SARS-CoV-2 and Systemic Lupus Erythematosus

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Abstract

Purpose of Review To summarize current knowledge of the impact of coronavirus disease 19 (COVID-19) on patients with systemic lupus erythematosus (SLE).

Recent Findings Several observational studies, including case series, patient surveys, and patient registries, have examined the incidence and severity of COVID-19 in patients with SLE. Due to methodologic limitations (focus on sicker patients, exclusion of asymptomatic or mild cases, limited or inaccurate viral testing), it is difficult to determine the risk and outcomes of COVID-19 in SLE patients. Corticosteroids might be associated with increased hospitalizations from COVID-19 in individuals with autoimmune rheumatic diseases. Some immune suppressive treatments do not appear to significantly increase the risk of contracting COVID-19 or poor subsequent outcomes; however, data on the safety of specific drugs remain scarce. Studies in non-autoimmune cohorts have shown more severe COVID-19 in ethnic and racial minorities, populations also more heavily impacted by SLE. Such results have been attributed to highly prevalent socioeconomic disparities and comorbidities. The complex interplay between SARS-CoV-2 and the host immunologic milieu may have particular implications for patients with SLE that remain to be explored. Concerns have been raised of COVID-19 heightening the risk of thromboembolic events in the presence of an SLE-induced procoagulant state.

Summary Limitations in epidemiologic data available to date do not allow for assessing the risk and severity of COVID-19 in patients with SLE. Other than corticosteroids, prior use of some immune suppressive medications does not appear to increase the risk for infection with SARS-CoV-2 however, more comprehensive studies are needed.

Keywords Systemic lupus erythematosus · COVID-19 · Immunosuppression

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with protean manifestations and a chronic fluctuating clinical course [1]. The emergence and rapid global spread of the coronavirus-associated disease 19 (COVID-19) pandemic has raised multiple questions for rheumatologists about infection risk and the proper use of immune suppressive medications by patients with SLE and other chronic autoimmune rheumatic diseases (AIRDs) [2]. Individuals with SLE might be at increased risk for contracting SARS-CoV-2 and a more severe clinical course once infected, due to SLE-related innate immune perturbations and increased baseline inflammation [3]. Immune suppressive medications are associated with increased infections, while they may also dampen exuberant immune responses seen in severe COVID-19. Social determinants of health and comorbidities prevalent in SLE cohorts have been independently associated with COVID-19 in other populations [4, 5]. While the pandemic evolves, research on the impact of COVID-19 in patients with SLE and other autoimmune diseases has been ongoing, providing preliminary evidence to assist clinical decision-making and generate hypotheses to be tested.
COVID-19: Immunopathologic and Clinical Highlights

SARS-CoV-2 is a novel RNA coronavirus of the same family as SARS-CoV and Middle East respiratory syndrome coronavirus that mainly spreads through the respiratory tract [6]. SARS-CoV-2 enters cells by binding to the angiotensin converting enzyme 2 (ACE2) receptor [7] suggesting that factors enhancing ACE2 expression could increase viral entry and COVID-19 susceptibility. Infection can be mild or asymptomatic in up to 80–90% of infected individuals, and clinical disease mainly manifest with systemic and respiratory symptoms that range from mild to severe [8].

Both innate and adaptive immune mechanisms are involved in the early immune response against SARS-CoV-2 [6]. Macrophages, neutrophils, and dendritic cells appear important in early defense, the latter cells being the main inducers of an early type I interferon (IFN) response at the infection site that limits viral replication and systemic immune activation. Both the robustness and timing of this response are considered critical in COVID-19, with delayed or low responses resulting in elevated lung cytokine/chemokine levels, impaired virus-specific T cell responses, and late clinical deterioration [9*]. Cytotoxic CD8 T cell responses emerge in the next few days, and are control COVID-19 and lead to viral elimination. Antibody responses are generated within 12–14 days of infection, and might be protective against future infection or reinfection, although B cells and immune globulins are probably not obligate for a protective immune response to SARS-CoV-2 [10].

