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Lupus and SARS-CoV-2: What have we learned after the pandemic?

Rachele Francese, Massimo Rittà, David Lembo and Manuela Donalisio

Abstract

After the end of the COVID-19 public health emergency, we analysed the relationship between Systemic Lupus Erythematosous (SLE) and COVID-19 from the virologist's perspective based on recent findings. SLE and COVID-19 comorbidity present unique challenges, as individuals with SLE may be at increased risk for severe COVID-19 illness due to immune system abnormalities and ongoing therapies. Effective management of both diseases requires careful monitoring, adherence to vaccination programs, preventive measures and approved and patient-tailored therapies. This review covers various aspects, including the clinical outcome of SLE patients infected by SARS-CoV-2, the impact of this infection on SLE onset or flare-ups and the benefits of vaccination for this population. Furthermore, this review presents the most recent recommendations on clinical management of COVID-19 in rheumatic patients, including those with SLE, discussing the currently available therapeutic options. Finally, we explore the most effective tools for SARS-CoV-2 diagnosis in autoimmune conditions and examine prognostic biomarkers in COVID-19 rheumatic patients with potential implications on their clinical oversight. By adopting a comprehensive approach, we address these complexities from the virologist's perspective, aiming to improve health care for this vulnerable population.

Keywords

Systemic lupus erythematosus, SARS-cov-2, COVID-19 vaccines, COVID-19 testing, COVID-19 drug treatment, biomarkers

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Key points

- A fourth booster dose of the 2023–2024 updated vaccine is recommended in SLE, regardless of the immunosuppressant therapy, to reduce the risk of SARS-CoV-2 infection and protect against serious consequences of COVID-19
- Vaccination does not appear to trigger lupus flares in most cases
- Since individuals with untreated or active SLE experience more severe COVID-19 outcomes, priority vaccination, close monitoring and prompt antiviral appropriate therapies in case of SARS-CoV-2 infection are strictly recommended
- An early viral direct diagnosis based on nucleic acid amplification tests (NAATs) is crucial for the proper management of COVID-19 SLE-patients
- New potential prognostic biomarkers have been proposed for clinical use, with the potential to improve patient care

Introduction

COVID-19 and rheumatic diseases: A multimorbidity clinical condition

Globally, as of April 1, 2024, more than 775 million COVID-19 cases and more than 7.0 million related deaths have been reported worldwide.[1] Among people with rheumatic diseases, the study from the COVID-19 Global Rheumatology Alliance registry reported rates of hospitalization and death of 49% and 10.5% respectively.[2] However other studies showed lower rates, closer to

Department of Clinical and Biological Sciences, University of Torino, Orbassano, Italy

Corresponding author:
Manuela Donalisio, Department of Clinical and Biological Sciences, University of Torino, Regione Gonzole, 10, Orbassano (TO) 10043, Italy.
Email: manuela.donalisio@unito.it

those of the general population. Effectively, the epidemiology of SARS-CoV-2 infection in patients with immune-mediated inflammatory diseases has many biases, including timing, population-related factors and different disease severity.[3]

Although many SARS-CoV-2 infected immunocompetent individuals are asymptomatic or develop mild symptoms, patients with immune-mediated inflammatory diseases are at higher risk of severe infections, mainly due to immune dysfunction and immunosuppressant therapies. In this group, the risk of symptomatic COVID-19 is two times higher than in the general population.[3,4] Of note, it has been widely documented that patients with systemic autoimmune rheumatic diseases are at higher risk of severe COVID-19 outcomes and prolonged symptoms.[5] The main risk factors for worse prognosis due to COVID-19 are older age, male gender, cardiovascular diseases, chronic lung diseases and higher and longer corticosteroid administration.[2] Immunocompromised patients experiencing persistent and protracted SARS-CoV-2 infections have been described in case reports and case series. They are referred to as "long persisters" and tentatively proposed diagnostic criteria are persistently positive SARS-CoV-2 PCR ≥21 days, persistent/relapsing symptoms (fever, dyspnoea, hypoxemia) and persistent/relapsing changes on chest-X ray or CT scan. Their symptoms vary from recurrent severe pneumonia to asymptomatic course. The main predisposing factor for such a condition is B-cell depletion due to haematological malignancies, hematopoietic cell transplantation or anti-CD20 monoclonal antibodies used to treat rheumatologic conditions.[6]

Clinical outcomes in SARS-CoV-2 infected SLE patients

People affected by Systemic Lupus Erythematosous (SLE), a multi-system auto-immune disease, have the highest risk for infections and related morbidity among the rheumatic diseases group.[7] This increased risk of infections is mainly associated with several endogenous factors, including impaired neutrophils chemotaxis, lymphopenia, altered T-cell cytotoxicity, reduced complement levels and iatrogenic immunosuppression.[8] As for SARS-CoV-2 infected SLE patients, several studies have shown an increased COVID-19 morbidity and the worse outcomes are related to older age, male gender and comorbidities such as cardiovascular and pulmonary disease.[9] Generally, the development of symptomatic COVID-19 has been associated with increased concentrations of C-reactive protein.[3] Higher numbers of disease flares have been reported after infection in patients with systemic autoimmune rheumatic diseases, being associated with development of neurological, cardiological and musculoskeletal inflammatory diseases.[3,10] Furthermore, several medical conditions have been identified as negative prognostic factors in SLE patients including chronic kidney insufficiency, chronic pulmonary disease, cardiovascular disease, high disease activity and history of lupus nephritis.[7,9,11]

SLE-specific treatments that target type I interferon pathway (anifrolumab) have been associated with increased risk of both primary viral infections and reactivation of latent viruses.[8] Furthermore, immunomodulatory/immunosuppressive treatments and comorbidities trigger an increased risk of serious infections in people with rheumatic diseases.[12] In this context, rituximab, mycophenolate and cyclosporin have been linked to severe COVID-19 outcomes, such as hospitalization, mechanical ventilation, intensive care unit admission and death.[7,13] In detail, rituximab-treated patients can exhibit persistent COVID-19 symptoms, long viral shedding and relapsing SARS-CoV-2 infections. Furthermore, under rituximab-treatment, during the course of the infection, an intra-host viral evolution has been shown, characterized by mutations in critical viral genes such as that encoding for the spike protein.[13]

