilst there is no clear evidence [135].

- Type 1 Diabetes (T1D)

Since the pandemic COVID-19 beginning, there are evidence about the relation between COVID-19 and Type 2 Diabetes (T2D). However, recent studies have portrayed the effects of SARS-CoV-2 infection and T1D [136]. T1D is an autoimmune disease, with a genetic influence, where auto-reactive T CD4+ and T CD8+ cells recognize pancreatic antigens as insulin or glutamic acid and, subsequently, destroy β cells insulin producers [137]. As T1D starts at an early age, it was thought that it had a viral etiology [136]. There are two hypotheses to the β cell damage pathogenesis induced by virus. One hypothesis considers the cell damage caused by lytic effects of the viral replication and/or damage caused due to an inflammatory response of the host cell by T CD4+ self-reactive cells leading to autoimmunity [137]. The β cells damage hypothesis can still be strengthened, once in a case series of 52 patients with acute COVID-19, 8 patients presented with pancreatic injury, manifesting lipase or amylase increase [136]. It is known that hyperglycemia induce a pro-inflammatory and pro-coagulant state due to changes in the immunological response and cytokines' dysregulation. Therefore, in T1D, as occurs with T2D, a poor glycemic control is a condition of high risk to bacterial and viral infection, including SARS-CoV-2 and its complications [136]. It must be considered that a sudden hyperglycemia has been associated to COVID-19 in adults with no previous history of diabetes. The inflammation induced by the infection and cytokines activation, as well as insulin resistance, can lead to stress hyperglycemia, generating a vicious cycle.

However, it is uncertain if the pancreatic islets destruction by virus leads to a decrease of the insulin production and release. In addition,

there are reports about severe metabolic decompensation provoked by COVID-19, as diabetic ketoacidosis in patients with a recent or pre-existing diagnosis of diabetes [138]. Possible explanations to this condition include β cell damage or ACE2 downregulation after the virus entrance, leading to angiotensin II without opposition, which can stop insulin secretion [138]. Thus, COVID-19 does not only increase the risk of death in T2D and T1D patients, but may also induce a new T1D condition [136].

- Rheumatoid Arthritis (RA)

The known mechanism of alveolar inflammation on SARS-CoV-2 is shared with RA, especially regarding the pattern of cytokines [139]. Despite the hierarchical order of the cytokines involved in SARS-CoV-2 infection remaining unknown, the pattern of effective pro-inflammatory cytokines on alveolar membrane shares similarities to those presented on RA, as much as in most of the aforementioned autoimmune diseases, where the excessive activation of IL-6 is a characteristic [120]. RA is a systemic and autoimmune disease that affect peripheral joints, especially feet and hands. There is no consensus about RA etiology, but it is known that there is an association between inflammation and synovial hypertrophy that leads to cartilage and bones destruction and, as a result, it generates damage and joint instability [140]. In general, RA patients have a high COVID-19 infectious risk compared to the general population, because these patients have a general impairment of the immune system which is also associated with an iatrogenic effect, due to the use of suppressive drug corticosteroids (see Section 4.2). In addition, these patients, when infected, are of great concern because these infections can contribute to the disease worsening [141]. A study shows that 2 of 4 patients diagnosed with RA and COVID-19 who stopped having rheumatic medications progressed to a severe COVID-19 state. It suggests that interruption rheumatic therapy can be considered a risk factor for the disease progress, particularly if the RA does not remain stable for a long time. Therefore, it is notable that patients diagnosed with immune rheumatic diseases are more prone to progress to a severe or critical COVID-19 state, especially if there is no control of the rheumatic disease [142].

- Systemic Lupus Erythematosus (SLE)