A small minority (5%) of patients with COVID-19 pneumonia show sudden rapid clinical deterioration late in the disease course, despite declining levels of SARS-CoV-2 viral load. These patients progress to acute respiratory distress syndrome (ARDS) and a systemic cytokine storm associated with considerable mortality [9*, 11]. Proinflammatory cytokines (IL-1β, IL-18, IFN-γ, and IL-6) are induced by excessive innate immune activation resulting from delayed or impaired early immune responses, and are key mediators of late phase hyperinflammation in COVID-19. Similar to other types of cytokine storm, this appears to be primed by decreased T cells and impaired T cell functions, and culminates in tissue damage [9*]. Lung tissue from patients with severe COVID-19 shows hemophagocytosis, a central pathologic feature of cytokine storm [12], and an expanded inflammatory macrophage phenotype, possibly driven by IFN-γ and TNFα, is demonstrated in bronchoalveolar lavage of these patients [13]. Exuberant neutrophil responses with release of neutrophil extracellular traps (NET) are also implicated in lung endothelial damage in COVID-19. Affected patient sera could robustly stimulate NETosis of control neutrophils in vitro [14]. Consistent with these observations, peripheral blood lymphopenia and neutrophilia are prominent and have prognostic value in severe COVID-19 [15].

Abnormal coagulation panels and a variety of antiphospholipid (aPL) antibodies have been described in COVID-19, along with a range of thromboembolic complications occurring despite standard thromboprophylaxis [16, 17]. Thromboses are usually venous and less commonly arterial, and can be widespread with cases of thrombotic microangiopathy (TMA), usually in the lungs [18–20]. COVID-19-related TMA involves complement and platelet activation without the extent of platelet consumption observed in diffuse intravascular coagulation (DIC) [17]. Contrary to DIC, schistocytes are absent, platelet counts are mildly decreased, and bleeding is uncommon. Pathogenesis of COVID-19-induced thrombosis appears to involve multiple mechanisms related to inflammation, including endothelial injury and dysfunction, macrophage activation, NET formation, dysregulated complement activation, and renin-aldosterone-angiotensin system (RAAS) activation [15]. The clinical relevance of the observed aPL antibodies remains under investigation [16].

COVID-19 in SLE: Immunologic Implications

Innate and adaptive immunologic perturbations prevalent in SLE may increase susceptibility to COVID-19, lead to prolonged viral shedding, or predispose to more severe disease [3, 21, 22]. In SARS-CoV-2-infected patients with SLE, underlying DNA methylation defects, potentially exacerbated by oxidative stress, could increase ACE2 expression and enhance viremia [23]. Defects in T cell–mediated cytotoxicity in patients with SLE have been associated with increased viral susceptibility, and could be particularly relevant in severe COVID-19 [24]. At the same time, the increased type I IFN signature characteristic of SLE could enhance protection at the early phases of SARS-CoV-2 infection [25]. The impact of SARS-CoV-2 on the immunologic scaffold of SLE and on lupus disease activity nonetheless remains largely unknown. Viral infections are potential triggers of flares in SLE, while viruses like EBV have been implicated in SLE pathogenesis [26]. The SLE-induced procoagulant state with predisposition to thromboembolic events [27] may be further heightened in face of COVID-19 [17]. Overall, both the short- and long-term impact of COVID-19 on SLE remains to be explored.

COVID-19 Infection in Patients with SLE: Observational Studies

Early on in the COVID-19 pandemic, observational studies employing clinical registries, patient surveys, and reviews of hospital records attempted to capture the epidemiology and clinical course of COVID-19 in SLE and other AIRDs. Despite large cumulative numbers of patients, methodologic issues (e.g., focusing on the most sick, exclusion of...
asymptomatic or mild disease, limited availability or accuracy of PCR testing) limit the assessment of incidence or severity of COVID-19 in SLE and other AIRDs.

In a telemedicine survey of 126 Italian SLE patients, 12 cases of confirmed or suspected COVID-19 were reported. Symptoms remained mild to moderate (except for one ICU admission), with a confirmed COVID-19 incidence (2.5%) appearing increased compared to the general population [28]. In another survey of 62 Italian SLE patients, 8 reported consistent but self-resolving symptoms [29]. COVID-19 incidence was low in 225 surveyed SLE patients from Belgium, with 18 cases of infection (5 confirmed), 2 of them requiring hospitalization [30]. In a telephone survey of 845 SLE patients across multiple locations in India, 17 reported self-limited symptoms suggestive of COVID-19. Only 2 were tested, one of whom was positive and required hospitalization [31].

