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As the world navigates the coronavirus disease 2019 (COVID-19) pandemic, there is a growing need to assess its impact in patients with autoimmune rheumatic diseases, such as systemic lupus erythematosus (SLE). Patients with SLE are a unique population when considering the risk of contracting COVID-19 and infection outcomes. The use of systemic glucocorticoids and immunosuppressants, and underlying organ damage from SLE are potential susceptibility factors. Most patients with SLE have evidence of high type I interferon activity, which may theoretically act as an antiviral line of defense or contribute to the development of a deleterious hyperinflammatory response in COVID-19. Other immunopathogenic mechanisms of SLE may overlap with those described in COVID-19, thus, studies in SLE could provide some insight into immune responses occurring in severe cases of the viral infection. We reviewed the literature to date on COVID-19 in patients with SLE and provide an in-depth review of current research in the area, including immune pathway activation, epidemiology, clinical features, outcomes, and the psychosocial impact of the pandemic in those with autoimmune disease. (Translational Research 2021; 232:13 – 36)

Abbreviations: Act-1 = Adaptor protein NF-κ activator; ACE2 = Angiotensin-converting enzyme 2; AZA = Azathioprine; C5aR1 = C5a receptor; COVID-19 = Coronavirus disease 2019; C-19-GRA = COVID-19 Global Rheumatology Alliance; CYC = Cyclophosphamide; EBV = Epstein-Barr virus; HCQ = Hydroxychloroquine; ICU = Intensive care unit; IFN = Interferon; IRF = Interferon regulatory factor; ISG = Interferon-stimulated gene; IFNAR = Interferon-α/β receptor; IL = Interleukin; JAK = Janus kinase; LOF = Loss-of-function; MASP-2 = Mannan-binding lectin associated serine protease-2; mTOR = Mechanistic (mammalian) target of rapamycin; MMF = Mycophenolate mofetil; MyD88 = Myeloid differentiation primary response 88; NAC = N-Acetylcisteine; NET = Neutrophil extracellular trap; NYC = New York City; pDC = Plasmacytoid dendritic cell; PI3K = Phosphatidylinositol 3-kinase; pS6 = Ribosomal protein 6; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; STAT = Signal Transducer and Activator of Transcription; SDH = Social determinants of health; sGC = Systemic glucocorticoids; SLE = Systemic Lupus Erythematosus; Th17 = T helper 17; TBK1 = TANK-binding kinase 1; TLR = Toll-like receptor; TNF = Tumor necrosis factor; TRAF = Tumor necrosis factor receptor-associated factor; TRIF = TIRdomain-containing adapter-inducing interferon-β
INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19), has infected millions of people worldwide. The mortality of the virus is likely underestimated in official counts, as we have observed a 20% increase in deaths over the average expected number between March 1 and August 1, 2020 in the United States. It is clear that outcomes following COVID-19 infection vary considerably between people, and some populations are at particularly high risk. Thus, there has been a need to assess the impact of COVID-19 in patients with autoimmune disease, including those with systemic lupus erythematosus (SLE).

Patients with SLE are a unique population when considering the risk of contracting COVID-19 and the outcomes of the infection. The underlying organ damage from SLE and the use of systemic glucocorticoids (sGC) and immunosuppressants could be risk factors for the development of severe COVID-19. SLE is more prevalent and severe in ancestrally African and Hispanic patients, which overlaps with high-risk groups associated with poor outcomes of COVID-19, although the association with the latter may be mediated more by social determinants of health (SDH) as opposed to biologic factors. In contrast, SLE is a female-predominant disease which may represent a protective factor, as COVID-19 has been shown to affect males more severely. One interesting feature is that inflammation in SLE is often characterized by elevation of type I interferon (IFN), which has antiviral properties and could potentially be protective. This is not known, however, and even if true, it could be offset by other sociodemographic, biologic, and clinical aspects of the disease and its management. In addition, excessive complement activation with consequent development of thrombotic microangiopathy has been identified in many patients with COVID-19 and seems to at least partially mediate organ dysfunction in severe cases, resembling a complement-mediated thrombotic microangiopathy. Although complement consumption is a classic feature of SLE, the classical pathway is often the main target of activation by immune complexes in SLE, whereas the alternative and lectin-based complement pathways seem to play a greater role in COVID-19 pathogenesis.

There have been substantial scientific efforts around the world to elucidate COVID-19 pathogenesis, risk factors, optimal management, and prevention strategies. Similarly, data on the impact of the pandemic in patients with SLE has grown significantly in recent months. Accordingly, we provide an overview of the susceptibility factors to viral infections in patients with SLE and potential immunologic and pathologic overlaps between COVID-19 and SLE, as well as data regarding the epidemiology, clinical features, outcomes, and psychosocial impact of COVID-19 in SLE patients.

RELATIONSHIP BETWEEN SLE AND RISK OF VIRAL INFECTIONS

SARS-CoV-2, a single-stranded RNA virus and the causal agent of COVID-19, has infected millions of people worldwide. The virus enters the cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which determines viral tropism. The type 2 transmembrane serine protease is also required to complete the fusion process by cleaving the ACE2 molecules and activating the SARS-CoV-2 S protein. The clinical spectrum of COVID-19 is broad, ranging from asymptomatic infection to life-threatening cytokine storm, acute respiratory distress syndrome, and multiorgan dysfunction.

SLE is a chronic multisystem autoimmune disease characterized by dysregulated type I IFN responses and defective immune tolerance mechanisms. Patients with SLE have an increased risk of mortality that is 2—5 times the rate of the general population. Bacterial, viral, and opportunistic infections are common in SLE and account for the second leading cause of death in this group in developed countries, ranging from 25% to 50% of mortality cases. Infections in patients with SLE tend to be more frequent during the initial 5 years after diagnosis, which could reflect underlying disease pathogenesis or aggressive immunosuppressive therapy at the outset of disease.

Functional abnormalities in the immune system due to intrinsic factors and the use of immunosuppressive therapies both contribute to infection risk in patients with SLE. Immune cells are affected in SLE in both number and function. Lymphopenia and neutropenia can occur either due to active inflammation in SLE with increased apoptosis of immune cells or as a side effect of immunosuppressants. CD8 T cell responses are impaired in SLE patients, including defects in phagocytosis and chemotaxis. Interestingly, Katsuyama et al recently reported the presence of CD8+T cells highly expressing CD38 in a subset of patients with SLE and high incidence of infections, independent of disease activity, organ damage and disease flares. These CD8CD38high T cells exhibited decreased cytotoxic capacity, degranulation, and expression of perforin and granzymes, providing a mechanism by which abnormalities in cellular immunity may lead to an increased susceptibility to infections in patients with SLE. Complement dysregulation is common in SLE and worsens with
disease activity. Hypocomplementemia has been identified as an independent predictor of infection in SLE patients. Interestingly, genetic deficiencies in complement components can predispose to SLE, as well as other primary immunodeficiency disorders. Furthermore, low immunoglobulin (Ig) levels, particularly IgG subclasses and IgM, have been identified in patients with SLE, which may also contribute to the increased susceptibility to infections.

Herpes zoster is frequent in SLE, occurring in up to 40% of patients. Certain SLE-specific factors have been associated with herpes zoster, including lymphopenia and anti-Ro antibodies. As expected, the use of sGC and immunosuppressants such as cyclophosphamide (CYC) are also associated with a greater risk of herpes zoster and other viral infections. Cyto-megalovirus and upper respiratory tract viral infections are common in the SLE population, and may present with severe and atypical manifestations that mimic SLE flares.