SLE if a chronic inflammatory disease predominantly female that can affect any organ [143]. The etiology or the physiopathology that initiate the autoimmune response in the SLE is still unknown [144], however, it is known that SLE is characterized by IFN type I unregulated responses and defective immune responses tolerance mechanisms [145]. Therefore, it manifests as an aberrant immune response, with the presence of circulating autoantibodies, lymphopenia, aberrant T cells and pro-inflammatory cytokines, conditions that result in immune-mediated damage in the tissues [143]. Patients with SLE present high risk of mortality 2 to 5 times the general population, whereas bacterial, viral and opportunistic infections represent the second cause of death in developed countries [145]. Such innate and adaptative disturbances in SLE can increase susceptibility to COVID-19, leading to prolonged viral shedding or predispose to severe illness [144]. Besides, in patients with SLE, DNA methylation, which is exacerbated by oxidative stress, can increase ACE2 expression and as a consequence the SARS-CoV-2 viremia. It is worth mentioning that pro-coagulant state induced by SLE, due to the presence of antiphospholipid antibodies that occurs in about 40% [146] of these patients, predisposes to thrombotic events, which can be even more pronounced in COVID-19 infection [144]. The management of SLE involves the use of antimalarials, biological and non-biological immunosuppressive agents [145] and steroids [144]. During the pandemic, several questions about the use of steroids increasing the risk and severity of COVID, due to their immunosuppressive action, were raised. However, immunosuppressive drugs, as well as steroids, do not appear to increase the risk or severity of COVID-19 infection, although more data on specific drugs is needed [144].

Influence of Drugs Used in the Treatment of Autoimmune Diseases

Based on the growing knowledge of the biology of SARS-CoV-2 and the pathophysiology of COVID-19, different studies recommend the use of several rheumatological drugs as potential treatments for COVID-19, especially in its severe form, further strengthening the relationship between COVID-19 and autoimmunity (Figure 3) [147,148]. Immunosuppressive, immunomodulatory, and anti-inflammatory activities are observed by using glucocorticoids (GC), drugs of choice for the treatment of most autoimmune and inflammatory diseases [149]. The binding of the GC to the glucocorticoid receptor (GR), a steroid receptor belonging to a family of nuclear receptors, activates signaling pathways for a transcriptional machinery involved in various mechanisms of suppression and modulation of immune responses, inducing apoptosis of various cell types of hematopoietic origin and suppression of the expression of several pro-inflammatory cytokine genes such as IL-1β, IL-4, IL-6, IL-8, IL-10, IL-12, IFN-γ, monocyte chemoattractant protein (MCP)-1, and TNF-α [8,150]. Similar to what occurred in the 2002-2004 severe acute respiratory syndrome outbreak of SARS-CoV-1, glucocorticoids have been recently used to treat severe SARS-COV-2 [151]. Thus, researchers have been exploring if patients presenting autoimmune diseases that permanently use glucocorticoids would be somehow protected from developing severe COVID-19.

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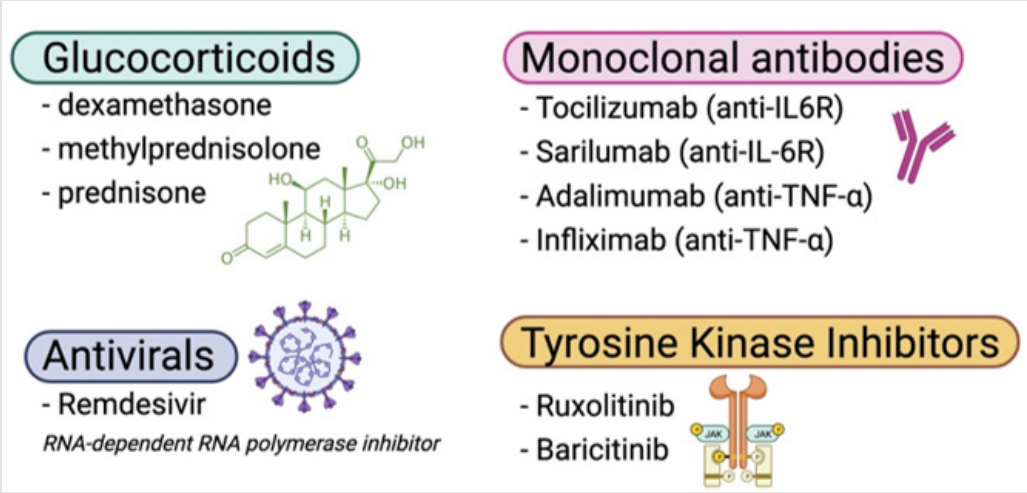

Figure 3: Drugs used for autoimmune diseases and COVID-19.