SLE onset after SARS-CoV-2 infection

Case reports suggest that COVID-19 may trigger the development of *de novo* immune-mediated inflammatory conditions mainly inflammatory rheumatic musculoskeletal diseases (RMD) including reactive arthritis, with symptom resolution within 6 months.[14,15] Up to 37% of patients with COVID-19 were reported to develop reactive arthritis within a 120-day interval. Interestingly, less prevalent musculoskeletal pain cases have been reported following Omicron in comparison to Delta SARS-CoV-2 variants, as well as in the vaccinated population.[14,16] However reactive arthritis is not a paradigm of systemic immune condition, not comparable to SLE. The incidence of RMDs after SARS-CoV-2 infection can't be estimated precisely since the level of evidence of the available studies is low, the number of cases investigated is limited and prospective observational studies are required to confirm associations.[14] A potential association between SARS-CoV-2 infections and new onset of auto-immune connective tissue diseases, particularly in young female subjects, has been suggested, including idiopathic inflammatory myositis, SLE, antisynthetase syndrome, systemic sclerosis and lupus nephritis.[10] After a mean interval between COVID-19 symptoms and SLE onset of 24.9 days, the most frequent SLE symptoms were pulmonary and renal involvements, followed by impaired liver functionality. The most commonly reported auto-antibody was ANA.[17] Remarkably, SLE patients reported symptom resolution within up to 1 year and two patients with SLE died of their illness.[14]

Notably, onset of cases of SLE have been reported even after SARS-CoV-2 vaccination.[18] In detail, vaccine-induced

SLE cases were associated with the first dose of vaccine, with an 1–30 day-interval to appearance of clinical manifestations (mainly musculoskeletal and cutaneous). Other comorbidities paired with SLE onset were Evans syndrome, acute pancreatitis, myocarditis and anti-phospholipid syndrome.[18]

Possible mechanisms underlying the association between COVID-19 disease and RMD development include autoimmune processes (molecular mimicry), excessive inflammatory responses, by-stander T-cell activation, viral persistence with colonization and damage of joint spaces by SARS-CoV-2 or immune complexes.[14,17] Even genetic predisposition is reported.[19] Many authors stress the importance of active vigilance for multisystem involvement after COVID-19 and propose medical investigations such as auto-antibody testing in case of high clinical suspicion, screening for differential diagnoses and synovial fluid analysis if joints are involved.[14] It must be pointed out that the level of evidence of the reported studies is low; most studies are case reports and case series. Therefore further investigations are demanding.

Similarly to SARS-CoV-2, other viral infections have been implicated in the development of SLE, including Epstein-Barr virus (EBV), cytomegalovirus, parvovirus B-19, retroviruses and dengue fever virus, likely by autoimmunity mechanisms.[15,17]

Methods

This is a narrative review. The literature review was performed by conducting electronic searches in PUBMED (National Library of Medicine (United States), National Centre for Biotechnology Information, available from https://pubmed.ncbi.nlm.nih.gov) and EMBASE (Elsevier Ltd., available from https://www.embase.com). The main keywords used for the electronic search are listed in the Supplemental Materials. Articles were chosen based on the following criteria: peer-reviewed papers; publication date from 01.07.2020 to 30.03.2024; English text; full-text available. Additionally, other relevant references were identified by consulting the most recent scientific information published by the Centre for Disease Control and Prevention (CDC), the World Health Organization (WHO) and the American College of Rheumatology (ACR).[20–22] All the selected materials were analysed by all authors to determine their relevance for inclusion in this review and were chosen with their unanimous consent.

SARS-CoV-2 vaccination in patients with rheumatoid diseases

In the post COVID-19 pandemic era there is a strong consensus that vaccination remains crucial to public health, especially for people who are moderately or severely immunocompromised, to protect against serious consequences of COVID-19 according to the major leading science-based service organizations' guidelines.[23] The Centers for Disease Control and Prevention (CDC) recommends the 2023–2024 updated vaccines that have met the agency's rigorous scientific standards for safety, effectiveness, and manufacturing quality, such as the multi-dose mRNA vaccines marketed by Pfizer-BioNTech and Moderna or the protein subunit vaccine Nuvaxovid™ by Novavax. The Johnson & Johnson/Janssen COVID-19 vaccine is no longer an FDA-authorized vaccine and is not available in the United States as of May 2023. The 2023–2024 updated vaccines are better at fighting the Omicron variants of interest currently in circulation, that mainly derived by the XBB.1.5 and BA.2.86 lineages with additional mutations.[24] The suggested COVID-19 vaccine doses vary for each immunosuppressed person over 6 months of age depending on the previously received vaccines: 2-3 doses of the same brand of an updated vaccine for those who have never been vaccinated, 1-2 doses for those who have got one previous Pfizer-BioNTech or Moderna COVID-19 vaccine before September 12, 2023, and one dose of the updated vaccine for those who have got 2 or more previous COVID-19 vaccines. The time interval between doses varies depending on the brand, generally 3-4 weeks (Table 1).[25] Additional updated vaccine doses are not boosters as the pre-portioned medicine is delivered completely.[26] However, despite these evidences, in the last period of pandemics and after pandemics, a minor adherence to the vaccine protocol has been registered even in the vulnerable population.

In accordance with the CDC guidelines the American College of Rheumatology (ACR) recommends the COVID-19 vaccines for people with autoimmune and inflammatory rheumatic diseases, including Lupus, who meet the age requirements. The initial mRNA vaccine series is defined as three doses for this category of subjects and a fourth booster dose is recommended. Vaccines are still the best way to prevent serious COVID-19 illness and death from the infection.[26–28]

During the Omicron era, recent papers confirmed the effectiveness of multi-dose COVID-19 vaccines in patients with systemic autoimmune rheumatic diseases with favourable outcomes.[29–34] Of note Hanberg et al., using a target trial framework, demonstrated that patients under disease-modifying anti-rheumatic drugs (DMARDs) treatment, receiving the fourth dose of a mRNA vaccine (BNT162b2 or mRNA-1273) during the 2022, showed a lower risk of SARS-CoV-2 infection and severe COVID-19 versus those not receiving, with a reduced risk of hospital admission or death. Furthermore, an improvement of humoral response has been well established in patients with systemic autoimmune rheumatic diseases using DMARDs after the fourth dose of a SARS-CoV-2 vaccine.[31–33] Indeed,

Table 1. Recommended COVID-19 vaccination schedules in adults who are moderately or severely immunocompromised.

