Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Immunopharmacology 101 (2021) 108254

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Immunopathological events surrounding IL-6 and IFN-α: A bridge for anti-lupus erythematosus drugs used to treat COVID-19

Bangyi Zhou [a,d,1], Siying Li [b,1], Jujian Ye [c,d,1], Yi Liu [e], Longtai Hu [b], Yan Tang [c], Zhijian Wu [f,*], Peidong Zhang [d,*]

[a] Nanfang Hospital, Southern Medical University/The First School of Clinical Medicine, Southern Medical University, People's Republic of China
[b] School of Traditional Chinese Medicine, Southern Medical University, People's Republic of China
[c] Zhujiang Hospital, Southern Medical University/The Second School of Clinical Medicine, Southern Medical University, People's Republic of China
[d] Department of Cardiology, Heart Center, Zhujiang Hospital, Southern Medical University, 253 Industrial Avenue, Guangzhou 510282, Guangdong, People's Republic of China
[e] School of Laboratory Medicine and Biotechnology, Southern Medical University, People's Republic of China
[f] Department of Cardiology, Boai Hospital of Zhongshan, Southern Medical University, People's Republic of China

ARTICLE INFO

Keywords:
COVID-19
SLE
IFN-α
IL-6
Treatment

ABSTRACT

With the outbreak and rapid spread of COVID-19, the world health situation is unprecedentedly severe. Systemic lupus erythematosus (SLE) is a common autoimmune disease, which can cause multiple organ damage. Numerous studies have shown that immune factors have important roles in the pathogenesis of both COVID-19 and SLE. In the early stages of COVID-19 and SLE pathogenesis, IFN-α expression is frequently increased, which aggravates the virus infection and promotes SLE development. In addition, increased IL-6 levels, caused by different mechanisms, are observed in the peripheral blood of patients with severe COVID-19 and SLE, stimulating a series of immune cascades that lead to a cytokine storm, as well as causing B cell hyperfunction and production of numerous of antibodies, aggravating both COVID-19 and SLE. In this review, we explore the background immunopathological mechanisms in COVID-19 and SLE and analyze the advantages and disadvantages of commonly used SLE drugs for patients with COVID-19, to optimize treatment plans for patients with SLE who develop COVID-19.

1. Introduction

COVID-19 has become a global public health emergency. In the early stage of the disease, the main symptoms are fever, cough and fatigue. In severe cases, dyspnea, chest pain, and even fatal respiratory diseases may occur. At present, no specific drugs for treatment of COVID-19 have been identified, and the focus remains optimized supportive treatment [1]. Vaccination is considered an effective means to control the pandemic [2], up to now, there are over 200 million confirmed cases of COVID-19 worldwide, including more than 4 million deaths.

In the context of such a severe global health situation, it is vital to explore the relationship between COVID-19 and systemic lupus erythematosus (SLE). Patients with SLE have increased susceptibility to infection [3], and immunosuppressants, which are the standard drugs for treatment of SLE, can also be used to treat patients with COVID-19 [4–5].

In the absence of clear understanding of the connection between COVID-19 and SLE, the rationale underlying the medication for SLE and COVID-19 remains open to question. In this review, we explore the advantages and disadvantages of commonly used SLE drugs in the context of COVID-19, with the aim of optimizing treatment plans for patients with SLE.

2. Immunopathological similarities and interactions between COVID-19 and SLE

SLE is an autoimmune disease characterized by abnormal autoantibody production and immune complex deposition. In addition to various skin lesions, SLE patients often have symptoms such as fever, fatigue, muscle soreness, scarring alopecia and diarrhea [6]. Immune factors are

* Corresponding authors.
E-mail addresses: 2388743877@qq.com (Z. Wu), zhangpd@smu.edu.cn (P. Zhang).
[1] These authors contributed equally to this work and should be considered co-first.

https://doi.org/10.1016/j.intimp.2021.108254
Received 24 May 2021; Received in revised form 26 September 2021; Accepted 8 October 2021
Available online 14 October 2021