The use of glucocorticoids (preferably dexamethasone and alternatively methylprednisolone or prednisone) in hospitalized patients with severe COVID-19 and hypoxemic respiratory failure has been encouraged and recommended as a therapeutic option by important entities such as the WHO, national health institutions, Infectious Diseases Society of America (IDSA), in addition to being included in the COVID-19 Treatment Guidelines Panel [152,153]. Among the evidences, better radiographic findings and shorter duration of supplemental oxygen therapy stand out [154]. However, the recommendation of steroids in patients without hypoxemia still remains without great incentives [155]. Nevertheless, the use, efficacy, and safety of GC have been controversial since the onset of this disease due to the risks of acute respiratory syndrome and increased viral replication [156,157]. It is important to mention that some studies show discouraging data on the use of glucocorticoids in viral lung infections (e.g., influenza-induced pneumonia and SARS-CoV-1) with an increase in the mortality rate and length of stay in intensive care units, prolonged viremia, increase of the risk of bacterial superinfection, and increased risk of systemic complications such as autoimmune and cardiovascular events, in addition to promoting resistance to neuromuscular blocking agents, which are widely used during mechanical ventilation in patients with SARS [158,159].

Other immunosuppressing drugs recommended to treat autoimmunity have also been studied to treat COVID-19. Among them is Tocilizumab (RoActemra®), a recombinant humanized monoclonal antibody targeting IL-6 receptor that has as its main use in the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis (JIAs), and idiopathic polyarticular juvenile arthritis (AIJp), which showed positive advances in the treatment of COVID-19 on 21 Chinese patients in critical conditions [160-162]. Moreover, a study carried out with 128 patients with COVID-19 needing ventilatory support, in two hospitals in Italy, concluded that Tocilizumab (TCZ) was not effective in modifying mortality in 30 days of critically ill and critical patients, but it improved survival and reduced the need for mechanical ventilation in living patients 5 days after starting treatment with TCZ [161]. Another single-center study carried out with 100 patients with COVID-19 and acute respiratory distress syndrome (ARDS) at Hospital University Spedali Civili in Brescia (Italy) showed that the intravenous administration of TCZ had as its main outcomes: improvement of acute respiratory failure with suspension of noninvasive ventilation (NIV) and NIV stability in patients in the ward; and extubation and stability of patients in the Intensive Care Unit (ICU). The clinical improvement was in more than three quarters of the patients and the response to TCZ was rapid, in 12 to 72 hours, and sustained, as all patients with an initial response continued to improve in the following ten days. However, some patients got worse and progressed from the ward to the ICU and others even died [163].

Although randomized clinical trials investigating the efficacy and safety levels of tocilizumab are still ongoing, countries such as China, Italy, and the United States of America have introduced it as a therapeutic option in patients with severe and high levels of IL-6 [147]. Another monoclonal antibody targeting IL-6 receptor and fully human used in the treatment of rheumatoid arthritis and considered a potential therapeutic option for COVID-19 is Sarilumab (Kevzara®) [147]. However, the first large global, randomized, placebo-controlled clinical trial with patients from Asia, Europe, North, and South America, did not show efficacy of it on critically COVID-19 patients when used together with standard treatment [164]. In SARS-CoV-2

infection, peak proteins can induce the release of ectodomain ACE2, a process strictly coupled with the production of TNF-α [165]. Increasing this cytokine can facilitate viral infection, causing damage to the lungs and other organs and the elevation of this cytokine may be associated with severe cases of COVID-19 [166]. Due to the homology between the protein S structure of the SARS-CoV-1 and SARS-CoV-2, treatment with anti-TNFα was suggested as a possible treatment option in COVID-19 [147]. Adalimumab (Humira®), an anti-TNF-α human monoclonal antibody, that binds to TNF-α by blocking interaction with its soluble and membrane-bound receptors [167], have been used to treat several autoimmune diseases (e.g., RA, psoriatic arthritis, and CD) [168].