COVID-19 vaccination history	Updated 2024-2025 vaccine	Doses recommended	Intervals
Unvaccinated	Moderna	3	1 - day 0 2 - 4 weeks after dose 1 3 - At least 4 weeks after dose 2 - Additional doses[a]
	Novavax	2	1 - day 0 2 - 3 weeks after dose 1 - Additional doses[a]
	Pfizer-BioNTech	3	1 - day 0 2 - 3 weeks after dose 1 3 - At least 4 weeks after dose 2 - Additional doses[a]
1 dose any Moderna	Moderna	2	1 - / 2 – 4 weeks after dose 1 3 – at least 4 weeks after dose 2 - Additional doses[a]
2 doses any Moderna	Moderna	1	1 - / 2 - / 3 – at least 4 weeks after dose 2 - Additional doses[a]
1 dose any Pfizer-BioNTech	Pfizer-BioNTech	2	1 - / 2 – 3 weeks after dose 1 3 – at least 4 weeks after dose 2 - Additional doses[a]
2 doses any Pfizer-BioNTech	Pfizer-BioNtech	1	1 - / 2 - / 3 – at least 4 weeks after dose 2 - Additional doses[a]
3 or more doses any Moderna or any Pfizer BioNTech, not including at least 1 dose of any 2024-2025 COVID-19 vaccine	Moderna	1	At least 8 weeks after the last dose - Additional doses[a]
	Novavax	1	At least 8 weeks after the last dose - Additional doses[a]
	Pfizer-BioNTech	1	At least 8 weeks after the last dose - Additional doses[a]
3 or more doses of any mRNA vaccine, including at least 1 dose of any 2024-2025 COVID-19 vaccine	- Additional doses[a]		- Additional doses[a]
1 dose any Novavax	Novavax	1	1 - / 2 – 3 weeks after dose 1 - Additional doses[a]
2 or more doses any Novavax, not including 1 dose of any 2024-2025 COVID-19 vaccine	Moderna	1	At least 8 weeks after the last dose - Additional doses[a]
	Novavax	1	At least 8 weeks after the last dose - Additional doses[a]
	Pfizer-BioNTech	1	At least 8 weeks after the last dose - Additional doses[a]

(continued)

Table 1. (continued)

COVID-19 vaccination history	Updated 2024-2025 vaccine	Doses recommended	Intervals
2 or more doses of any Novavax, including 1 dose of any 2024-2025 COVID-19 vaccine	- Additional doses[a]		- Additional doses[a]

COVID-19 vaccine doses from the same manufacturer should be administered whenever recommended. Exceptions include not unavailability, previous dose unknown and specific contraindications.
Adapted from "CDC – Clinical Guidance for COVID-19 Vaccination".[25]
[a]Additional doses of any 2024-2025 COVID-19 vaccines (Moderna, Novavax or Pfizer-BioNTech) can be administered at least 2 months following the last recommended 2024-2025 vaccine dose. Additional doses may be administered according to medical judgement at least 2 months after the last 2024-2025 COVID-19 vaccine dose.

a clear benefit in terms of seroconversion rates has been also documented after a mixed COVID-19 vaccine regimen without flares among persons with immune-mediated inflammatory diseases.[33]

Considering the current endemic profile of SARS-CoV-2 and common re-infections, it's relevant that in patients with immune-mediated inflammatory diseases the documented breakthrough Omicron infection after three original vaccine doses conferred a higher hybrid immune response than in those vaccinated and uninfected.[32] The most plausible explanation is associated with the increased number of viral antigens able to activate immunity. However, a vaccination plan should be tailored for each person with autoimmune inflammatory rheumatic diseases, considering that different immunosuppressive drugs have a different impact on the response to vaccines. The European Alliance of Associations for Rheumatology (EULAR) recommendations indicate that, in general, vaccines should be given, wherever possible, when the underlying autoimmune rheumatic disease is well controlled with treatment and possibly two to 4 weeks before the next anticipated rituximab dose.[28,35,36]

Previous studies, after receiving the second or third dose of Moderna or Pfizer mRNA vaccine, evidenced that glucocorticoids, mycophenolate, tacrolimus, belimumab, abatacept, leflunomide, methotrexate, high prednisone (≥10 mg/day) and rituximab were associated with a poor vaccine response with a variable impact.[7,29,37–39] However, both treated and untreated SLE patients showed a more pronounced decline in antibody levels over time compared to healthy subjects. Of note, a benefit was evident holding mycophenolate mofetil on the day of and for 1 week after the mRNA vaccine detecting significantly increased post-vaccine antibody levels without flares of the underlying disease.[39]

Data indicated that the fourth vaccine dose represents a benefit regardless of the immunosuppressant therapy. Other previous studies showed that increased anti-SARS-CoV-2 antibody concentrations were obtained also in patients undergoing a B-cell depleting therapy, although the protective effect was lower than in the co-presence of other medications.[29,30,32,34] Of note, rituximab-treated rheumatic patients retained a T cell-mediated immune response that is crucial contributing to protection.[40] Concerning the optimal timing to receive the vaccine dose in patients under rituximab or other anti-CD20 medications, an adopted strategy is the measurement of CD19 B-cells to time the booster and subsequent rituximab dosing.[27,41] It has been observed that rituximab-treated rheumatoid arthritis patients who were able to generate humoral responses, had a greater interval between the last rituximab infusion and the vaccination that likely assured the B-cell compartment reconstitution.[29]

The vaccine hesitancy registered recently in the healthy but also in the immunocompromised population is a widespread problem, partially due to fears regarding vaccine side-effects. In general, the potential side effects in patients with rheumatoid diseases are similar to those in the immunocompetent, including mild constitutional flu-like symptoms (tiredness, low-grade fevers or chills) and, more frequently, localized reactions (pain at the injection site, rash).[7,29] The COVID-19 vaccine safety was also confirmed in a global survey involving pregnant women with SLE: no vaccine-associated adverse events or signals of exacerbation of the mother's autoimmune disease were reported. The COVID-19 vaccine provides both an active immunisation to the mother and a passive immunisation to the foetus.[42]