In contrast to these reports, a more severe clinical course was described in a French series of 17 SLE patients with confirmed COVID-19. Fourteen (82%) were hospitalized, 7 were admitted to ICU, and 2 (14%) died [32]. SLE was quiescent in all patients except one, but comorbidities were high, with obesity and chronic kidney disease in 10 and 8 patients, respectively. Similarly, 4 out of 5 SLE patients with COVID-19 from Michigan were admitted to the hospital, 3 (60%) required invasive ventilation, and one died [33].

Among 16 (4%) patients with SLE and confirmed or suspected COVID-19 from the Columbia Lupus Cohort, 7 were hospitalized and 3 developed respiratory failure [34]. In another study of 226 SLE patients from New York City, 41 developed COVID-19 confirmed by PCR (remaining were asymptomatic, or symptomatic with negative or no testing) [35]. Among them, 24 (58%) were hospitalized, 4 required intensive care, and 4 died. In exploratory regression analysis (due to small sample size), non-white race, presence of at least one comorbidity, and BMI were independent predictors of hospitalization [35]. Two (8.3%) of the hospitalized patients developed micro- and macro-thrombotic events, raising awareness for this complication in SLE. Among 85 SLE patients with COVID-19 (suspected or confirmed) in the COVID-19 Global Rheumatology Alliance registry (C19-GRA), 45 (56%) required hospitalization versus 46% of the entire C19-GRA cohort [36]. Association of SLE with hospitalization was nonsignificant after adjusting for age and comorbidities. Results in other AIRD cohorts, some including few patients with SLE, have been consistent [37–46, 47].

This has been attributed to a disproportionate burden upon minorities of comorbidities like hypertension, cardiovascular disease, chronic lung disease, and kidney disease that are independently associated with incidence and severity of COVID-19 [4, 5]. It is furthermore likely that socioeconomic disadvantages prevalent in minority populations may prohibit adherence to social distancing guidelines (for reasons like employment in public-facing occupations, crowded or unstable living situations and financial constraints) or access to telemedicine [49].

Racial minority populations that are highly burdened by COVID-19 are also more frequently affected by severe SLE. Indeed, African Americans were overrepresented compared to the general population in series of COVID-19-affected SLE patients from Michigan [33], with similar results demonstrated in SLE cohorts from New York City [35] and in AIRD patients from Massachusetts [47]. Health disparities remain pronounced in SLE, with more severe disease, increased end organ damage, and higher mortality in racial/ethnic minorities and individuals of lower socioeconomic status [50–52]. Limited or fragmented access to subspecialty care, suboptimal prescribing and adherence to medications and delayed or limited use of standard-of-care immune suppressive therapy have been implicated, along with reliance on chronic glucocorticoid use for disease control [49]. In lupus patients, comorbidities associated with COVID-19 severity can often be traced to SLE-induced organ damage (e.g., chronic kidney disease due to lupus nephritis) and side effects of medications (e.g., steroid-induced obesity and diabetes).

**Immune Suppressive Treatments for SLE and COVID-19**

Early on during the COVID-19 pandemic, concerns were raised about immune suppressive therapies increasing susceptibility and severity of COVID-19. At the same time, protective effects of certain drugs were postulated by inhibiting viral entry and replication (antimalarials, mycophenolate mofetil (MMF), cyclosporine) or by dampening hyperinflammation at late stages of COVID-19 (Janus kinase (JAK) inhibitors, IL-1 and IL-6 inhibitors) [2, 53, 54].

In the early days of the pandemic, publicity was drawn on hydroxychloroquine (HCQ) for treatment of COVID-19, based on in vitro studies and preliminary open label clinical trials [6]. Despite little supportive data, a wave of overprescribing resulted in supply chain issues and drug shortage, concerning for SLE patients relying on HCQ for disease control [55, 56]. HCQ remains the cornerstone of therapy in patients with SLE, associated with decreased risk of flare, reduced longer-term morbidity and mortality, and improved pregnancy outcomes [57]. Supply issues of HCQ for SLE patients have since luckily resolved, following clinical trials in hospitalized COVID-19 patients, including a randomized controlled trial and three large observational