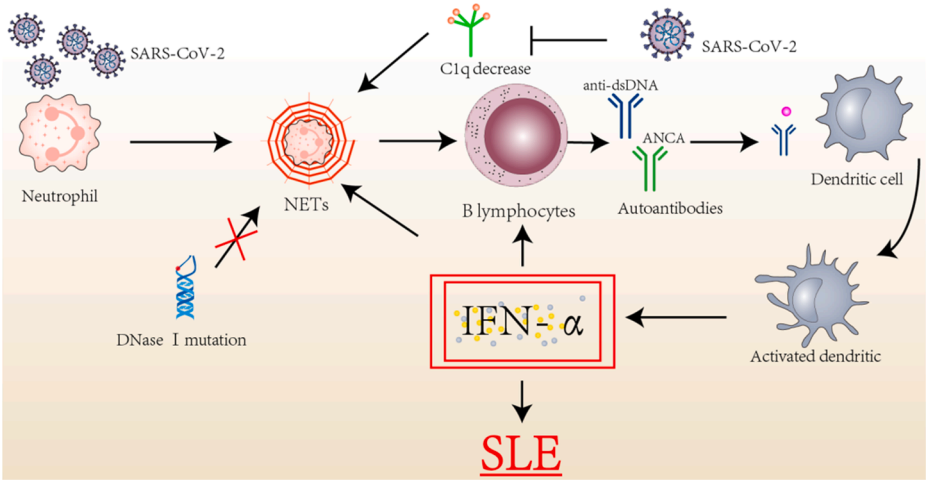

Fig. 1. Immunopathological events surrounding IFN-α. Decreased complement C1q or mutation of DNase I can limit the clearance of neutrophil extracellular traps (NETs), thereby exposing large amounts of autoantigens. Antigen and antibody form immune complexes to stimulate phagocytes, such as dendritic cells to produce large quantities of IFN-α, which can promote the occurrence of SLE, the production of NETs and B cell differentiation. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; IFN-α = interferon-alfa ; SLE = systemic lupus erythematosus; NETs = neutrophil extracellular traps.

important in the occurrence and development of SLE. In patients with COVID-19, immune dysfunction is also clearly observed. The condition of patients with COVID-19 can very easily be aggravated by changes in immune status; for example, development of cytokine storm can potentially lead to acute respiratory distress syndrome (ARDS) or even death. Clinically, SLE and COVID-19 can interact with one another. Slimani et al. [7] reported a previously healthy individual who developed varicella like rash and SLE after suffering from COVID-19, while Ramirez et al. [8] investigated 471 patients with SLE using questionnaires, 60% of whom said they had experienced symptoms related to COVID-19, such as myalgia, rhinorrhoea, fever, dry cough, fatigue, sore throat and diarrhea. 14 of them were diagnosed with the disease. Therefore, management of the co-occurrence of COVID-19 and SLE is an important clinical challenge.

3. COVID-19 can promote SLE occurrence and development

The occurrence and development of SLE is established as closely related to infection, primarily the complex immune response after infection, and there has been report of cases of SLE caused by COVID-19 [9]. Levels of IL-1β, IL-6, GCSF, IFN-γ, TNF-α, and other proinflammatory mediators are increased in the peripheral blood of patients with COVID-19 [10–12]. These proinflammatory mediators, especially IFN- α and IL-6, play an important role in the occurrence and development of SLE. This paper will be based on IFN- α and IL-6 as the centre to explore the immunopathological events that may be shared by COVID-19 patients and SLE patients.