Studies on cohorts of patients vaccinated with the fourth dose didn't evidence any serious adverse events and, in general, a minority of people affected by lupus or other autoimmune diseases developed a post-vaccine inflammatory disease flare, mainly referring to mucocutaneous and musculoskeletal symptoms.[8,32,38,39,43] Concerning the possible *de novo* development of new-onset SLE after COVID-19 vaccination, a few cases were reported during the pandemic but no etiological association has been demonstrated.[7]

Given the significantly high risk of COVID-19 death, patients with systemic autoimmune rheumatic diseases should be encouraged to remain up-to-date with COVID-19 vaccinations.[44]

Therapeutic management of COVID-19 in immunocompromised, rheumatoid disease and SLE patients

It has been widely demonstrated that the progression to severe COVID-19 is favoured by several risk factors, including age over 50 years, acute respiratory distress syndrome (ARDS) and an immunosuppressed status in unvaccinated or not-updated vaccinated individuals; especially a prolonged SARS-CoV-2 viral replication and persistent infection have been documented in immunocompromised patients, including individuals with untreated or active SLE, for whom specific antiviral treatments are crucial to reduce the risk of hospitalization and death.[5,6]

According to the recent Centers for Disease Control and Prevention (CDC) Interim Clinical Considerations, Infectious Diseases Society of America (IDSA) and National Institutes of Health (NIH) guidelines, the treatment of COVID-19 disease in immunosuppressed patients can involve a single or combined therapeutic regimen based on antivirals, corticosteroids and immunomodulators.[45–47]

Generally, therapies directly targeting SARS-CoV-2 have the greatest effect early in the course of the disease, whereas immunosuppressive, anti-inflammatory, and antithrombotic therapies are more beneficial in advanced stages of COVID-19, where hyperactive inflammatory response to SARS-CoV-2, endothelial dysfunction and hypoxemia are manifest.[45]

As for antivirals, the recommended treatments differ in community and hospitalized settings. For outpatients, the preferred antiviral drugs are nirmatrelvir/ritonavir and remdesivir. Oral nirmatrelvir/ritonavir should be started within 5 days of symptoms onset, for a 5-day course.[47,48] Nirmatrelvir is a novel SARS-CoV-2 main protease inhibitor which is paired to ritonavir for its activity as an inhibitor of cytochrome P450 3A4. Remdesivir, an inhibitor of the RNA-dependent RNA polymerase of coronaviruses, is administered with a 3-day intravenous course within 7 days of symptom onset. Immunocompromised patients with persistent COVID-19 symptoms may be prescribed longer or additional courses.[45,49] When nirmatrelvir/ritonavir or remdesivir aren't feasible or appropriate, oral molnupiravir maybe an available option for the treatment of adults with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, even though it has lower efficacy.[45,49,50] Molnupiravir is a cytidine nucleoside antiviral (prodrug) that introduces errors during viral RNA replication and hinders SARS-CoV-2 ability to proliferate.[51] It's administered in 5-day courses within 5 days of symptom onset. It is not recommended for use during pregnancy and breast-feeding is not recommended during treatment with molnupiravir or for 4 days after the last dose. Recent meta-analysis confirmed its ability in reducing mortality and hospitalisation of COVID-19 patients and showed that molnupiravir did not significantly reduce mortality in COVID-19 patients with high coverage of COVID-19 vaccine.[52,53]

In SARS-CoV-2 individuals with systemic rheumatic diseases, including SLE, undergoing immunosuppressive therapies, outpatient treatments with oral antivirals (mainly nirmatrelvir/ritonavir initiated within 3 days after the onset of symptoms and continued for 5 days) or monoclonal antibodies were associated with significantly reduced risk of severe COVID-19 outcome.[5,54] Of note, early antiviral outpatient treatment is highly recommended even among those vaccinated against SARS-CoV-2.[5,47] Additionally, remdesivir can be used with courses extended up to 10 days. Recent data evidenced that its use demonstrated survival benefit for all SARS-CoV-2 variants.[45,55]

As for immunocompromised and hospitalised COVID-19 patients with evidence of persistent ongoing viral replication, the optimal antiviral treatment is yet uncertain. Possible treatment options are longer and/or additional courses of nirmatrelvir/ritonavir, remdesivir or high titre COVID-19 Convalescent Plasma (CCP) from a vaccinated donor who has recently recovered from COVID-19, or combinations. However, the use of high titre CCP in hospitalised immunocompromised patients is controversial and not currently recommended.[49,56]

The treatment with corticosteroids, such as dexamethasone has demonstrated beneficial effects in hospitalised COVID-19 patient who are receiving Oxygen.[57] The most used immunomodulators in infected hospitalised patients with severe advanced disease are abatacept, baricitinib (or tofacitinib), dexamethasone, infliximab, tocilizumab or sarilumab, according to disease severity. Insufficient evidence is reported for the use of anakinra, inhaled corticosteroids and vilobelimab as immunomodulators for the treatment of COVID-19.[45,57] However, according to the NIH guidelines, corticosteroids shouldn't be used for patients who are not receiving supplemental oxygen.[57,58] Indeed, dexamethasone use in hospitalised COVID-19 patients not requiring Oxygen therapy did not exhibit any clinical benefits and did not reduce mortality.[59] Increased mortality in hospitalised COVID-19 patients not receiving Oxygen and treated with early dexamethasone was reported by Crothers et al. Corticosteroids may have harmful side effects, hamper the patients' adaptive immune responses to SARS-CoV-2 and increase the risk of secondary infections.[60] In immunocompromised patients receiving minimal levels of conventional Oxygen and earlier in the course of COVID-19 disease (<10 days of symptoms) supportive care and antiviral therapies should be preferred and corticosteroids avoided.[49] The CDC evidences that, for immunocompromised patients on chronic corticosteroid therapies prior to hospitalisation, dexamethasone should be introduced and maintenance doses for the underlying disease should be discontinued.[49,61] Notably, according to the European Alliance of Associations for Rheumatology (EULAR) recommendations, in patients with RMDs receiving long-term glucocorticoid treatment who

develop suspected or confirmed COVID-19 disease, glucocorticoid treatment should be continued, in order to prevent possible flares of the underlying disease.[7,62]