Respiratory infections are one of the most common causes of hospitalization and early mortality in patients with SLE. Elderly individuals (≥65 years of age) with rheumatic conditions are at greater risk of influenza and influenza-related complications. Influenza pneumonia often precedes bacterial infections, which may lead to prolonged hospitalizations and overall worse outcomes. In patients with SLE, viral infections can also trigger SLE flares after the virus is cleared. In comparison, Influenza A infection in lupus-prone Faspr mice is cleared effectively and is not associated with worsening autoimmune features in the acute setting, although these mice can subsequently develop severe pulmonary inflammation weeks after viral clearance. Notably, annual vaccination against influenza is associated with decreased hospitalization and intensive care unit (ICU) admissions in patients with SLE; hence this practice is highly encouraged.

In addition to the increased susceptibility to certain viral infections in SLE, the role of exogenous viruses in triggering autoimmunity has also been proposed. Epstein-Barr virus (EBV) is a potential environmental factor involved in SLE pathogenesis. Although most acute EBV infections occur during childhood, EBV remains latent in B cells and can subsequently reactivate. EBV stimulates the proliferation of autoreactive B cells, acts as a superantigen in T cells, and stimulates IFN- production by plasmacytoid dendritic cells (pDCs). Additionally, studies have demonstrated evidence of molecular mimicry between EBV proteins and nuclear antigens, and the EBV nuclear antigen 2 protein can bind to several SLE risk alleles, suggesting important mechanisms by which EBV can trigger autoimmunity. The role of other viruses such as cytomegalovirus in the pathogenesis of SLE is less clear.

CONVERGENT IMMUNOPATHOGENIC MECHANISMS OF COVID-19 AND SLE

Type I interferons. Various lines of evidence have suggested a crucial role of type I IFNs in the course of disease and outcomes of COVID-19. The antiviral properties of type I IFNs are well known and many viruses have developed strategies to escape their inhibitory effects. Furthermore, most patients with SLE have evidence of elevated circulating type I IFN or show overexpression of type I IFN genes in circulating immune cells; therefore, it is conceivable that IFNs are a critical point of convergence between SLE and COVID-19.

Previous murine studies on SARS-CoV had demonstrated that exuberant viral replication coupled with delayed type I IFN responses are associated with decreased survival. In vivo and in vitro models of SARS-CoV-2 infection have shown evidence of inappropriate antiviral and dysregulated inflammatory responses, characterized by low levels of type I and type III IFNs, high levels of multiple chemokines and IL-6. Consistent with these observations, a more recent study found that patients with severe and critical COVID-19 displayed significant impairment in the type I IFN response, with lack of IFN-β, low IFN-α activity and plasma levels, as well as a higher SARS-CoV-2 viral load, and increased tumor necrosis factor (TNF)-α and IL-6. As certain conditions such as obesity, cancer and aging may be associated with decreased type I IFN signaling, it is also possible that these conditions contribute to a dysfunctional IFN response in COVID-19. In addition, pDC depletion and functional impairment have also been identified in patients with COVID-19, with decreased production of IFN-α by these cells in vitro. A single-cell gene expression study of peripheral immune cells showed upregulation of several IFN-stimulated genes (ISGs) in CD14+ monocytes, although the IFN signature was heterogeneous among COVID-19 patients and cell types. Another study evaluating cells obtained from the respiratory tract of patients with COVID-19 via bronchoalveolar lavage showed marked expression of “proinflammatory” ISGs compared to cells from patients with community-acquired pneumonia and SARS-CoV infection. The ISG expression presumably decreased over time in COVID-19 patients who survived when comparing cells collected from different
patients ranging from days 4 to 15 from the onset of symptoms. In contrast, cells from the deceased patient showed robust ISG expression, despite being obtained at day 12 after symptom onset. Although the small sample size and lack of longitudinal data for each patient are potential limitations of this study, these findings could suggest that a persistent and/or delayed type I IFN response may be associated with worse outcomes. Results from a recent study also suggest a temporal shift in the cytokine response in patients with COVID-19, ranging from an early type I IFN-predominant response to a proinflammatory response in later stages of the disease. Interestingly, this study also found an impaired type I IFN response and marked reduction in proinflammatory cytokine production by circulating monocytes and myeloid dendritic cells, despite elevated levels of these cytokines in plasma, suggesting the source is likely to be the lungs rather than peripheral blood cells.

Several inborn errors that directly or indirectly involve type I and type III IFN pathways are also associated with life-threatening viral infections secondary to the influenza virus, live-attenuated vaccines, and other viruses. These include genetic defects in the IFN-α/β receptor-1 and -2 (IFNAR-1 and IFNAR-2), IFR3, IFR7, IFR9, IFIH1, TLR3, TBK1, TICAM1/TRIF, STAT1 and STAT2. TLR3 and IFIH1 (also known as MDA5) are pattern recognition receptors that bind
viral RNA. TLR3 and TLR7 induce type I IFN production via activation of IRF-3 (mediated by TBK1 and TICAM1/TRIM) and IRF7, respectively. IRF9, STAT1 and STAT2 are components of the IFN-stimulated factor gene 3 (ISFG3) complex, which is part of the intracellular downstream pathway activated by type I IFN (Fig 1).

Interestingly, the structural SARS-CoV-2 N protein has also been shown to antagonize IFN signaling by suppressing phosphorylation and translocation of STAT1 and STAT2, representing a potential viral mechanism to evade the innate immune response. GATA2 deficiency, a pleiotropic syndromic disorder, is also associated with increased susceptibility to viral infections, at least partially due to the absence of pDCs in this disorder, a major cell type in producing type I IFN.

In agreement with the antiviral role of type I IFN, a case series identified rare missense and nonsense putative loss-of-function (LOF) variants involving TLR7 in 4 young previously healthy males with critical COVID-19; these variants were associated with impaired type I and type II IFN response in these patients. A recent study showed that rare LOF variants involving TLR3- and IRF7-mediated type I IFN response were enriched in patients with life-threatening COVID-19 when compared to subjects with mild or asymptomatic SARS-CoV-2 infection. Genetic defects at 8 loci (TLR3, UNC93B1, TICAM1/TRIF, TBK1, IRF3, IRF7, IFNAR 1, and IFNAR2) involved in type I IFN signaling were identified in 3.5% of patients. Interestingly, prior to COVID-19, these patients had not had any life-threatening viral infection, which may relate to the increased virulence of SARS-CoV-2 compared to influenza and other common respiratory viruses (Fig 1). Some of the autosomal dominant genetic disorders were newly identified, including UNC93B1 (a chaperone that regulates endosomal TLR stability), IRF7, IFNAR1, and IFNAR2 deficiencies. Conversely, several risk genes linked to type I IFN have been associated with SLE, many of which are gain-of-function variants. One of such examples is the IFIH1 rs1990760 gene variant, which is associated with the presence of anti-double-stranded DNA antibodies and increased sensitivity to IFN-α in SLE.

Interestingly, other IFIH1 polymorphisms have been associated with increased risk or protection for the development of type 1 diabetes mellitus, suggesting a spectrum of immunomodulatory roles of type I IFN-related molecules that span from the development of autoimmunity to susceptibility to life-threatening viral infections.