3.1. Immunopathological events surrounding IFN-α

IFN-α has a key role in SLE pathogenesis [13], and the strong expression of IFN-α in the early stage of COVID-19 can lead to harmful inflammatory responses and immunopathological changes [14]. When SARS-CoV-2 infects the body, it proliferates rapidly, producing numerous neutrophil extracellular traps (NETs) and activating the neutrophil specific death program, NETosis, to capture and inactivate the virus. Decreased complement C1q in patients with COVID-19 or mutation of DNase I in patients with SLE can limit the degradation and clearance of NETs [15–16]. The presence of excessive NETs leads to immune system exposure to various autoantigens, including those against double-stranded DNA (dsDNA). These autoantigens can stimulate B lymphocytes, through the antigen presentation process, causing production of large numbers of autoantibodies, including anti-dsDNA and anti-neutrophil cytoplasmic antibodies, among others. The immune complex (IC) formed by antigen and antibody also stimulates various phagocytic cells, such as dendritic cells, which produce large quantities of IFN-α when clearing IC, potentially leading to serious organ damage. IFN-α can both disrupt regeneration of the lung epithelium, aggravating viral infection, and promote the occurrence of SLE [17]. Clinically, it can be observed that the IFN response was high in mild to moderate patients, whereas it was reduced in more severe patients, and it has been suggested that exogenous type 1 interferon can be used to inhibit the activity of SARS-CoV-2, which may be related to the effect that IFN-α can further stimulate NET production. However, it is undeniable that the wide expression of IFN-α can lead to immunopathological changes during virus infection, which may be related to up regulating BAFF expression and promoting B cell differentiation [6,14,18–25] (Fig. 1).

3.2. Immunopathological events surrounding IL-6

Levels of IL-6 are significantly increased in the plasma of patients with severe COVID-19 and correlate positively with disease severity [12]. Biologics targeting IL-6 have also been reported to be effective in treating COVID-19 infection [26]. Increased or imbalanced IL-6 levels also mediate tissue inflammation and organ damage in individuals with SLE [27–28]. Damage associated molecular patterns and pathogen associated molecular patterns released after virus infection can bind with pattern recognition receptors on macrophages, activate NF-κB, and promote a cascade involving the release of a series of chemokines, thus generating numerous cytokines, including IL-6, TNF-α, and IL-1β, and leading to cytokine storm [29]. In addition, the nucleocapsid and spike proteins on the virus surface can induce HEK293T cells (among other cells) to produce COX-2 through the ERK/NF-κB pathway, and COX2 can induce IL-6 production [30–31]. Further, large quantities of IL-6 can induce endothelial cells to activate and express factors such as VWF, FVIII and TF, resulting in hypercoagulable state. It can also induce neutrophil infiltration and nitric oxide (NO)-mediated increases in vascular permeability, resulting in lung injury [32]. In addition, IL-6 can activate JAK-STAT and MAPK cascades through the signal transducer, gp130 [33–34], thereby promoting SLE development.

Studies have shown that severe COVID and acute SLE flares show similarities in extrafollicular B cell response, which is mediated by the activation of immature CD11c + B cell clusters. These cells are differentiated into IgD-CD27- double negative B cells (DN2 cells), and are prepared for the differentiation of antibody secreting cells (ASC) through T-bet-driven networks and BAFF. The response of this extrafollicular reaction is closely related to IL-6 [35–36]. As activated B cells, ASC can produce cytokines such as IL-10, IL-35, TNF- α, IL-17 and GM-CSF [37]. Anti SARS-CoV-2 IgG in patients with severe coronavirus-19 can promote macrophage hyperinflammatory response and produce a large number of classical cytokine storm mediators, such as IL-1 β、 IL-6,