**Health Disparities Amidst COVID-19 and Relevance to SLE**

Data from public health departments across the USA highlight an increased incidence of COVID-19 in racial minorities, like African Americans, Hispanics, and American Indians [48].
studies, that failed to demonstrate benefit [58]. Furthermore, HCQ use in combination with azithromycin was associated with increased mortality due to cardiac arrhythmias in this population [58, 59]. Congruent to those results, observational studies in patients with SLE and other AIRDs and concurrent COVID-19 did not support a protective effect of HCQ against COVID-19 infection or hospitalization [28, 30, 32, 35•, 40, 45, 47•, 60, 61]. It still remains to be investigated whether antimalarials may have a role for prophylaxis against COVID-19 in high-risk individuals [59], or in thromboprophylaxis during COVID-19.

Steroids are extensively prescribed for acute management of SLE, as well as long-term in a substantial number of lupus patients. Amidst the COVID-19 pandemic, concerns were raised on corticosteroids increasing the risk and severity of COVID-19 by means of their broad immune suppressive actions and by prolonging viral shedding [62]. Besides a series of 18 patients with confirmed or suspected COVID-19 where prednisone dose was associated with positive SARS-CoV-2 PCR [30], data in SLE have been limited. Notwithstanding, in AIRD patients (14% SLE) with COVID-19 from the C19-GRA registry, prednisone-equivalent doses ≥10 mg/day were associated with higher odds of hospitalization (OR = 2.05, p = 0.03) [36•]. In 103 non-SLE patients with inflammatory arthritis and COVID-19, those on oral glucocorticoids had a higher likelihood of hospital admission (p = 0.001) after adjustment for BMI and comorbidities [45]. The relative contribution in patients with SLE of a direct effect of corticosteroids on viral physiology and host immune responses versus a steroid-heightened risk of cardiovascular disease and diabetes versus confounding by social determinants of health (i.e., poor access to care) remains open to further research. Based on those studies, the American College of Rheumatology (ACR) task force endorsed continuation of standard-of-care glucocorticoid administration, with avoidance of abrupt treatment withdrawal, along with utilization of the minimum effective dose and for minimum duration of time [63•]. Besides treatment of the underlying disease, a role of steroids in COVID-19-induced inflammation has been extensively explored. Retrospective studies suggested lack of benefit, and potential for harm of corticosteroids in hospitalized COVID-19 patients that are less sick or very early in the disease course (e.g., not requiring supplemental oxygen) [64]. Emerging data however support corticosteroid use in hypoxemic patients with COVID-19 and in the late phase of infection characterized by hyperinflammation and cytokine storm [65].

Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) like methotrexate, sulfasalazine, and leflunomide are routinely prescribed for lupus arthritis, mucocutaneous, and pleuropulmonary disease, whereas MMF and azathioprine are reserved for resistant manifestations, renal and hematologic disease, and tacrolimus and cyclosporine are used as 2nd- or 3rd-line treatment. A number of studies have examined associations of csDMARDs and severe COVID-19 in SLE and other AIRDs. Among 41 SLE patients with confirmed COVID-19 from New York City, use of immune suppressants (csDMARDs and biologics combined) was not associated with hospitalizations [35•]. In series of 18 SLE patients from New York City with confirmed or presumed COVID-19, intake of immune suppressants before admission did not seem to influence the severity of infection [34]. Use of csDMARDs, alone or in combination with biologic and targeted synthetic DMARDs (b/tsDMARDs), prior to COVID-19 diagnosis, was similarly not associated with hospitalizations in AIRD patients from C19-GRA [36•]. Observations in other AIRD cohorts have been consistent [30, 40, 43, 45]. Similarly, in patients with solid organ transplants on chronic immune suppression, no difference in exposure to csDMARDs could be shown in patients with mild versus severe COVID-19 [66].