The presence of neutralizing autoantibodies to certain type I IFNs, mainly IFN-α2 and IFN-α1, was recently demonstrated in 101 out of 987 (10%) patients with severe outcomes of COVID-19, including death, who were predominantly male (94%). Interestingly, in 5 of these patients, the authors were able to demonstrate that the autoantibodies preceded the development of COVID-19, suggesting their development is a cause rather than a consequence of the viral infection. Furthermore, none of the patients with asymptomatic or mild COVID-19, and only 4 of 1227 healthy individuals had detectable type I IFN autoantibodies. In addition, none of the patients with LOF mutations affecting IFN pathways had neutralizing antibodies against type I IFN, strongly suggesting there seem to be at least 2 independent mechanisms by which dysfunctional IFN signaling leads to an increased susceptibility to life-threatening COVID-19. Previous studies have found that approximately 25% of patients with SLE have anti-IFN antibodies. The most common type I IFN autoantibodies in SLE are against IFN-α2 and IFN-α1, as seen in severe COVID-19. In addition, some of these anti-IFN antibodies were shown to be effective at neutralizing type I IFN activity in vitro, and patients with neutralizing antibodies tended to have lower SLE disease activity. Whether patients with SLE and anti-IFN antibodies are more susceptible to contracting COVID-19 or experience worse outcomes remains to be elucidated.

Given the evidence that the lack of an appropriate type I IFN response is associated with worse outcomes and retrospective data suggesting improved inflammatory markers and a shorter duration of detectable virus in COVID-19 patients treated with IFN-α2b, various clinical trials assessing the efficacy of type I IFN therapy in COVID-19 are ongoing. A recent phase 2 trial of nebulized IFN-β1a met its primary outcome of clinical improvement in COVID-19. In contrast, interim results of the World Health Organization Solidarity trial suggest IFN-β-1a was not effective at improving COVID-19 overall mortality, initiation of mechanical ventilation, or duration of hospital stay. However, it is possible that the timing of administration is crucial to ensure the benefit of exogenous type I IFN administration in COVID-19, as an early IFN surge may be needed to achieve optimal antiviral effects, whereas a delayed response could contribute to the deleterious hyperinflammatory response. This hypothesis may help explain some of the contradictory findings with respect to type I IFN in COVID-19, and inconsistent definitions of severe COVID-19 likely also contributes to the dissimilar observations. It may be that type I or type III IFN pathway-enhancing agents are beneficial in the early stages of SARS-CoV-2 infection, while immunosuppressive drugs, such as Janus kinase (JAK) inhibitors, anti-IL1 drugs, or sGC would provide the most benefit at treating the excessive and deleterious inflammatory response (ie, cytokine storm) that ensues in later phases of COVID-19 course.
SARS-CoV-2 enters the host cells by binding to ACE2 in the cell membrane, hence the viral tropism depends on the level of ACE2 expression in each cell type. For instance, ACE2 expression is abundant in type II pneumocytes, enterocytes, and nasal goblet secretory cells. Interestingly, ACE2 has been postulated as an ISG, as IFN-α drives ACE2 expression in human upper airway basal cells, which would suggest potential deleterious effects of type I IFN by eliciting an increased risk of SARS-CoV-2 infection and viral dissemination. However, this issue is not settled as a consequence of the epigenetic dysregulation present in patients with SLE, demethylation of ACE2 can lead to overexpression and increased susceptibility to SARS-CoV-2, while demethylation of IFN-regulated genes and other genes related to cytokine expression may lead to the development of a cytokine storm in the setting of COVID-19.

Finally, most studies evaluating the risk of viral infections in patients with SLE are observational and confounded by long-term sGC and immunosuppressant use. However, it is possible that the baseline increased IFN activity in SLE exerts a protective role against contracting or developing worse outcomes of COVID-19; hence, this concept should be investigated further.

Neutrophil extracellular traps. Neutrophil extracellular traps (NETs) are web-like chromatin fibers with microbialicidal proteins and granule enzymes released by neutrophils as a host defense mechanism against microbes. NETs are of high relevance in SLE, as they can enhance inflammation and type I IFN responses. NETs are also thought to potentiate thrombosis in antiphospholipid syndrome. Recent studies have suggested a key role of dysregulated NETs in COVID-19. Zuo et al identified that circulating NET-specific markers were significantly elevated in COVID-19 patients compared to healthy controls and in patients with critical COVID-19 on mechanical ventilation compared to those with milder disease; in addition, sera from patients with COVID-19 can trigger NET formation when exposed to control neutrophils in vitro. Similarly, Middleton et al demonstrated a correlation between plasma NETs and severity of respiratory manifestations of COVID-19. NETs are also abundant in respiratory secretions and lung tissue from patients with COVID-19, a process that may be driven by SARS-CoV-2-induced neutrophil activation and NET release. This inflammatory reaction could contribute to microthrombi formation in the lungs in COVID-19. Therapeutic interventions to dissolve NETs or prevent their release may be beneficial in managing severe COVID-19. A clinical trial evaluating dipryidamole, an antiplatelet agent and adenosine A2A receptor agonist with NET-suppressing properties, is ongoing (NCT04391179).

Antiphospholipid antibodies and thrombosis. Various observational studies have identified a high prevalence of antiphospholipid antibodies in hospitalized patients with COVID-19. Lupus anticoagulant positivity has been commonly found in patients with COVID-19, ranging from 42% to 83% in severe and critical COVID-19, although the prevalence may be lower when patients with milder forms are included. The presence of IgG or IgM anti-cardiolipin and anti-beta2-glycoprotein I antibodies in patients with COVID-19 seems to be less prevalent and more variable across different studies, ranging from 0% to 13.

Interestingly, there has been conflicting evidence on how well the presence of antiphospholipid antibodies correlate with clinically significant thrombotic episodes, with various initial studies suggesting that these represent innocent bystanders instead of pathogenic antibodies. However, a recent study has demonstrated a potential pathogenic role of antiphospholipid antibodies in severe COVID-19. This cross-sectional study showed that 50% of hospitalized patients with COVID-19 had antiphospholipid antibodies, and higher titers were associated with elevated circulating NET markers and a more severe COVID-19 course. In addition, IgG fractions of antiphospholipid antibodies promoted NET release in vitro and induced accelerated venous thrombosis in mice. Nonetheless, there is still a lack of longitudinal studies assessing the persistence of antiphospholipid antibodies several weeks after COVID-19 diagnosis, and it is possible that this represents a transient event as it has been demonstrated in the setting of other infections.

Dysregulation of the complement system. Complement dysregulation is a classic feature of SLE, and hypocomplementemia is a marker of disease activity. Complement activation has been associated with the excessive inflammatory response seen in patients with severe COVID-19, and the presence of a complement-mediated microvascular injury syndrome has been proposed based on the observed pattern of tissue damage.

SARS-CoV-2 is thought to predominantly trigger the lectin and alternative complement pathways, although the classical complement pathway could also be activated in this setting by immune complexes. The C3a and C5a anaphylatoxins are potent inflammatory mediators and chemoattractants. C5a plasma levels were shown to rise proportionally to COVID-19 severity, suggesting sustained complement activation, likely triggered by SARS-CoV-2 antibodies and high levels of...
C-reactive protein. Additionally, COVID-19 patients have a large number of monocytes and neutrophils in bronchoalveolar lavage expressing the C5a receptor (C5aR1), suggesting a role of C5a in cell recruitment to the inflamed tissues. C5a may help generate thrombogenic NETs, promoting a complement and/or NET-driven cycle that leads to immunothrombosis.

Disorders of the complement system can be genetic or acquired. Age-related macular degeneration, in which the complement system is overactive, is associated with worse COVID-19 outcomes. In addition, genetic variants previously reported in association with age-related macular degeneration were found to also predispose to hospitalization for COVID-19. Variants affecting the C3 gene were protective, whereas complement decay-accelerating factor (CD55) variants were associated with adverse outcomes of COVID-19. Conversely, patients with complement deficiency disorders may have a milder disease course.