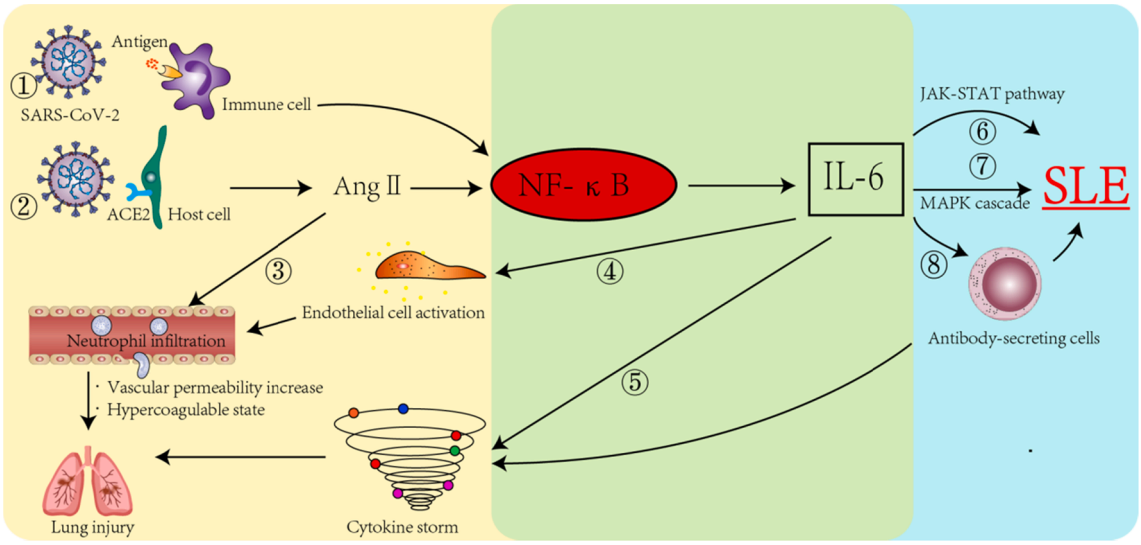

Fig. 2. Immunopathological events surrounding IL-6. ① After SAR-Cov-2 invades the body, it can activate NF-κB in immune cells and promote the transcription and production of IL-6. ② SARS-CoV-2 can interact with ACE2 through its S glycoprotein. Viral invasion of host T-lymphocytes causes downregulation of ACE2 expression on the cell membrane, a compensatory increase in Ang II, which binds to NF-κB and promotes IL-6 transcription and production. ③ Ang II acts on angiotensin type 1 receptor (AT1R), increasing the permeability of pulmonary blood vessels, promoting lung injury and leading to hypercoagulable state. ④ IL-6 induces endothelial cell activation resulting in hypercoagulable state. It can also induce neutrophil infiltration, NO-mediated increase in vascular permeability, and lung injury. ⑤ IL-6 has a mutually promoting relationship with cytokine storm, thereby inducing lung injury. ⑥ IL-6 can activate the JAK-STAT and MAPK cascades and promote the development of SLE. ⑧ IL-6 can also lead to B lymphocyte hyperfunction, promoting SLE development and cytokine storm. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ACE2 = angiotensin-converting enzyme 2; AngII = angiotensin II; NF-κB = nuclear factor kappa-B ; IL-6 = interleukin-6.

IL-8 and TNF [38].

Current evidence suggests that SARS-CoV-2 can invade host T-lymphocytes by binding of its S-glycoprotein with the ACE2 receptor [10,39]. On virus invasion, ACE2 expression on the cell membrane is down regulated, affecting the normal function of the renin angiotensin system. The resulting compensatory increase of angiotensin II (Ang II) and its effect on angiotensin type 1 receptor increase the permeability of pulmonary vessels, promote lung injury, and induce endothelial cells to express TF and plasminogen activator inhibitor 1 (PAI-1), resulting in hypercoagulable state [11,40–41]. Ang II can also bind to NF-κB to promote the transcription and production of IL-6, TNF-α, TNF-β, IFN-γ, GM-CSF, and other inflammatory cytokines, thereby promoting SLE development (Fig. 2).

4. Patients with SLE are more susceptible to infection

The prevalence of COVID-19 in patients with SLE patients is only somewhat increased [6,8]. This may be related to the beneficial effects of treatment for SLE, which will be discussed in detail later in this review. Patients with SLE may be more likely to be infected with SARS-CoV-2 [6,42–43]. The underlying mechanism may be related to genetic factors shared between SLE and primary immunodeficiency disease, where genes involved in SLE susceptibility also participate in the occurrence and development of immunodeficiency [44]. Immune abnormalities in patients with SLE, such as lymphocytic reduction and IL-2 deficiency [45], also increase their susceptibility to infection. Moreover, patients with SLE are often treated with corticosteroids and immunosuppressants, which also increase their risk of infection to some extent.