As for pre-exposure prophylaxis, the only monoclonal antibody approved by the US Food and Drug Administration (FDA) was tixagevimab/cilgavimab. However, it was de-authorised in 2023 for the emergence of resistant Omicron subvariants of SARS-CoV-2.[7]

Notably, the possible interactions between anti-SARS-CoV-2 drugs and background immunosuppressants taken by the patients are remarkable. Ritonavir-mediated inhibition of cytochrome P450 3A may lead to increased levels of immunosuppressants such as tacrolimus, with adverse drug reactions.[63] Doses of Calcineurin inhibitors and m-TOR inhibitors should be adjusted when nirmatrelvir/ritonavir is being administered. The possible drug interactions of ritonavir change with time: both inhibition of cytochrome P450 3A4 in 5-day courses and enzymatic induction in longer courses are reported.[7,63,64]

SARS-CoV-2 diagnosis in autoimmune diseases

Generally, all people, regardless their immunological status, should be tested in presence of symptoms of COVID-19 or if an exposure to someone with COVID-19 is known.

Starting from the first months of the pandemic it was clear that the definitive diagnosis of SARS-CoV-2 had to be based on direct viral tests, including nucleic acid amplification tests (NAATs) and antigen tests used to detect current viral infection. During the emergency status and after, there has been a general consensus to use both viral tests indifferently to produce qualitative positive or negative results in overall population, considering that both targets, viral antigens or nucleic acids, can be detected after a window period of up to 5 days. Nevertheless, it's well known that antigen tests have lower sensitivity compared to molecular assays based on the genome detection. For this reason, the FDA recommends that negative results of antigen tests should be treated as presumptive and confirmed repeating the exam three times, with each test 48 hours apart, especially when there is a high clinical suspicion in asymptomatic or symptomatic people.[45] Currently available diagnostic assays for SARS-CoV-2 (viral tests including nucleic acid amplification tests – NAATs – and antigen tests) are summarized in Table 2.[65]

In immunocompromised patients living with autoimmune rheumatic diseases, the SARS-CoV-2 diagnosis plays a crucial role given the high risk of severe COVID-19, prolonged virus replication and intra-host SARS-CoV-2 evolution of mutated variants.[29,66,67] Prolonged infectious viral shedding has been frequently documented especially after post B-cell depletion therapy.

In subjects affected by autoimmune diseases, SARS-CoV-2 rebound is a complication after the antiviral treatment, for which a negative SARS-CoV-2 diagnostic test is followed by a newly positive test and recurrent symptoms after regimen completion.[5] This condition does not necessarily mean a person has been re-infected since intermittent detection of viral RNA can occur. In this case, the viral sequence comparison from both tests allows to distinguish between the persistent presence of viral genetic fragments and re-infection. Alternatively, the virologist may analyse the cycle threshold (Ct) value, that is the number of PCR cycles at which the nucleic acid target in the sample becomes detectable by real-time PCR, that is inversely related to SARS-CoV-2 viral load. The Ct value may provide information to differentiate between re-infection or the persistence of viral fragments.

Indeed, SARS-CoV-2-infected immunocompromised patients with lower RT-PCR Ct-values from respiratory samples showed markedly slower viral clearance.[68] Increasing evidence suggest that plasma SARS-CoV-2 viremia correlates with the severity of pneumonia, with RNA levels greater than 6000 copies/mL being strongly associated with mortality. Plasma SARS-CoV-2 RNA levels were also reported to correlate with lower respiratory tract RNA levels, and associated with several inflammatory biomarkers.[6,69]

Furthermore, understanding the level of infectivity in patients with prolonged SARS-CoV-2 nucleic acid test positivity by quantitative RT-PCR can guide clinical decisions, both therapy and public health policies.[6,67] Although the clear correlation between the Ct values and culture positivity and recurrence of symptoms in immunocompromised individuals, a standardization for the use of Ct values to guide treatment in the clinical setting is still lacking.

The use of Ct PCR values as a surrogate marker for COVID-19 outcome in immunocompromised patients deserve investigation in further larger studies. It may be intriguing to investigate whether immunocompromised individuals infected with SARS-CoV-2 may benefit from prolonged treatment with antivirals till negativization of plasma RNA levels.[6] This approach may improve clinical outcome and prevent protracted SARS-CoV-2 infection.[67]

Subgenomic RNA (sgRNA) species are synthesized during the replication phase of SARS-CoV-2 by a discontinuous transcription mechanism, with a potential regulatory role in the replication and expression of the viral genome. They have been proposed as diagnostic markers of ongoing viral replication, disease progression and prognosis in COVID-19 patients. However, the data on their diagnostic utility are mixed. Some studies suggest that sgRNA levels correlate with active virus replication. Conversely, others indicate that sgRNAs can persist in clinical samples long after the active replication phase, diminishing their reliability as indicators of active infection.[70,71] Notably,

Table 2. Currently available diagnostic tools for SARS-CoV-2 (viral tests including nucleic acid amplification tests – NAATs, antigen tests and serology tests) with a focus on rheumatic patients.