Together, these findings suggest a detrimental role of hyperactive complement. Therefore, a role of complement inhibitors to target thromboinflammation in COVID-19 has been suggested, and clinical trials assessing various agents are ongoing. Results from a small single-arm study of narsoplimab, a mannan-binding lectin associated serine protease-2 (MASP-2) blocker, are encouraging. Similarly, although data remain limited, eculizumab therapy also seems to improve clinical outcomes and biomarkers of inflammation and coagulation in patients with severe COVID-19.

The mechanistic (mammalian) target of rapamycin (mTOR) pathway. Mechanistic (mammalian) target of rapamycin (mTOR) is a ubiquitous kinase and nutrient sensor that modulates cell differentiation, growth, proliferation, and survival. The mTOR pathway has been shown to regulate T-cell and macrophage differentiation, and is thought to play a critical role in the pathogenesis of autoimmune and inflammatory diseases such as SLE. Accordingly, phase 1/2 trials of agents blocking the mTOR pathway, including N-Acetylcysteine (NAC) and rapamycin, have demonstrated potential benefits in SLE. Interestingly, a role of mTOR in the dysregulated inflammatory response in COVID-19 has been postulated. For instance, mTOR signaling has been shown to be decreased in pDCs from COVID-19 patients, on the basis of reduced ribosomal protein S6 (pS6) expression, translating into impaired IFN-α production by these cells which may negatively impact the host antiviral response (Fig. 1).

Conversely, it has been hypothesized that mTOR pathway hyperactivation in certain conditions such as obesity may enhance SARS-CoV-2 replication, providing at least a partial explanation for worse COVID-19 outcomes in obese patients. Therefore, targeting the mTOR pathway may reduce SARS-CoV-2 replication and inhibit the deleterious immune hyperactivation by reducing hyper-reactive T cells, while maintaining regulatory T (Treg) cell number and function in COVID-19. In agreement with this hypothesis, hospitalized patients with critical COVID-19 treated with NAC showed significant clinical improvement and reduction of inflammation markers, suggesting a beneficial effect of NAC in COVID-19, possibly mediated by mTOR inhibition. Limited observational studies of patients with tuberous sclerosis complex and/or lymphangioleiomyomatosis on long-term mTOR inhibitors (sirolimus or everolimus) have not identified an increased risk of COVID-19 or poor outcomes of the infection and clinical trials of mTOR inhibitors in COVID-19 are ongoing. However, whether activation of the mTOR pathway plays a role in SARS-CoV-2-infected patients with SLE remains to be elucidated.

Dysregulated adaptive immune responses. Lymphopenia is a common feature of SLE, thought to be due to complement-mediated or antibody-dependent cytoxicity, excess apoptosis, and decreased lymphopoiesis. In addition, T cell function is also impaired in SLE, which may predispose these patients to infections (see the previous section on Relationship between SLE and risk of viral infections). Reversible lymphopenia has been observed in patients with COVID-19, especially those with severe disease. Although transient lymphopenia is common in the setting of viral infections, COVID-19-associated peripheral lymphopenia may persist for longer and be more severe than in other viral illnesses. Among the potential mechanisms that contribute to lymphocyte depletion in COVID-19 are infection of lymphocytes by SARS-CoV-2, exhaustion, and induction of apoptosis by cell hyperactivation and/or an increase in proinflammatory cytokines and proapoptotic signals. Although more pronounced in CD8+ T cells, lymphopenia has also been shown to affect CD4+ T cells.

Various studies have also identified functional impairment or alterations in the differentiation status of T cells, with marked heterogeneity in immune cell responses. T cells in COVID-19 may range from an exhausted to an overactive phenotype. It has been proposed that a more severe disease course could be associated with a reduced CD8+ T cell pool and less activated T cells, with increased expression of co-inhibitory signals including PD1, TIM3, CTLA4, and CD38. However, differentiating between an exhausted phenotype and hyperactive T cells represents a challenge as they both demonstrate increased expression of inhibitory receptors. A recent multi-omics study identified that certain CD8+ subpopulations correlated with COVID-19 severity, with an increase of naïve...
clusters and lower activated effector T cells identified in severe cases when compared to patients with moderate disease.140 Another study using high-dimensional flow cytometry identified distinct immunotypes related to disease severity in hospitalized patients with COVID-19. Interestingly, the immunotype characterized by robust CD4+ T cell activation, a paucity of circulating T follicular helper cells, and highly activated or exhausted CD8+ T cells was associated with more severe disease.137

A potential role for T helper 17 (Th17) cells in COVID-19 has also been suggested, and significant skewing towards a Th17 functional phenotype with decreased Treg levels have been described.136,138,141,142 Similarly, patients with SLE have impaired Treg cells, greater numbers of Th17 cells and increased production of IL-17, which seems to correlate with disease activity.143,144

A central immunopathogenic role of dysregulated B cell responses in COVID-19 is also likely. A stronger B-cell immune response in patients with severe COVID-19 compared to milder disease has been described.145 Poor COVID-19 outcomes are associated with suppression of germinal centers, extrafollicular B cell activation, and a large expansion of the antibody-secreting cell compartment, similar to what is seen in SLE.146 However, whether infection-induced autoreactive B cell responses persist after the acute phase of COVID-19 or if they contribute to long-lasting symptoms experienced by some patients with COVID-19, the so-called “long-haulers”, remain to be determined. Moreover, the effect of B-cell depleting therapy on COVID-19 outcomes needs to be addressed, although very limited data to date have suggested the potential for detrimental effects.148-150

Overall, the findings of pathogenic adaptive immune responses in COVID-19 further support the notion that the timely implementation of immunomodulatory therapy in selected patients may be beneficial.

COMMONLY USED DRUGS IN SLE AND PREDISPOSITION TO VIRAL INFECTIONS

SLE management involves the use of multiple therapeutic strategies to treat the specific manifestations, lower disease activity, and prevent irreversible organ dysfunction.151 General standard treatment strategies involve the use of antimalarials, non-biologic and biologic immunosuppressive agents, and sGC, if necessary. sGC are generally considered a first-line treatment in the management of organ- and life-threatening manifestations of SLE. Although sGC are effective in decreasing disease activity, their undesirable side effect profile has led to widely accepted recommendations to limit the dose and duration of treatment as much as possible.2,152-154 Multiple studies to date have reported significantly increased risk of serious infections in patients on sGC, with doses as low as 10 mg prednisone-equivalent, although this mostly corresponds to bacterial infections.28,155-160

Hydroxychloroquine (HCQ) use is recommended in most patients with SLE, owing to multiple health benefits in patients with SLE and overall safety.161-164 Various observational studies have indicated a protective effect of HCQ against serious infections in SLE.165-168 In vitro studies have also suggested potential anti-viral effects of HCQ by means of increasing lysosomal pH and preventing post-translational modification of synthesized proteins that are crucial for replication and dissemination of viruses.165,167,169 However, human studies have failed to identify any benefit of HCQ in preventing or managing viral infections, including dengue, chikungunya, and SARS-CoV-2.170,171

Azathioprine (AZA), mycophenolate mofetil (MMF), and CYC are commonly used in SLE to manage moderate to severe manifestations. In a retrospective study from France, exposure to CYC led to an increased incidence of herpes zoster in patients with SLE during the first year after initiating therapy.172 A systematic review and meta-analysis identified a higher incidence of infections in the CYC compared to the MMF group.173 However, a large propensity-score matched study showed no significant differences in rates of infection or mortality between Medicaid patients with SLE using CYC vs MMF after 6 months of initiation of therapy.174 A study from the Hopkins Lupus Cohort that followed 214 patients after MMF initiation reported an increased risk of developing bacterial infections but no change in the risk of viral infection.175 Furthermore, a recent review did not find sufficient evidence to conclude that AZA, MMF, or CYC increased the risk of acute respiratory viral adverse events in patients with SLE or other rheumatic diseases.156 Tacrolimus, a calcineurin inhibitor used as a single agent or in combination with MMF in SLE, has been associated with a relatively low incidence of serious infections in various reports, although data are scarce.156,176,177 A comparison between SLE patients on sGC and tacrolimus vs those on sGC and CYC showed a similar incidence rate of herpes zoster and varicella between the 2 groups.178