5. New uses for old medicines based on the shared mechanisms underlying COVID-19 and SLE

Researchers continue to have different opinions regarding whether immunosuppression should be used to treat patients with SLE. Therefore, we comprehensively analyzed relevant available data, including clinical research and investigations of pathological mechanisms, and applied the available information to provide new medication recommendations based on possible common mechanisms underlying both COVID-19 and SLE (see Table 1).

5.1. Antimalarial drugs

From the mechanism and the results of in vitro experiments, hydroxychloroquine (HCQ) may be able to inhibit SARS-CoV-2 infection and transmission by blocking virus-receptor binding [46–48]. In the early stage when there were no vaccines and specific treatments, many people used these mechanisms to perform empirical treatments. At that time, opinions on the clinical benefits of hydroxychloroquine were widely divided. Some support the use of it [49], others oppose it because of concerns that the side effects of HCQ, such as retinopathy and rash, will exceed its potential benefits [50–51]. Then a recent large-scale randomized clinical trial proved that hydroxychloroquine has no clinical benefit in inhibiting SARS-CoV-2 infection and spread and no treatment-related serious adverse events were reported [52]. And a study found that there is no difference in terms of either clinical symptoms, severity or proportion of positive nasopharyngal PCR in patients on HCQ compared to matched controls [53]. Therefore, we believe that it is safe to continue taking hydroxychloroquine for SLE patients who have been taking chloroquine or hydroxychloroquine safely even if they suffer from COVID-19. However, based on current studies, we no longer recommend hydroxychloroquine as a treatment for COVID-19.

5.2. Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are mainly used to relieve symptoms in patients with SLE and act by inhibiting COX [54–55]. As the SARS-CoV-2 infection induced COX-2 upregulation [56], leading to a cascade of pro-inflammation cytokines [57], the use of NSAIDs in the early stage of virus invasion could effectively prevent the development of ARDS [58]. And current studies support that NSAIDs use are not associated with higher mortality or increased severity of COVID-19 [59–60]. Therefore, we believe that NSAID can be safely used to relieve the symptoms of COVID-19 patients. And we propose that

patients with SLE should continue to take NSAIDs to maintain the stability of their symptoms during the COVID-19 pandemic. Patients with co-morbid SLE and COVID-19 may benefit from increasing their dose of NSAIDs during the early stage of virus infection.

5.3. Glucocorticoids

As glucocorticoids inhibit the activity of lymphocytes important for combatting the new coronavirus [61] and prednisone (dose $\geq$ 10 mg/day) is associated with increased hospitalization rates of patients with COVID-19 [60], there has been considerable focus on whether glucocorticoid use should continue during the pandemic. Nevertheless, glucocorticoids also inhibit the infiltration of excessive macrophages, T-lymphocytes, and neutrophils, as well as the associated release of large quantities of IL-2, IL-6, TNF-α, and other cytokines, thereby reducing the risk of immune storm [62–64] and respiratory distress symptoms [65–66]. In addition, glucocorticoids can prevent the complications of COVID-19 [67]. Hence, glucocorticoid treatment may be beneficial for patients with severe COVID-19. In addition, glucocorticoids can induce the production of inducible nitric oxide synthase, and the NO generated by this factor can inhibit the SARS-CoV replication cycle [68], which may be beneficial for patients with SLE who have long-term reliance on glucocorticoids. Clinically, some studies have shown that dexamethasone can effectively reduce the mortality rate of patients with COVID-19 [69–70].