	NAATs	Antigen tests	Antibody (or serology) tests
Intended use	To detect current SARS-CoV-2 infection	To detect current SARS-CoV-2 infection	Not recommended to diagnose ongoing SARS-CoV-2 infection. Primarily used for public health surveillance and epidemiologic purposes
Methods	Most PCR (for RNA genes)	Immunoassays (for viral antigens)	Immunoassays (detect specific IgM/IgG antibodies that target nucleocapsid or spike protein of the virus)
Sensitivity	High	Less sensitive than most NAATs	High[a] Commercially available serological tests present significantly different performances[b]
Specificity	High	High	High[a] Commercially available serological tests present significantly different performances[b]
Where	Most need to be performed in a laboratory, some can be performed at the point-of-care (POC)	Available for at-home testing (self-testing), at the POC, or in a laboratory. Available over-the-counter	Available for use at the POC, or in a laboratory
Costs	More expansive than antigen tests	Most are less expensive than NAATs	Cost-effective
Turn-around time (TAT)	Minutes-hours	Minutes	Minute-hours
Results	Most NAATs produce qualitative (+/−) results	A negative antigen test in individuals with signs or symptoms of COVID-19 should be repeated or confirmed by NAAT	Detection of anti-Nucleocapsid antibodies indicates SARS-CoV-2 infection; anti-spike protein antibodies may be induced by COVID-19 vaccination or SARS-CoV-2 infection
Positive results	Indicate current infection	Indicate current infection	Their ability to predict protective immunity has not been validated. Antibodies recognizing viral nucleocapsid proteins are due to natural infections. Antibodies recognizing spike protein may be due to both vaccination or natural infections
Negative results	A negative result means the test did not detect the virus	A negative result means the test did not detect the virus. Negative results should be treated as presumptive. Negative antigen tests should be repeated up to three times with each test 48 hours apart to confirm a negative result	See above
Vaccination and SARS-CoV-2 testing	Vaccination does not affect the results of SARS-CoV-2 NAAT tests	Vaccination does not affect the results of SARS-CoV-2 antigen tests	Anti-spike protein antibodies may be induced by COVID-19 vaccination or SARS-CoV-2 infection
Advantages	Higher sensitivity	Short turnaround time (~15 minutes) for POC tests Cost effective	Serological assays are key elements in sero-survey design, emergency pandemic surveillance and public health policies
	Usually they do not need to be repeated to confirm results	Some can be used as POC	Antibody tests can be used in the diagnosis of multisystem inflammatory syndrome in children (MIS-C) or multisystem inflammatory syndrome in adults (MIS-A)

(continued)

Table 2. (continued)

	NAATs	Antigen tests	Antibody (or serology) tests
Disadvantages	Longer TAT for lab-based tests	Negative tests should be confirmed by NAAT or repeated	Impossibility to discriminate between vaccination and infection status by detecting antibodies against the spike protein
	Higher costs People may have detectable RNA (positive) for up to 90 days after an infection has ended	Less sensitive than NAATs, especially among asymptomatic people	Serological assay performance is assay dependent
Use in autoimmune rheumatic disease patients	They are the gold standard for SARS-CoV-2 diagnosis	Antigen tests play a role in distinguishing a reinfection from persistent shedding for weeks or months	Not recommended to diagnose ongoing SARS-CoV-2 infection False positive results for IgG and IgM may be a result of polyclonal hypergammaglobulinemia (e.g. in SLE, rheumatoid arthritis, systemic sclerosis, etc.)

NAAT, Nucleic acid amplification test.
POC, point-of-care.
Adapted from "CDC. Overview of Testing for SARS-CoV-2".[65]
[a]Sensitivity and specificity of the serological assays may vary depending on the testing population, according to prevalence of the disease, stage of infection, population characteristics and test reactivity.[77]
[b]Ref. 78.

PCR Ct-values for sgRNA have been reported to align with total viral RNA on respiratory samples from immunocompromised individuals.[72] Their possible role for diagnostic or prognostic purposes is still to be clarified.

Although NAATs are considered the gold standard for SARS-CoV-2 diagnosis, for the above-mentioned difficulties of interpretation and use of quantitative tests, the antigen tests should be preferred to distinguish reinfection from persistent shedding for weeks or months, especially in patients with symptoms compatible with SARS-CoV-2 infection and who are within 90 days of recovering from a previous SARS-CoV-2 infection.[73] Alternatively, the virus cultivability and the detection of infectious viral particles in respiratory samples could be performed to identify false positive results of NAATs in persistent COVID-19, but the complex laboratory equipment required for viral cultures limits its use in the diagnostic routine.

Moreover, the viral direct diagnosis has an essential role to solve a major challenge for the practicing physician without any clear epidemiological data: the ability to differentiate severe COVID-19 manifestations from a relapse of severe autoimmune disease. In fact, viral non-specific symptoms, such as fatigue, fever, myalgia, arthralgia, lymphopenia, thrombocytopenia and interstitial lung disease could resemble a possible autoimmune disease flare in a rheumatic patient.[74]

Generally, the serology is not recommended to diagnose ongoing SARS-CoV-2 infection not only in immunosuppressed patients but also in the overall population since the seroconversion may take 21 days or longer after symptom onset and some people may not develop measurable levels of antibodies.[61,75] A further limit of serology is the impossibility to discriminate between vaccination and infection by detecting antibodies against the spike protein. Therefore, their ability to predict protective immunity has not been validated and this limits the routine use in making individual medical decisions. An option to distinguish between antibody responses to natural infection and vaccine-induced antibody responses may be the detection of antibodies recognizing nucleocapsid proteins since they are not a constituent of the vaccines that are currently approved by the FDA.

In the context of autoimmune diseases, a relevant drawback of serology is the production of false-positive results for SARS-CoV-2-IgG and IgM, as a result of polyclonal hypergammaglobulinemia. Many studies showed false positive antibody detections in patients with SLE, rheumatoid arthritis, systemic sclerosis, and other related pathologies and discouraged the use of serology to avoid a rushed SARS-CoV-2 misdiagnosis.[74,76–78]

Potential prognostic biomarkers and commonly altered pathways in COVID-19 rheumatic patients

A biomarker is a biological factor used to identify the likelihood of a clinical event, disease recurrence, or progression in patients who have the disease or medical condition of interest. Many prognostic biomarkers are used in

clinical contexts where an individual is diagnosed with a disease or condition and there is interest in assessing the likelihood of a future clinical event. Examples of future events include death, disease progression, disease recurrence, or development of a new medical condition.[79] In the context of COVID-19 rheumatic patients, several papers report potential prognostic biomarkers that could be useful in predicting the development of severe COVID-19 or the onset of a new autoimmune disease (Table 3). Additionally, some authors have described biomarkers that could predict the vaccination response and the impact of SARS-CoV-2 vaccination on rheumatic disease onset or flares (Table 3). Despite great effort, the currently available studies present preliminary results, sometimes have been performed in small cohorts of patients, and require further investigations and clinical validation.