Belimumab, a B lymphocyte stimulator inhibitor, is currently the only biologic approved for use in SLE.179 Based on data from randomized controlled trials and open-label extensions, there is no suggestion of a significantly increased risk of severe respiratory viral infections with Belimumab use.156 Rituximab (RTX), a
B-cell depleting agent, has been associated with progressive multifocal leukoencephalopathy arising from John Cunningham virus reactivation.\(^{159,180}\) Additionally, hepatitis B (HB) reactivation is a potentially life-threatening complication from RTX therapy in patients with positive HB surface antigen or HB anticore antibody.\(^{181}\) Although data on other viral infections with RTX use are scarce, the frequency of upper respiratory tract infections is variable among trials but generally similar to the placebo arms.\(^{186,182,183}\) Recently, 2 small studies reported high rates of severe COVID-19 and mortality in patients on RTX for various indications.\(^{148,149}\) However, larger studies and longer follow-up are needed to confirm these observations.

Anifrolumab, a type I IFN blocking agent, is awaiting FDA approval for use in SLE.\(^{184}\) Overall, in the randomized controlled trials, there were increased rates of herpes zoster, upper respiratory tract infections, nasopharyngitis, bronchitis, and influenza in the anifrolumab group, although the differences were not statistically significant.\(^ {196,185,186}\) Further longitudinal studies are needed to assess the risk of viral infection in anifrolumab-receiving patients with SLE; however, considering its mechanism of action, an increased risk of viral infections with the use of anifrolumab is biologically plausible.

**EPIDEMIOLOGY AND OUTCOMES OF COVID-19 IN PATIENTS WITH SLE**

As COVID-19 was increasingly recognized as a rapidly spreading global threat, the urgent need to describe the characteristics and outcomes of patients with rheumatic diseases became evident. Early reports suggesting a potential beneficial role of chloroquine and HCQ, which are commonly used in patients with rheumatic diseases, also drove the need to evaluate this population closely. The first studies on patients with SLE and COVID-19 emerged from the heaviest hit regions in the early phases of the pandemic and consisted of mostly case reports or small case series (Table 1).

Mathian et al described 17 patients with SLE who were diagnosed with COVID-19 in France between March 29 and April 6, most of whom were on long-term HCQ and had therapeutic levels of the drug.\(^{187}\) Seven (41%) patients required admission to an intensive care unit, and 2 out of 14 hospitalized patients died of COVID-19; notably, comorbidities were highly prevalent in these SLE patients, as was use of sGC (71%) and immunosuppressants (41%), and most patients had clinically quiescent SLE. This study represented one of the first to note that patients with SLE on HCQ were not protected against COVID-19.\(^{187}\) Several other groups have now also suggested the lack of benefit of HCQ against contracting or developing severe COVID-19 in patients with SLE and other rheumatic diseases.\(^{188-194}\)

A retrospective study from Spain included 62 patients with several different rheumatic or autoimmune diseases, nine of which had SLE. They found no statistically significant between-group differences for rheumatologic diagnosis or baseline use of immuno-suppressive therapy except for sGC use, which was more frequent in hospitalized patients. SLE was not a risk factor for severe COVID-19 requiring hospitalization, but male sex, previous lung disease, and sGC use (≥ 5 mg/day of prednisone) were significantly associated with hospital admission.\(^{195}\) Similarly, a study from Belgium which included 18 patients with confirmed or suspected COVID-19 did not find differences in the proportion of patients who developed COVID-19 between patients on immunosuppressants and those not on these medications. However, sGC dose was found to be positively associated with a positive reverse transcription polymerase chain reaction (RT-PCR) test for COVID-19, hospitalization, and various COVID-19 symptoms.\(^{193}\) Several other studies from Spain, Italy, France, and Brazil have also suggested that the main risk factors for poor COVID-19 outcomes are similar to those previously reported in the general population, including age and the presence of comorbidities.\(^{189,196-198}\) Additional potential risk factors suggested by studies of SLE and other autoimmune diagnoses included the presence of interstitial lung disease, moderate or high rheumatic disease activity (or flare preceding the COVID-19 diagnosis), history of neuropsychiatric lupus, and known exposure to a confirmed COVID-19 case.\(^{199-201}\) However, the small sample size, lack of confirmatory testing for many of the included patients, selection biases, insufficient identification and adjustments for confounders, and several other limitations from these observational data preclude from making definitive statements about these observations.

In response to the scarcity of data on the impact of COVID-19 in patients with immune-mediated diseases, a number of registries were established to better characterize these patients and assess their outcomes. The largest of these registries addressing rheumatic diseases is the COVID-19 Global Rheumatology Alliance (C-19-GRA). The C-19-GRA was formed over the course of a few days in response to an urgent need for information, as the rheumatology community gathered in social media.\(^{202}\) The largest C-19-GRA publication to date reported on the first 600 patients entered to the registry, including 85 patients with SLE, of whom 55% were hospitalized.\(^{203}\) This study found that a prednisone dose ≥ 10 mg/day was associated with higher odds of
### Table 1. Main published studies by October 31, 2020 including patients with SLE and presumptive or confirmed COVID-19

| Reference and country/region | Study timeline | Number of SLE patients included and COVID-19 status | Age (years) and gender (% female patients) | % Medication use | Hospitalizations and deaths due to COVID-19 | Main findings |
|-----------------------------|---------------|-----------------------------------------------------|------------------------------------------|-----------------|------------------------------------------|---------------|
| Chen et al230 Wuhan, China  | Feb 29        | N = 101 (LN only)  Confirmed: 2                    | Median age: 42  Gender: F: 89 (88%)      | HCQ: 52 (51%)  sGC: 95 (94%)  ISx: aggregate data | Hospitalization: 2/2  (100%)  Death: 0  | Low prevalence of confirmed COVID-19 in lupus nephritis patients during the Wuhan peak. |
| Singer et al191 USA          | Jan 20 to Jul 13 | N = 35  Confirmed: NA  Presumptive: NA  NA for SLE subgroup | NA for SLE subgroup  | NA for SLE subgroup  | NA for SLE subgroup  | HCQ did not prevent COVID-19 in patients with SLE. Age, male gender and comorbidities are risk factors for severe COVID-19. |
| Huang et al251 Wuhan, China  | Jan 29 to Mar 8 | N = 3  Confirmed: 3                                  | NA for SLE subgroup  | NA for SLE subgroup  | NA for SLE subgroup  | Age, male gender and comorbidities are risk factors for severe COVID-19. |
| Holubar et al189 Montpellier, France | Feb 1 to Apr 24 | N = 120  Confirmed: 0  Presumptive: 30          | Age: On HCQ: 42 ± 12  Not on HCQ: 52 ± 12  Gender: F: 110 (92%) | HCQ: 72 (60%)  sGC: 50 (42%)  | Hospitalization: 0  | No severe forms of COVID-19 were identified. |
| Gendebien et al193 Liège, Belgium | Feb 4 to Jun 6' | N = 225  Confirmed: 5  Presumptive: 13       | Mean age ± SD: 52 years ± 14.9  Gender: F: 209 (93%) | HCQ: 151 (68%)  sGC: 23 (25%)  | Hospitalization: 2/18  (11%)  Death: 0  | sGC dose was associated with COVID-19 diagnosis and hospitalization. |
| Bozzailla Cassione et al194 Northern Italy | Feb 15 to Apr 290 | N = 165  Confirmed: 4  Presumptive: 8       | Mean age, range: 53, 25–81  Gender: F: 112 (84%) | HCQ use: 127 (77%)  sGC: 53 (32%)  | Hospitalization: NA  Death: 0  | No protective effect of HCQ against COVID-19 in SLE patients. |
| Fredi et al196 Brescia, Italy  | Feb 24 to May 1 | N = 12 (10% of 117 patients with rheumatic diseases)  Confirmed: 5  Presumptive: 7 | NA for SLE subgroup  | NA for SLE subgroup  | NA for SLE subgroup  | Poor outcomes of COVID-19 were associated with older age and the presence of comorbidities. |
| Favalli et al210 Lombardy, Italy | Feb 25 to Apr 10 | N = 62  Confirmed: 0  Presumptive: 8          | Mean age: 44  Gender: F: 56 (91%) | HCQ: 30 (48%)  sGC: 4 6 (75%)  | Hospitalization: 0  Death: 0  | Very low impact of COVID-19 in SLE patients. |
| D’Silva et al206 Massachusetts, USA  | Mar 1 to Apr 8 | N = 10  Confirmed: 10                              | NA for SLE subgroup  | NA for SLE subgroup  | NA for SLE subgroup  | COVID-19 outcomes similar between patients with and without rheumatic diseases, except for ICU/MV. |
| Wallace et al205 Michigan, USA | Mar 1 to Apr 20 | N = 5  Confirmed: 5                                | Mean age, range: 54, 26–67  Gender: F: 5 (100%) | HCQ: 4 (80%)  sGC: 4 (80%)  | Hospitalization: 4/5  (80%)  Death: 1/5 (20%)  | Patients with quiescent SLE may develop severe COVID-19. |