Vechi et al. [169] reported a case of a 36-year-old female patient with a medical history of severe Crohn's disease who presented pneumonia caused by COVID-19 and favorable evolution even with the use of immunosuppressive drugs used to treat the disease before and after the onset of COVID -19. Among the drugs, the patient used 40 mg of Adalimumab every other week. Another case reported by Narcisi et al. [170] involved a 57-year-old male patient with a 9-year history of psoriasis and psoriatic arthritis treated with adalimumab every 2 weeks for nearly two years before the onset of symptoms of COVID-19 who coursed with pulmonary pneumonia without the need for oxygen support. In addition to anti-TNF-α antibody that plays an important role in the control several autoimmune diseases, such as inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondylitis, is Infliximab (IFX) [171]. A series of cases with seven COVID-19 patients who were treated with IFX showed a rapid and temporary reduction in inflammatory markers and pro-inflammatory cytokines (such as IL-6) by 85.71% (6 patients), who previously had a gradual hyperinflammation before the administration of IFX [172]. Studies have shown the use of anti TNF-α as a mechanism to treat viral pneumonia [173]. It is also reported that the use of this type of monoclonal antibody can decrease TNF-α levels [174] and be a possible tool to treat COVID-19 [175]. However, the use of this antibody may imply side effects, including risk of infection by fungal or bacteria (176) and ACE2 expression downregulation and shedding [176,177].

An important step in SARS-CoV-2 infection is the viral invasion of pneumocytes by clathrin-dependent endocytosis [178]. This transport is promoted by members of a family in the group of tyrosine kinases (JAK), the kinases associated with numbness (NAK) [147]. Therefore, tyrosine kinase inhibitors, such as Baricitinib and Ruxolitinib, targeted at members of the NAK family, became potential therapy to inhibit SARS-CoV-2 viral activity, also limiting the systemic inflammatory response and cytokine production through inhibition of the JAK-STAT canonical pathway [179]. Baricitinib (Olumiant®) is a reversible oral inhibitor of JAKs [180], preferably JAK 1 and JAK 2 [111]. Inhibition of JAKs autophosphorylation prevents the phosphorylation of the intracellular tails of the receptors, which act as anchorage sites for the Transducers and Signal Transcription Activators (STAT), and consequently the transduction of intracellular signaling for the expression of cytokines [181]. It is approved for the treatment of moderate to severe RA in more than 40 countries [182] and plays roles in signaling surface receptors for various inflammatory mediators that are associated with RA pathogenesis, such as IL-6 and IL-23 [183,184], in addition to have clinical utility in autoimmune dermatological diseases, such as psoriasis [177].

It is now known that Baricitinib is a suppressor of multiple cytokine signaling implicated in COVID-19 immunopathology [183] as IFN-γ, macrophage granulocyte colony stimulating factor, IL-2, IL-10 [185], and, especially, IL-6, whose high levels seem to be a predictor of mortality [182]. However, there are important concerns about the mechanism of action of the drug, its safety, and efficacy profile. Primarily, because it was pointed out that SARS-CoV-1 uses several endocytic pathways for the entry of the virus and, if the same occurs with SARS-CoV-2, the mechanism of action of Baricitinib can be circumvented [183]. It has also been proposed that Baricitinib has an inhibitory effect on type I interferon (IFN) signaling, since it uses the JAK/STAT signaling pathway [186]. Type I IFN is known to be an innate antiviral response that suppresses viral replication in the early stage of infection [183,186].

However, recent studies have shown that IFN-I and, to a lesser extent, IFN type II, increase the expression of ACE2 in several cell lines, including upper airway epithelial cells and primary bronchial cells. Theoretically, suppression of IFN-I reduces the expression of ACE2 and, consequently, interferes with the virus's ability to infect the cell. However, ACE2 is also a counter-regulator of the angiotensin-aldosterone system and has a protective action against damage to organs belonging to this system, which includes acute lung injury. It is observed that one of the main virulence factors of SARS-CoV-2 is the ability to decrease the expression of ACE2 after infection, avoiding protection against lung injuries. It is believed that the suppression of INF type I by Baricitinib amplifies the negative regulation of ACE2, further depreciating these protective effects [187]. It has also been observed that suppression of the IFN type I-mediated antiviral response further increases the risk of herpes zoster and herpes simplex infection, therefore, the use of the drug should be considered with great caution [186]. Similarly, Ruxolitinib (Jakaf®) is a JAK1 and JAK2 protein kinase inhibitor indicated for those diagnosed with JAK2 mutated myeloproliferative neoplasms, also covering polycythemia vera and myelofibrosis [187,188]. Moreover, a study demonstrated that the treatment of Hemophagocyte lymphohistiocystosis (HLH) with Ruxolitinib led to symptoms improvement and inflammatory markers betterment [189-191]. HLH is a disease characterized by an increase of pro-inflammatory cytokines, that regularly leads to a cytokine storm event [189,192]. As it happens with HLH, severe cases

COVID-19 also shows a pro-inflammatory cytokines increase [192]. To have an anti-inflammatory result in COVID-19 cases, the use of Ruxolitinib would target cytokines (IL-2, IL-7, IL-10, IFN- γ, G-CSF and GM-CSF) that use JAK1 and or JAK2 signal.