Among the rheumatic diseases group, SLE patients have the highest risk of infections and an increase in COVID-19 morbidity.[7,9] Generally, the development of symptomatic COVID-19 has been associated with a high concentration of C-reactive protein.[3] More recently, some authors tried to identify other specific biomarkers potentially predictive of severe COVID-19 development, both in SLE patients and the rheumatic patient category. Nln et al. developed multivariate prediction models that combined genetics and known biomarkers of COVID-19 mortality (C-reactive protein, troponin, and D-dimer).[80] They showed that genetic variants that are protective against SLE and associated with reduced type I IFN responses are associated with increased mortality in acute COVID-19. In particular, in acute COVID-19 patients of European-American origin, they found that a haplotype of interferon regulatory factor 5 (IRF5) and alleles of protein kinase cGMP-dependent 1 (PRKG1) were associated with COVID-19 mortality and variants in the IRF7 and IRF8 genes were associated with a worse outcome in African-American subjects. Their data supported the idea that several IFN pathway risk alleles for autoimmune disease had a significant impact on mortality following COVID-19 infection. Some authors evidenced a higher risk of severe COVID-19 associated with the production of autoantibodies, especially ANA, ANCA, rheumatoid factor (RF) anti-PM/Scl 100, and AMA-M2 and they proposed them as prognostic biomarkers. These findings were observed in intensive care unit (ICU) patients developing severe COVID-19 with multi-organ involvement and long-term complications.[81,82] As far as regards long-term post-acute sequelae of COVID-19 (PASC or long COVID), it has been reported that female gender, pre-existing systemic autoimmune rheumatic diseases, type 2 diabetes, asthma, and severe COVID-19 represent strong risk factors.[83] Herman et al. proposed potential prognostic markers to identify individuals at high risk of developing PASC among patients with pre-existing systemic rheumatic disease. They showed that common cold coronavirus imprinting, i.e. the presence of a previous antibody response against the endemic coronavirus OC43, is associated with post-acute sequelae of COVID-19. Markers like OC43 spike protein-specific FcγR binding antibodies, found in this study, could identify individuals at high risk of developing PASC and be useful for their clinical management.[83]

As previously described, some reports suggest the association between SARS-CoV-2 infections and the development of *de novo* immune-mediated conditions, with authors proposing the need for active vigilance for multisystem involvement after COVID-19.[10,14] Bakshi et al. investigated the presence of four markers of inflammation, known to be altered in some autoimmune disorders, including SLE, in blood samples from patients with COVID-19 infection, SARS-CoV-2 IgG seropositivity, and various SARS-CoV-2 vaccination status.[84] In particular, cathepsin S (CTSS), human complement receptor type 2 (CR2, CD21), myeloperoxidase (MPO), and cell-free DNA (cf-DNA) were investigated. Overall, the authors reported significant differences in these biomarker levels in all the tested groups, suggesting a correlation between COVID-19 status and the development of autoimmune disorders, as well as a potential link between SARS-CoV-2 infection and strong immune response. Interestingly, the SARS-CoV-2 nucleocapsid-specific IgG+ and COVID-19 groups had higher levels of MPO, a neutrophil protein linked to inflammation and tissue damage, suggesting a higher risk of autoimmune rheumatologic diseases. In the same context, other authors examined the production of autoantibodies in COVID-19 patients as biomarkers correlating with autoimmune diseases. Shortly after the outbreak of the pandemic, Sacchi et al. evidenced in a small cohort of COVID-19 individuals, a significant production of ANA, ANCA, and ASCA, indicating how SARS-CoV-2 infection could be associated with an autoimmune response and development of autoantibodies.[85] They also observed that patients having a *de novo* autoimmune response had the worst acute viral disease prognosis and outcome. Consistently, a multicentric study conducted in a larger cohort of 175 COVID-19 patients followed up to 1 year after infection, confirmed that there is transient autoantibody (such as ANA and ANCA) production during acute SARS-CoV-2 infection and that their presence correlated with increased antiviral humoral immune responses and inflammatory immune signatures.[86] A work focused on a specific rheumatic disease (i.e. arthritis) suggests, on the contrary, that the underlying mechanism of post-COVID-19 arthritis is the hyperinflammatory process associated with COVID-19 infection, and not the result of an autoimmune reaction. The authors, indeed, observed a strong association with inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) and an insignificant association with serologic markers of autoimmunity (ANA and anti-CCP). The authors' final suggestion is to test

Table 3. Potential prognostic biomarkers in the context of COVID-19 rheumatic patients.

Biomarker category	Examined rheumatic disease (if indicated)	Biomarker name	Potential impact on the clinic	References
Biomarkers predictive of severe COVID-19 development	SLE	SLE risk alleles: IRF5, PRKG, IRF7, IRF8	Some SLE genetic variants may predict COVID-19 mortality	Nln et al.[80]
	Autoimmune disorders	ANA, ANCA, RF, anti-PM/Scl 100, AMA-M2	Autoantibodies could be used as prognostic biomarkers in hospitalized COVID-19 patients	Jeong et al., mosavat et al.[81,82]
	Rheumatic diseases	OC43 spike protein-specific FcγR binding antibodies	A previous antibody response against the endemic coronavirus OC43 could predict long-term post-acute sequelae of COVID-19	Herman et al.[83]
Biomarkers potentially predictive of the onset of immune-mediated conditions after COVID-19	Rheumatic diseases	Markers of inflammation: CTSS, CR2, CD21, MPO, and cf-DNA	The biomarker levels were correlated with the development of autoimmune disorders; higher levels of MPO in COVID-19 patients may suggest a higher risk of autoimmune rheumatic diseases	Bakshi et al.[84]
	Autoimmune disorders	ANA, ANCA, and ASCA	SARS-CoV-2 infection could be associated with an autoimmune response and development of autoantibodies; a transient autoantibody production during acute SARS-CoV-2 infection is correlated with increased antiviral humoral immune responses and inflammatory immune signatures	Sacchi et al., Taeschler et al.[85,86]
	Arthritis	IL-6	The dosage of IL-6 levels before therapy could predict post-COVID-19 arthritis	Taha et al.[87]
Biomarkers predictive of SARS-CoV-2 vaccination response	SLE	IL-18	Higher mean levels of serum IL-18 could predict an impaired antibody response	Parsons et al.[38]
	Rheumatic diseases	Anti-SARS-CoV-2 antibodies	Antibody response at 1-month post-vaccination may predict susceptibility to breakthrough infections and be useful for prioritizing patients for booster doses	Ahmed et al.[88]
	Rheumatic patients under rituximab-treatment	B-cell and CD19	B-cell count is a candidate biomarker for cellular and humoral response after vaccination; monitoring CD19 may identify the optimal timing to administer the vaccine dose	Avouac et al., Stefanski et al.[89,90]
Biomarkers predictive of SARS-CoV-2 vaccination impact on rheumatic diseases	Autoimmune disorders	CD21, cf-DNA, CTSS	A strong immune response to the vaccination may be associated to the potential development of autoimmune disease	Bakshi et al.[84]
	Rheumatic diseases	ds-DNA, IFNI signature genes, frequency of DN2 cells	The monitoring of multiple disease biomarkers after vaccination was useful to demonstrate the efficacy and safety of repeated COVID-19 mRNA vaccines	An et al.[43]