(continued on next page)
| Reference and country/region | Study timeline* | Number of SLE patients included and COVID-19 status | Age (years) and gender (% female patients) | % Medication use | Hospitalizations and deaths due to COVID-19 | Main findings |
|-----------------------------|-----------------|----------------------------------------------------|------------------------------------------|----------------|------------------------------------------|---------------|
| Santos et al\(^{190}\)       | Mar 1 to Jun 1   | N = 5 (13% of 38 patients with rheumatic diseases). Confirmed: 5 | NA for SLE subgroup | NA for SLE subgroup | Hospitalization: 5 (100%) Death: 1 (20%) | Comorbidities, rheumatic disease activity and laboratory abnormalities were associated with mortality |
| Gentry et al\(^{190}\)       | Mar 1 to Jun 30  | N = 7117 (22% of 32,109 patients with rheumatic diseases) Confirmed: 23 | NA for SLE subgroup | HCQ: 2642 (37%) ISx and sGC: NA for SLE subgroup | NA for SLE subgroup | HCQ was not associated with COVID-19 prevention or improvement in outcomes of the infection |
| Montero et al\(^{195}\)      | Mar 4 to Apr 24  | N = 9 (15% of 62 patients with various autoimmune/inflammatory diseases) Confirmed: 9 | NA for SLE subgroup | NA for SLE subgroup | Hospitalized: 6/9 (67%) Death: 2 (22%) | Factors associated with COVID-19 hospitalization: Baseline sGC use, male sex, preexisting lung disease |
| Emmi et al\(^{252}\) Tuscany, Italy | Apr 1 to Apr 14 | N = 117 Confirmed: 0 Presumptive: 4 | NA for SLE subgroup | NA for SLE subgroup | Hospitalized: 0 Death: 0 | No clear evidence of increased risk of COVID-19 in patients with SLE |
| Konig et al\(^{188}\) Worldwide (C-19-GRA) | Apr 17 | N = 80 Confirmed/ presumptive status: NA | Age <65: 69 (86%) Gender F: 72 (90%) | HCQ/CQ: 51 (64%) ISx and sGC: NA for SLE subgroup | Hospitalization: 45/80 (56%) Death: 0 | No difference in the frequency of COVID-19 hospitalizations based on HCQ use |
| Gianfrancesco et al\(^{203}\) Worldwide (C-19-GRA) | Mar 24 to Apr 20 | N = 85 (14% of 600 patients with rheumatic diseases) Confirmed: 80 Presumptive: 5 | NA for SLE subgroup | NA for SLE subgroup | Hospitalized: 48/85 (56%) Death: NA for SLE subgroup | Age, comorbidities and sGC use are associated with increased odds of hospitalization |
| Mathian et al\(^{187}\) France | Mar 29 to Apr 6 | N = 171 Confirmed:17 | Mean age, range: 54 (27–69) Gender: F: 13 (76%) | HCQ: 17 (100%) ISx: 7 (41%) sGC: 12 (71%) | Hospitalization: 14/17 (82%) Death: 2/14 (14%) | No role of HCQ preventing severe COVID-19 in patients with SLE |
| Gartshteyn et al\(^{204}\) New York, USA | Apr 26 | N = 18 Confirmed: 10 Presumptive: 8 | Mean age ± SD: 41 ± 11 Gender: F: 16 (89%) | HCQ: 13 (72%) ISx: 15 (83%) sGC: 7 (39%) | Hospitalization: 7/18 (39%) Death: 0 | COVID-19 severity was not affected by SLE medication use. |
| Zen et al\(^{253}\) Padua, Italy | Apr 9 to Apr 25 | N = 397 Confirmed: 1 Presumptive:14 | Mean age ± SD: 48 ± 13 Gender: F: 340 (86%) | HCQ: NA ISx: aggregate data NA sGC: 42 (11%) | Hospitalization: 1/1 (100%) Death: 0 | COVID-19 incidence was comparable to the general population |

(continued on next page)
Table 1. (Continued)

| Reference and country/region | Study timeline* | Number of SLE patients included and COVID-19 status | Age (years) and gender (% female patients) | % Medication use | Hospitalizations and deaths due to COVID-19 | Main findings |
|-----------------------------|-----------------|---------------------------------------------------|------------------------------------------|-----------------|------------------------------------------|--------------|
| Fernandez-Ruiz et al192     | Apr 13 to Jun 1 | N = 226 Confirmed: 41 Presumptive: 42            | Confirmed: Mean age ± SD: 47 ± 17 Gender: F: 38 (93%) Presumptive: Mean age ± SD: 41 ± 13 Gender: F: 39 (93%) | Confirmed: HCQ: 32 (78%) ISx: 24 (59%) sGC: 18 (44%) Presumptive: HCQ: 33 (79%) ISx: 24 (57%) sGC: 5 (12%) | Confirmed only: Hospitalization: 24/41 (59%) Death: 4/41 (10%) | Predictors of hospitalization in confirmed COVID-19 patients: non-white race, the presence of ≥ 1 comorbidities and BMI per increase in kg/m² |
| Marques et al197            | May 19 to Jun 16| N = NA for SLE subgroup | NA for SLE subgroup | Hospitalized: NA for SLE subgroup Death: 4 | No rheumatic disease-specific factors were associated with death from COVID-19. High frequency of comorbidities in deceased patients. Only 3 COVID-19 cases were identified in a cohort of 3375 SLE patients. All patients required escalation of SLE therapy around the time of COVID-19 diagnosis Low prevalence of confirmed COVID-19 in SLE patients compared to most systemic autoimmune diseases |
| Cho et al199                | Jun 3†          | N = 3375 Confirmed: 3                             | Confirmed: Mean age: 40 ± 16 Gender: F: 3 (100%) | Confirmed: HCQ: 2 (67%) ISx: 2 (67%) sGC: 3 (100%) | Hospitalized: 3/3 (100%) Death: 1/3 (33%) |
| Pablos et al208             | NA              | N = 2253 Confirmed: 17                           | Confirmed: Mean age, IQR: 51 (42–66) Gender: F: 77% | NA for SLE subgroup | NA for SLE subgroup |

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; F, female; HCQ, hydroxychloroquine; ICU, intensive care unit; IQR, interquartile range; ISx, immunosuppressants; LN, lupus nephritis; MV, mechanical ventilation; NA, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sGC, systemic glucocorticoids; SLE, systemic lupus erythematosus.