We suggest that patients with SLE who do not have COVID-19 should continue to take low-dose glucocorticoids to maintain the stability of their condition. Patients with SLE and COVID-19 should be managed according to disease severity, where patients with mild complications should continue to use glucocorticoids to maintain a stable condition and use antiviral drugs to counter the side effects of glucocorticoids, and those with severe comorbid disease can be treated with high dose glucocorticoids to prevent the development of cytokine storm.

5.4. Cyclophosphamide

Serum IgG in the COVID-19-infected lung can promote severe lung damage [71]. Cyclophosphamide, which can inhibit B lymphocyte proliferation and antibody production, may also prevent severe lung symptoms in patients with COVID-19 [72]. Further, there is evidence that cyclophosphamide can effectively alleviate SARS-CoV-2 related ARDS by reducing cytotoxic T-lymphocytes [73]. Moreover, clinical studies do not provide sufficient evidence that cyclophosphamide increases the risk of SARS-CoV-2 infection in SLE patients [61]. Based on these pieces of evidence, we encourage patients with SLE to continue taking cyclophosphamide to maintain stable disease, while for patients with comorbid SLE and COVID-19, cyclophosphamide can be used to help prevent lung injury.

5.5. Mycophenolate mofetil

Mycophenolic acid (MPA), an in vivo metabolite of mycophenolate mofetil, has anti-SARS-CoV-2 activity in vitro [74]. This may reflect the role of MPA as an inhibitor of inosine monophosphate dehydrogenase, which downregulates purine biosynthesis and thus inhibits virus replication. Further, MPA can inhibit MERS-CoV papain-like protease (PLpro) and may also inhibit SCoV2-PLpro [75], the expression of which weakens the host antiviral IFN pathway and is also involved in viral RNA synthesis [76]. Furthermore, MPA can also inhibit IL-6 production [77], and high levels of IL-6 have consistently been reported in patients with COVID-19, and are associated with poor prognosis and risk of death [64]. Finally, the half-maximum effective concentration of mycophenolate mofetil is only 0.87 μm, which is very easy to achieve at the therapeutic dose [74]; hence, the use of mycophenolate mofetil may reduce inflammatory storms and improve patient prognosis.

As mycophenolate mofetil does not increase the risk of respiratory virus infection, nor did it cause worse clinical outcomes [61,78], we support its continued use for treatment of patients with SLE, according to their original prescription. Further, patients with both SLE and COVID-19 can continue taking this drug with confidence. In addition, as the inhibitory effect of MPA on SARS-CoV-2 is not clear, combinations of other drugs may be more effective to facilitate rehabilitation of patients with both COVID-19 and SLE.

5.6. Methotrexate

As a JAK/STAT pathway inhibitor [79], methotrexate may cooperate with SARS-CoV-2 to rapidly disable JAK-STAT signaling, thereby reducing the sensitivity of host T-lymphocytes to interferon therapy [80]. Therefore, methotrexate treatment may be detrimental to patients with early SARS-CoV-2 infection; However, are also vitro experiments demonstrating that methotrexate can effectively inhibit SARS-CoV-2 replication which may be related to purine biosynthesis inhibition by methotrexate [81–83]. Further, clinical reports indicate that the use of methotrexate may prevent the spread of SARS-CoV-2 and does not influence mortality and hospitalization rates in patients with COVID-19 [84–85].

In addition, activation of the JAK-STAT pathway can stimulate IL-6 production, along with that of other inflammatory cytokines and Ang II-induced thromboinflammation [80,86]. Blocking JAK-STAT can both antagonize IL-6 production and block the production of various other inflammatory and pro-inflammatory factors, thereby preventing hypercoagulable state and lung injury in patients with COVID-19 [87–88]. Hence, high dose methotrexate treatment may benefit patients with severe COVID-19 [89].

Since there is currently no evidence that methotrexate can increase the SARS-CoV-2 infection rate, we recommend that patients with SLE continue to take methotrexate to maintain stable symptoms, and that patients with severe COVID-19 and SLE should receive high dose methotrexate to reduce the risk of immune storm.