IL-6 levels before therapy to predict post-COVID arthritis for early management.[87] Although the above reported literature, further studies are required to define the utility of the routinely analysis of systemic parameters.

Potential predictors of the vaccination response were described, especially for patients under DMARDs. It was described that, among SLE patients vaccinated with two doses of either the BNT162b2 (Pfizer-BioNTech) or the mRNA-1273 (Moderna) COVID-19 vaccines, the group having low IgG Spike antibody titer (non-responder) had higher mean levels of serum IL-18 than the responder group, as well as lower C3 levels. The authors observed a trend towards vaccine no-response in BNT162b2 recipients and a relationship between IL-18 and impaired antibody response, suggesting the potential use of this proinflammatory cytokine as a predictive biomarker of vaccination response.[38] More generally, Ahmed et al., after a study conducted on a cohort of 630 patients with autoimmune rheumatic diseases, suggested that antibody response at 1-month post-vaccination can be used as a biomarker for vaccination response, potentially predicting susceptibility to breakthrough infections.[88] Consequently, the routine use of post-vaccination antibody titers as a biomarker could be useful for prioritizing patients for booster doses. Two studies focused on rituximab-treated patients, who are at higher risk of poor COVID-19 outcomes and show substantially impaired humoral immune response to the anti-SARS-CoV-2 vaccine.[89,90] Both authors described that B-cell count is a candidate biomarker for an appropriate cellular and humoral response after vaccination and that monitoring CD19 may be of interest to identify the optimal timing to administer the vaccine dose. Other scientists, driven by the vaccination hesitancy registered in the immunocompromised population, investigated potential biomarkers to predict *de novo* development of autoimmune diseases after vaccination, along with a post-vaccine disease flare. Bakshi et al. reported that vaccinated people showed higher average values for 2 inflammatory biomarkers, such as CD21 and cf-DNA, compared to the non-vaccinated group, while the opposite was observed for CTSS, suggesting that even in the absence of the disease, it may have a stronger immune response to the virus potentially related to post-recovery development of autoimmune disease.[84] More recently, An et al. evaluated sero-reactivity, clinical manifestations, and multiple disease biomarkers (ds-DNA, IFNI signature genes, frequency of DN2 cells) after 2 or 3 doses of COVID-19 mRNA vaccines in a cohort of patients with rheumatic diseases.[43] Patients with SLE or psoriatic arthritis (PsA) remained without significant flares post-vaccination, presenting highly variable disease biomarker levels without a consistent or significant increase. Therefore, the authors provided experimental evidence indicating the efficacy and safety of repeated COVID-19 mRNA vaccination in rheumatic disease patients.

Interestingly, we evidenced the emergence of a new field of study in which scientists performed deep bioinformatic and statistical analyses on transcriptome databases to identify shared pathological processes in rheumatic and COVID-19 patients.[91–97] The final objective of these studies is to unveil new prognostic and diagnostic biomarkers and, when possible, to define new potential therapeutic targets. Some authors focused on the analysis of potentially similar pathogenesis between SLE and COVID-19 with a common approach.[92,94,96] These studies were conducted on transcriptome data from COVID-19 and SLE patients collected in the GEO data platform. The common differentially expressed genes (DeGs) were extracted from the selected datasets and functional enrichment analysis was then performed to highlight a significant enrichment in pathways related to both viral and rheumatic disease. A protein-protein interaction (PPi) analysis was subsequently carried out using bioinformatic tools, resulting in the identification of several hub genes with predictive/diagnostic potential. Of note, some authors,[92] starting from the identified hits, performed a drug discovery analysis, showing new potential treatment options for patients with SLE.[92]

Conclusion

The current review describes the virologist's perspective on several aspects of SLE and COVID-19 co-morbidity. We adopted a comprehensive approach to describe the updated literature on the topic and identify some key findings. Since SLE patients, especially those under treatment, showed increased COVID-19 morbidity and persistent COVID-19 symptoms, a fourth booster dose of the updated vaccine is recommended, regardless of the immunosuppressant therapy, to protect this category. Indeed, it has been demonstrated that vaccination has a favourable risk-benefit ratio, with a shallow risk of trigger lupus flares and mild constitutional side effects. For the same reasons, COVID-19 SLE patients require early viral direct diagnosis, close monitoring, and prompt antiviral therapies, mainly nirmatrelvir/ritonavir, to reduce the risk of severe COVID-19 outcomes. New molecular aspects have emerged, with numerous preliminary studies investigating potential prognostic biomarkers that could be useful in a clinical context. They could help predict the development of severe COVID-19, the onset of a new autoimmune disease, the vaccination response, and its repercussions on rheumatic disease onset or flares. However, further investigations and clinical validation are still necessary to ensure that these results can have an important clinical impact.

The clinical management of COVID-19 SLE patients is complex and requires close collaboration and direct communication among healthcare providers from different sectors. Additionally, it is important to share new insights and maintain heightened attention to this issue, ensuring a

constant production of updated research data for drafting new guidelines. Novel predictive and therapeutic molecular approaches have the potential to enhance patient care and clinical outcomes.

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ORCID iD

Manuela Donalisio https://orcid.org/0000-0001-7883-1523

Supplemental Material

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