* unless otherwise specified, if the start date of the observation period is not reported in the article, the end of observation date is presented in the table.

†Latest date the article was received by the journal.

One patient was admitted to the intensive care unit. Other patients had a milder course but it is unclear if they were hospitalized.

Sixteen patients met the classification criteria for systemic lupus erythematosus (SLE) and one patient had antiphospholipid syndrome with additional features of SLE.

Date survey was sent.
hospitalization in patients across all rheumatic diseases. Immunosuppressant use was not found to be associated with hospital admission for COVID-19, with the exception of tumor necrosis factor inhibitor users, in whom the odds of hospitalization were lower.\textsuperscript{203} As New York City (NYC) was the initial epicenter of the pandemic in the United States, many patients living with rheumatic diseases were affected by COVID-19. Gartshteyn et al published the first case series describing patients with SLE and COVID-19 in NYC. The study included 10 patients with real-time RT-PCR confirmed COVID-19 and 8 with suspected infection; 7 of these patients were hospitalized. Most patients (83\%) in this case series were taking immunosuppressants, 39\% were on sGC, and 61\% had lupus nephritis. Although limited by the small number of cases, the study did not find significant differences in immunosuppressant use in patients with mild vs severe COVID-19.\textsuperscript{204} As COVID-19 rapidly extended to other regions of the United States, other groups published on the outcomes of patients with rheumatic diseases and COVID-19. Wallace et al described their COVID-19 experience at a tertiary care academic center in Michigan, reporting 5 patients with SLE, of whom 4 were hospitalized, 3 required invasive ventilation, and 1 died of COVID-19. Overall, when compared to 31 patients with various rheumatic diseases, patients with SLE and COVID-19 seemed to have worse outcomes in this study; however, SLE patients were noted to have a high prevalence of comorbidities, sGC use, and more likely to be African-American, which are all known risk factors for hospitalization and mortality in COVID-19.\textsuperscript{205}

To further close the information gaps concerning the impact of COVID-19 in patients with immune-mediated diseases in one of the heaviest hit regions in the world by the initial phases of the pandemic, our NYC-based institution established a prospective cohort of patients with immune-mediated diseases, the Web-based Assessment of Autoimmune, Immune-Mediated, and Rheumatic Patients during the COVID-19 Pandemic (WARCOV). An initial report on patients with various immune-mediated diseases from the WARCOV cohort, which did not include any patients with SLE, identified sGC use as one of the main factors associated with higher odds of hospitalization.\textsuperscript{157} We later reported the characteristics and COVID-19 outcomes of patients with SLE, including 41 confirmed and 42 suspected cases of COVID-19, as well as 19 patients who were tested for COVID-19 and were negative, and 124 patients with SLE from our lupus registry who did not develop COVID-19 symptoms on prospective follow-up.\textsuperscript{192} Out of the 41 patients with RT-PCR confirmed COVID-19, 24 patients with SLE required hospitalization. Notably, no SLE-specific factors, such as immunosuppressant use, were noted to increase the odds of hospitalization. However, there was a higher proportion of patients on sGC in the hospitalized (54.2\%) compared to the ambulatory group (29.4\%), although the difference was not statistically significant. Non-white race, having 1 or more comorbidities, and body mass index were identified as independent predictors of hospitalization in our patients with SLE and COVID-19, similar to the general population.\textsuperscript{192} These findings were in agreement with smaller studies assessing outcomes of COVID-19 in patients with SLE, as previously discussed.

Several studies have compared patients with and without rheumatic/autoimmune diseases to investigate differences in risk of contracting SARS-CoV-2 and experiencing poor outcomes of the disease. In a matched study of 52 patients with various rheumatic diseases, including 10 patients with SLE, compared to 104 without rheumatic diseases, D’Silva et al found that the proportion of patients who were hospitalized for COVID-19 and mortality from the disease were similar between the 2 groups; however, patients with rheumatic diseases had significantly higher odds of requiring mechanical ventilation or admission to the intensive care unit ventilation compared to patients without rheumatic diseases.\textsuperscript{206} Various studies have addressed the question of whether patients with autoimmune diseases, including SLE, increase the risk of contracting COVID-19. A recent large study from Milan, Italy, comparing 20,364 SARS-CoV-2 test-positive and 34,697 test-negative subjects, did not find an association between having an autoimmune disease (in aggregate), including SLE, and having a positive test for COVID-19.\textsuperscript{207} A study from 7 hospitals in Spain also suggested patients with SLE were not at a higher risk of testing positive for COVID-19 in the hospital setting compared to a reference population of 2.9 million people.\textsuperscript{208} In contrast with these observations, a meta-analysis of 7 case-control studies of patients with autoimmune diseases and COVID-19 showed 2-fold higher odds of contracting COVID-19 in this population compared to controls.\textsuperscript{209} On meta-regression analysis, sGC use was significantly associated with the risk of COVID-19. Furthermore, patients with SLE, Sjogren’s syndrome, and systemic sclerosis, in aggregate, had a higher prevalence of hospitalization when compared with the other disease groups. Notably, sGC was highly prevalent in this group (60\%).\textsuperscript{209}

Overall, studies seem to suggest that most patients with SLE may not be at an increased risk of contracting COVID-19. However, patients with SLE have likely
implemented more strict protective behaviors to avoid exposure to SARS-CoV-2 out of fear of having worse outcomes, so this element should be factored in when considering risk for developing COVID-19 in patients with SLE.\textsuperscript{201,210} Other than sGC use, there is no clear evidence to suggest that the SLE population is at risk of worse COVID-19 outcomes due to specific factors related to their underlying autoimmune disease. Although studies to date have significantly improved our understanding of the associations and outcomes of COVID-19 in the SLE population, it is important to note that there are several limitations to these observational data and the results should be interpreted with caution.

ASSOCIATION OF COVID-19 WITH SLE FLARES AND DE NOVO SLE

There have been reports in the literature of COVID-19 shortly preceding a de novo diagnosis of SLE, presenting concomitantly or mimicking SLE, raising the possibility of SARS-CoV-2 being a trigger of autoimmunity, as it has been postulated for other viruses.\textsuperscript{19,111,211} However, we need to use caution when making a diagnosis of SLE in patients with COVID-19 for various reasons. Certain clinical diagnostic criteria of SLE overlap with COVID-19 symptoms. Also, autoantibodies can occur in response to infections, and these are usually transient and of unclear significance in this setting.\textsuperscript{113,114,212} Hence, longitudinal evaluation of these patients is required to offer insights into the association between COVID-19 and de novo SLE.

Similarly, various reports have indicated that COVID-19 may worsen SLE manifestations.\textsuperscript{213-215} However, attributing SLE flares to a biologic mechanism is challenging because many of these patients have had greater difficulty accessing health care during the pandemic and may suffer worsened disease control due to lack of medical care or difficulty continuing their SLE medications, in addition to the psychosocial stressors of the pandemic. Therefore, it is currently unclear whether COVID-19 could predispose to SLE or cause a flare of disease in SLE patients. Long-term longitudinal studies are needed to ascertain these associations.