5.7. Leflunomide

Leflunomide, a type of dihydroorotate dehydrogenase inhibitor, is effective in infected animals by inhibiting virus replication and ameliorating cytokine/chemokine storms [90]. Teriflunomide, an active metabolite of leflunomide, also has definite antiviral effects at the cellular level [90] and patients treated with leflunomide had better inflammation level control and were discharged more quickly than those in the control group [91]. This feature of leflunomide may be beneficial to patients with SLE and COVID-19 and available data indicated that leflunomide is beneficial for SLE patients, regardless of whether they have COVID-19.

5.8. Calcineurin inhibitors

Calcineurin inhibitor (CNI), including Cyclosporin A (CsA) and tacrolimus, can block NF-κB by inhibiting calcineurin, may interfere with the initial steps of cytokine storm release in severe COVID-19 [92], and can inhibit the replication of a variety of coronaviruses at low micromolar concentrations without cytotoxicity [93]. These mechanisms may be of benefit to patients with COVID-19. Indeed, there is clinical evidence that CsA and tacrolimus are beneficial for COVID-19 patients [92,94]; however, patients with COVID-19 often have accompanying hypertension and hypercoagulable state, due to the compensatory increase in angiotensin II and CNI can cause high blood pressure and thrombosis as side effects [95–96], emphasizing the need to monitor blood pressure when treating patients with SLE and COVID-19, and to consider the safety of CNI in cases with hypertension or hypercoagulable state occurs. Nevertheless, due to the strong immunosuppressive function of CsA and tacrolimus, alisporivir, a non-immune substitute molecule for CsA, may be a better choice. alisporivir can effectively inhibit

Table 1
Anti-lupus erythematosus drugs and their use in the treatment of COVID-19.