Studies have shown that the use of Ruxolitinib has not being associated to a clinical improvement of COVID-19 severe cases, although it did showed a quantitative faster clinical improvement in Ruxolitinib recipients [193]. Besides, it was reported, in two COVID-19 patients that used it, adverse reactions, resulting in Ruxolitinib discontinuation [194]. In May 2020, the first phase of the Adaptive Covid-19 Treatment Trial (ACTT-1), demonstrated that the drug Remdesivir (Veklury®; Gilead Sciences) had an effective action in patients hospitalized with COVID-19 pneumonia [185]. Remdesivir, formerly called GS-5734, is an adenosine nucleotide analogue that has broad-spectrum antiviral activity on viruses such as respiratory syncytial virus, Nipah virus, Ebola virus (EBOV), Middle East respiratory syndrome (MERS-CoV), and SARS-CoV-1 [195,196]. Pharmacologically, the drug was designed to deliver the nucleoside monophosphate analog GS-441524 to cells. Thus, Remdesivir acts by inhibiting viral RNA polymerases, through its intracellular metabolism, in which it is converted into an ATP analogue [195]. Remdesivir had an inhibitory capacity on all animal and human coronaviruses in vitro. In the preliminary report of the randomized, double-blind, placebo-controlled trial, it was found that Remdesivir had a recovery time 31% faster compared to placebo in patients with COVI-19. The fact led the United State Food Drug Administration (US FDA) to admit the emergency use of Remdesivir to treat children and adults with severe COVID-19 defined by SpO2 ≤ 94% in ambient air, with the need for supplemental oxygenation, mechanical ventilation, or extracorporeal membrane oxygenation [195].

Multinational clinical trials in adaptive progress evaluated the combined use of Remdesivir and Baricitinib versus Remdesivir plus placebo in adults hospitalized with COVID-19 [185]. It was then observed that the combination of Remdesivir and Baricitinib was superior to Remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, especially in those who received high flow oxygen or non-invasive ventilation. This combination is associated with fewer serious adverse events [185]. The security profile of Remdesivir is not yet fully understood in the context of COVID-19. Adverse events (≤5%) in healthy subjects such as phlebitis, constipation, headache, bruising, nausea and extremity pain were observed in 4 blind phase I studies. Special attention is given to hepatic and renal aspects, as there is an increase in the liver enzyme ALT and a decrease in the Glomerular Filtration Rate (GFR) during treatment with Remdesivir. The drug has shown some positive results in patients infected with SARS-CoV and MERS-CoV, although its effectiveness in treating COVID-19 is not fully understood. Therefore, future trials will be essential to establish the cost-effectiveness of Remdesivir [196]. In conclusion, several immunoregulatory therapies used to treat autoimmune diseases have also been used in the treatment of COVID-19, such as corticosteroids, monoclonal antibodies targeting cytokines/cytokines' receptors and tyrosine kinase inhibitors.

SARS-CoV-2 Inducing Autoimmunity

The possible development of autoimmunity following SARS-CoV-2 infection brings to the current context of the pandemic a well-known scenario: the cross-link of infection and autoimmunity [197]. It is known that COVID-19 presents an inflammatory response profile similar to autoimmune diseases [198]. Autoimmune diseases can be trigged by different mechanisms [9,10]. Among these mechanisms, molecular mimicry is the main mechanism by which a pathogen induces autoimmunity [199]. The classic example of molecular mimicry is represented by rheumatic fever [200], in which the person develops rheumatic carditis following a throat infection caused by Streptococcus pyogenes, an autoimmune condition characterized by the molecular mimicry of epitopes between group A streptococci and surface proteins of the valves from heart endothelium (e.g., laminin) [200,201]. However, it should be noted that molecular mimicry is only one of the hypotheses for the pathogenesis of rheumatic fever. The mechanisms involved in the loss of self-tolerance and how the immune system targets the heart valve tissue are not yet fully understood [202].