ANCESTRAL BACKGROUND, SOCIOECONOMIC FACTORS AND INDIRECT CONSEQUENCES OF THE COVID-19 PANDEMIC IN PATIENTS WITH SLE: CHALLENGES IN ACCESS TO HEALTH CARE, MEDICATION SHORTAGES, AND PSYCHOSOCIAL FACTORS

It is well established that SLE is more prevalent and severe in ancestrally African and Hispanic patients.\textsuperscript{3} In addition, patients with SLE from minority racial and ethnic groups are known to experience substantial inequities in care and are much less likely to enroll in clinical trials when compared to white patients, owing to structural racism, implicit bias, previous experiences of discrimination and injustices.\textsuperscript{2216} The COVID-19 pandemic has magnified the impact of health disparities and barriers to health care experienced by marginalized populations around the world. Consequently, COVID-19 has disproportionately affected Indigenous communities, Black and Hispanic populations\textsuperscript{45,2,17-219}, comparable to what has been identified in patients with SLE and COVID-19.\textsuperscript{192,220} Interestingly, a recent study suggested African ancestry populations showed a genetic predisposition for lower expression of both ACE2 and type 2 transmembrane serine protease, suggesting decreased susceptibility to contracting SARS-CoV-2 in this population.\textsuperscript{221} Although these findings suggest genetic determinants of COVID-19 transmissibility and severity across populations exist, SDH are more likely responsible for the different outcomes in racial and ethnic minorities, as it has been suggested by a recent retrospective cohort study from New York.\textsuperscript{222} Therefore, assessing the impact of SDH on severity and mortality related to COVID-19 in patients with rheumatic diseases is essential.\textsuperscript{223-226}

Although telemedicine has played a significant role in securing continuity of care for patients with SLE and other rheumatic diseases during the pandemic-related lockdowns\textsuperscript{194,227,228}, concerns have been raised about specific situations where a virtual consultation may be insufficient.\textsuperscript{229} For instance, patients with SLE require routine monitoring of laboratory parameters. New patients or those with urgent concerns may require a more thorough evaluation than what is feasible by telemedicine. Furthermore, special consideration should be given to those patients who lack reliable internet connection or access to smartphones or other devices suitable for telemedicine.

Even when imperfect, telemedicine has allowed patients with SLE to be evaluated by health care professionals, preventing major gaps in medical attention during the pandemic, which may lead to discontinuation of SLE therapies and subsequent flares. This concept was exemplified in a study from Wuhan, China, where 60% of 101 respondents with lupus nephritis had been unable to attend their rheumatology appointments. In addition, 25% of patients discontinued their medications, mostly due to limited access to health care, and 5% experienced a disease flare. Interestingly, only 2 patients in this study contracted SARS-CoV-2 and both had a mild COVID-19 course.\textsuperscript{230} Similarly, in a study of 1040 patients with SLE in India, over 50% of patients had missed their follow-up appointments, 37% were unable to perform routine laboratory exams,
40% needed to change their medications due to lack of availability, and 25% presented financial difficulties during the lockdown period.\textsuperscript{231} suggesting additional sources of stressors experienced by these patients.

HCQ is a mainstay of treatment in SLE, as it is associated with multiple health benefits in this population, including reducing the risk of flares and organ damage.\textsuperscript{163,232} In the early phases of the COVID-19 pandemic, limited data including in vitro and small observational studies suggested a potential benefit of HCQ in COVID-19.\textsuperscript{233,234} Multiple recent studies, including observational data from patients with immune-mediated diseases on long-term HCQ as well as large randomized clinical trials, have consistently demonstrated the lack of efficacy of HCQ in preventing the viral infection or improving any COVID-19-related outcomes.\textsuperscript{171,190,235-238} However, for several weeks after the preclinical studies and limited observational data came to light, HCQ shortages ensued in many countries as its use was redirected toward prophylaxis or management of COVID-19, leading to inadequate supplies of the drug for many patients with SLE worldwide.\textsuperscript{239,240}

An electronic survey distributed to the SLE International Collaborating Clinics members with SLE-affiliated centers aimed to evaluate physicians’ experiences with HCQ shortages during the pandemic.\textsuperscript{241} Out of 31 responses, 55% reported HCQ shortages among patients with SLE. Most respondents (65%) in this study had been contacted by patients and pharmacies regarding difficulties accessing HCQ.\textsuperscript{241} Similarly, a national survey to Canadian rheumatologists in April, 2020 found that 50-94% of respondents, depending on the region, had been contacted by pharmacies or patients regarding difficulties accessing HCQ.\textsuperscript{242} In a patient-centered study in Germany, 70% of 369 respondents expressed concerns about being unable to receive HCQ prescriptions, and 9% had already reduced their HCQ dose in an attempt to overcome potential drug supply issues.\textsuperscript{243}

One of the main concerns that HCQ shortages prompted was the risk of SLE flares, which are known to occur as soon as 2 weeks after drug discontinuation for most patients with SLE, especially in the younger SLE population.\textsuperscript{163,244} In addition, due to fears of contracting SARS-CoV-2, many patients fail to seek prompt medical attention in emergent and urgent situations.\textsuperscript{245,246} A report from Malaysia found a 65.4% decline in hospitalizations in patients with SLE during the lockdown period compared to 2019 rates. However, the patients with SLE who presented to the hospital in 2020 were significantly sicker when compared to those admitted in 2019 with respect to SLE Disease Activity Index, intensive care unit requirement, and mortality. Strikingly, only 1 death was attributed to COVID-19.\textsuperscript{247} These findings are likely multifactorial; while patients with SLE may have avoided presenting to the hospital due to fear of contracting COVID-19 until it was inevitable, it is also possible that different factors such as lack of close monitoring of clinical or laboratory parameters, issues with access or self-adjustments of the doses of SLE medications, have also contributed to higher severity and mortality rates in this population.

Finally, it is evident that the COVID-19 pandemic has had a profound psychosocial impact in patients with SLE. Multiple factors inherent to the pandemic have acted as stressors in the general population, potentially increasing the risk of mental health disorders; these include disinformation, uncertainty, collective fear, in addition to the declared states of emergency and lockdowns, resulting in financial concerns and social isolation.\textsuperscript{248} Patients with SLE have faced numerous additional challenges during the pandemic. The fears of worse outcomes if contracting COVID-19, as well as the aforementioned concerns about access to health care and medication availability in this population, may affect the emotional and mental health of patients with SLE even further. Accordingly, a study from Poland showed a higher risk of anxiety, depression, and sleep disorders in SLE patients when compared to non-SLE patients during the COVID-19 pandemic.\textsuperscript{245} In addition, in a cohort of patients with rheumatoid arthritis and SLE in the Philippines, a considerable proportion of patients were experiencing moderate to severe stress (12%), moderate to extremely severe anxiety (39%), and depression (28%).\textsuperscript{250}

CONCLUSION

Many of the immune system pathways important to COVID-19 infection are active in SLE, providing a valuable comparison and lessons to be learned in instances when the two conditions co-exist. It seems that besides sGC use, most risk factors for worse outcomes of COVID-19 in patients with SLE are similar to those identified in the general population. However, the impact of additional factors, including those related to SDH, requires further study. It is possible that some of the factors in SLE offset one another, such as any potential protective effect from type I IFN being offset by immunosuppressive agents, for example. These complexities hold promise for a greater understanding of COVID-19 immunopathogenesis in the broader population, and lessons learned through years of human SLE research seem highly relevant to challenges presented by this new viral pathogen.
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