In addition to FDA-approved belimumab, a number of biologics (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) are used off label in SLE. Evidence of their safety during COVID-19 remains sporadic, derived from cohorts with other AIRDs [40–42], or extrapolated from other infections. With paucity of COVID-19 specific data, assessment of belimumab risk rests entirely on previous reports of an overall benign safety profile [67]. Similarly, decision-making on use of abatacept during COVID-19 relies on older studies in patients with rheumatoid arthritis not showing increased risk of infection compared to other biologics [68]. Data on rituximab during COVID-19 refer to patients with granulomatosis with polyangiitis reporting severe COVID-19 [69, 70], but also mild disease clearing in the absence of antiviral antibodies [71]. Rituximab selectively eliminates B cells [71], not affecting innate immunity and mildly suppressing T cell responses considered important in early defense against SARS-CoV-2 [10]. Severe infections after rituximab were notably associated with concurrent steroid use in older reports [72]. Beyond any controversy on COVID-19 risk, blunting of immunologic response to an anticipated SARS-CoV-2 vaccine by rituximab-induced B cell depletion remains a concern [73]. JAK inhibitors (JAKi) and rarely TNF inhibitors (TNFi) are used off label in treatment of SLE. In 103 patients with rheumatoid arthritis or spondylarthritides from New York City (60% on a biologic, 11% on JAKi), JAKi use was associated with increased hospitalizations in multivariate analysis (OR 10.23, P = 0.007) [45]. Four deaths occurred in patients with other risk factors, one of them on TNFi while none on JAKi [45]. In AIRD patients (39% on biologics or JAKi) with COVID-19 from C19-GRA, biologics or JAKi were associated with lower odds of hospitalization, largely driven by TNFi (OR 0.46, p = 0.03) [36•]. Caution on causal inference was advised by authors of both studies, due to small numbers of patients and significant potential for residual confounding.

Although data remain limited to allow conclusions on specific agents, no association has thus far become evident
between immunosuppressive drug use and severe COVID-19 with a likely exception of corticosteroids [74]. Guidelines by the ACR and the European League against Rheumatism (EULAR) support the continued use of cs/b/tsDMARDs in the absence of exposure to SARS-CoV-2 and confirmed or suspected COVID-19 infection [63•, 75]. Notably, ACR recommendations on JAKi use during COVID-19 have been more guarded, due to concerns of dampening innate antiviral pathways by their broad immune suppressive effect [63•]. Biologics targeting IL-1 and IL-6 signaling may have a role in treatment of hyperinflammation associated with severe COVID-19 [9•, 11], but research is ongoing. Continuation of IL-6 inhibitors after SARS-CoV-2 exposure or infection was endorsed by the ACR on a case-by-case basis; nonetheless, it remains unclear if these drugs are safer compared to other biologics in early stages of COVID-19. Off-label use of these drugs in SLE however remains sporadic. In the setting of severe COVID-19 with TMA, anticoagulation and corticosteroids, IVIG therapy, plasma exchange, and therapies targeting complement activation are being increasingly explored [17]. Regarding ACE inhibitors and angiotensin receptor blockers, concerns have been raised about increasing levels of ACE2 and possibly susceptibility to infection [7], but clinical data have been insufficient to support beneficial or detrimental effects, and recommendations continue to support their standard of care use in patients with SLE [63•].

Conclusions

The multifaceted relation of COVID-19 with SLE has been a matter of ongoing research, with an agenda spanning from the immunologic interplay of SARS-CoV-2 and the SLE host to the role of comorbidities, socio-demographic factors, and immune suppressive treatments. Data on COVID-19 in patients with SLE nevertheless remain limited, mostly derived from case reports, case series, and registries with many potential sources for bias, or extrapolated from other AIRDs. With those limitations in mind, it is difficult to ascertain from currently available patient data if SLE per se will be a significant risk factor for contracting COVID-19 or developing poor subsequent outcomes. Immune suppressive medications beyond steroids do not appear to increase the risk or severity of COVID-19 infection, although more data on specific medications are needed. On the contrary, such risks were heightened by high-risk exposures to SARS-CoV-2, concomitant corticosteroids, and comorbidities. Overall, consensus guidelines by the ACR and EULAR recommend immune suppressive medications to be continued and steroids minimized in patients with SLE in the absence of confirmed or suspected COVID-19 infection. The rapidly evolving landscape of COVID-19 research does not however favor firm and durable conclusions. Meanwhile, maintaining disease remission in SLE patients continues to be key to preventing SLE complications, hospitalization, and risk of exposure to COVID-19. While awaiting more comprehensive studies, our focus will remain on sound clinical practice, individualized decision-making, and adherence to general preventive measures in caring for patients with SLE amidst the pandemic.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by the authors. For referenced studies with human or animal subjects coauthored by Dr. Sawalha, compliance with ethical guidelines is addressed in the corresponding manuscripts.

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