Other well-known association of autoimmunity following infection is the development of Guillain Barre Syndrome (GBS) after Campylobacter jejuni infection [203]. COVID-19 has a broad clinical spectrum, ranging from mild presentations such as oligosymptomatic grippe to systemic presentations with repercussions on multiple organs, such as kidneys, heart, lungs and brain [204,205]. Although the mechanism of the disease severity is still unclear, studies have shown that molecular mimicry may be one of the causes of the COVID-19 severity [3]. The fact is that the long-term effects of chronic diseases such as COVID-19 cause cell stress through hypoxia and systemic inflammation, resulting on the overproduction of anti-stress proteins, molecules that share immunogenic epitopes with SARS-CoV-2 [204]. Anti-stress proteins are intracellular molecules that, in certain circumstances (e.g., COVID-19), can undergo post-translational modifications being externalized on the cell surface. This phenomenon can induce break of self-tolerance resulting in autoimmunity [206-208].

Moreover, a proteomic study pointed heat shock proteins and chaperones share antigenic epitopes with the SARS-CoV-2 virus, which could be responsible for triggering autoimmunity through molecular mimicry. Indeed, heat shock proteins are very similar in all organisms, from unicellular to the most complex multicellular and there is evidences of autoimmunity following cross-reactivity

between chaperones and microbial molecules [204,209,210]. In the current context, neurological damage as a result of SARS-CoV-2 infection still has an unknown pathogenesis [211,212]. However, there is a hypothesis that neuropathies in COVID-19 may be a consequence of molecular mimicry between SARS-CoV-2 and human self-molecules involved in inflammatory polyneuropathies such as GBS and Myasthenia Gravis [213,214].

Actually, there is evidence of autoantibodies targeting heat shock proteins in the cerebrospinal fluid of patients with GBS, MS, and other immune-mediated neurological diseases [215]. For instance, two epitopes (KDKKKK and EIPKEE) shared between human HSPs (HSPs 60 and 90) and Sars-CoV-2 have been associated with immune-mediated neuropathies [214]. Nevertheless, it is not known if these peptides are among the immunodominant epitopes of SARS-CoV-2 [210,216]. In addition, neurons' proteins such as DAB1, AIFM, and SURF1 demonstrated to share antigenic epitopes with SARS-CoV-2. Thus, through molecular mimicry between neural proteins and viral proteins, damage to the respiratory pacemaker can occur, which can contribute to COVID-19 respiratory failure. The autoimmune activity to the pacemaker may explain the clinical dissociation between well-preserved pulmonary mechanics and the severity of hypoxemia [217,218]. A similar hypothesis has been raised to explain the anosmia during COVID-19. The erroneous attack of the immune system to 7D4 odor receptors (OR7D4), which are proteins in the plasma membrane of olfactory sensory neurons [21,22]. Vascular damages during COVID-19 can also be caused by molecular mimicry. The immune attack of the integral membrane protein Solute Carrier Family 12 Member 6 (SLC12A6) has been documented, a protein responsible for the reduction of intracellular chloride [217-218].

The most important of protein from this class is KCC3 [219] found in endothelial cells of several organs, including vessels of the heart, brain, kidney, liver and lungs. The disseminated intravascular coagulation, thrombosis, multiple organ failure and Kawasaki vasculitis may be evolutions of these vascular damages [217]. Therefore, molecular mimicry may be one of the most important mechanisms that could generate autoimmunity following COVID-19, even though others such as epitope spreading, bystander activation, production of superantigens, and aberrant activation of the immune response, could also be involved [220-226].

Conclusion

Despite being more than a year and a half into the COVID-19 pandemic, the potential association between COVID-19 and autoimmune diseases remains largely unexplored. However, emerging evidence suggests that COVID-19 has the potential to trigger autoimmunity, while pre-existing autoimmune conditions may worsen COVID-19 outcomes. Therefore, the correlation between COVID-19 and Autoimmunity is a genuine concern, although the underlying mechanisms that drive this association are yet to be fully understood.

Conflict of Interest

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

The main idea for this work was conceived by RM, MNF, and MP. FC took charge of elaborating the figures, while all authors provided manuscript corrections and made important contributions during the work's development. The final submitted version of the review has been approved by all authors.

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