Drug	Pre-clinical experiments	Clinical outcome	Possible mechanisms for the treatment of comorbidities
Hydroxychloroquine	In Vero E6 cells, the EC 90 value of chloroquine for 2019-nCoV is 6.90 μM [46].	Randomized controlled meta-analysis: the total mortality rate of the HCQ group was 2.5 times higher than that of the control group. Compared with the control group, the rate of reduction of mild and moderate symptoms in patients treated with HCQ was 1.2 times higher [49]. Randomized Trial: Postexposure therapy with HCQ did not prevent SARS-CoV-2 infection or symptomatic COVID-19 in healthy persons exposed to a PCR-positive case patient(n=2314, RR=0.86, 95% CI=0.52-1.42]) [52].	
NSAIDs	NSAID treatment inhibited the upregulation of pro-inflammatory cytokines induced by SARS-CoV-2 in mice[58].	Cohort study: Among Danish individuals (n = 9,236) who were SARS-CoV-2-positive, the use of NSAIDs (n = 248) was not associated with 30-day mortality, hospitalization, ICU admission, mechanical ventilation or renal replacement therapy [59]. Case-control study: The use of NSAIDs was not associated with hospitalization status (OR = 0.64, 95% CI, 0.39–1.06) [60].	Inhibition of COX-2 by NSAIDs may inhibit the cascade of pro-cytokine inflammation, thereby effectively preventing ARDS [54,55,57].
Glucocorticoid		Meta-analysis of clinical randomized controlled trials: For patients with severe COVID-19 (n = 1703), use of systemic corticosteroid stimulation reduced 28-day all-cause mortality compared with conventional treatment or placebo [70]. Case-control study: Prednisone (dose ≥ 10 mg/day) was associated with a higher chance of hospitalization (OR = 2.05, 95% CI, 1.06–3.96) [60]. Case report: Glucocorticoids can help reduce ARDS in patients with COVID-19 [65,66,106,107]. Retrospective cohort study: Corticosteroid use in patients with COVID-19 may not be associated with hospital mortality [108]. Glucocorticoids have no effect on virus clearance time in patients with mild COVID-19 [109].	Glucocorticoids can inhibit infiltration of excessive macrophages, T-lymphocytes, and neutrophils and release of large amounts of IL-2, IL-2R, IL-6, IL-7, IL-8, IL-10, IP10 , MIP1A, TNF-α, and other cytokines, reducing the risk of immune storm [63,64]. Glucocorticoids can also stimulate production of inducible nitric oxide synthase, and the resulting NO can inhibit the SARS-CoV replication cycle [68].
Cyclophosphamide		Case report: Re-administration of high-dose cyclophosphamide did not cause recurrence of COVID-19-related symptoms [110].	Cyclophosphamide can inhibit B lymphocyte proliferation and antibody production, and may reduce the production of serum IgG, which promotes lung injury, to a certain extent [71].
Mycophenolate mofetil	MPA shows significant anti-SARS-CoV-2 activity [74].	Meta-analysis: MPA does not increase the frequency or risk of respiratory viral events [61]. Cohort study: Among COVID-19 hospitalized adults, long-term use of MPA has nothing to do with risk of mechanical ventilation (HR=0.79; 95% CI=0.46-1.35), hospital mortality (HR= 0.66; 95% CI=0.28-1.55) length of hospital stay (HR=1.16; 95% CI=0.92-1.47) [78].	MPA may inhibit purine biosynthesis to suppress virus replication, and may inhibit SCoV2-PLpro [75]. MPA can also inhibit the production of IL-6 in B lymphocytes, which reduces the risk of poor prognosis and death, to some extent [64,111].
Methotrexate	Methotrexate effectively inhibits SARS-CoV-2 replication in vitro [83]. Methotrexate diminishes replication of the coronavirus SARS-CoV-2 [81].	Case report: Methotrexate may have a protective effect on SARS-CoV-2 infection [84]. Case control: The use of methotrexate is not associated with mortality or hospitalization rates of patients with COVID-19 (n = 53,511,836; RR = 0.87, 95% CI, 0.42–1.78, p = 0.6958) [85].	Methotrexate, a purine biosynthesis inhibitor, can effectively inhibit viral RNA replication, viral protein synthesis, and virus release.
Leflunomide		Randomized controlled trial: No significant effect of leflunomide on virus clearance time detected (n = 50, RR = 0.70; 95% CI, 0.391–1.256, P = 0.186) [112]. Randomized controlled trial: C-reactive protein levels were significantly reduced in the leflunomide treatment group. No obvious adverse reactions were observed and the rate of discharge was faster than that of the control group (n = 10, P = 0.046) [91].	Leflunomide can inhibit virus replication and fight a broad-spectrum of viruses that cause severe infections [90]. Ameliorate pathogen-induced inflammation by preventing excessive cytokine/chemokine storm [90].
Teriflunomide	Showed definite antiviral effects at the cellular level [90].		
Cyclosporin A	Cyclosporine, alone or in combination with remdesivir and other drugs, can exhibit antiviral effects [113].		CsA can inhibit the replication of many coronaviruses at low micromolar concentrations [93]. CsA can block NF-κB by inhibiting calcineurin. This mechanism may interfere with the initial steps of cytokine storm release in patients with severe COVID-19 [92].
Azathioprine	Ferret experiment: Led to increased clearance of SARS-CoV-2 virus and low SN titer, leading to prolonged infection time [98].	Cohort study: Thiopurine drugs may be associated with an increased risk of severe COVID-19 [99]. Cohort study: The use of azathioprine in COVID-19 patients is associated with higher mortality [114].	

HCQ = Hydroxychloroquine; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; PH = potential of hydrogen; ICU = intensive-care unit; CI = confidence interval; NSAIDs = nonsteroidal anti-inflammatory drugs ; COX-2 = cyclooxygenase-2; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; IL-6 = interleukin-6; IP10 = 10 kDa interferon γ-induced protein; MIP1A = eukaryotic macrophage inflammatory protein 1 alpha; TNF-α = tumor necrosis factor-α; NO = nitric oxide; MPA = mycophenolic acid; NF-κB, = nuclear factor kappa-B.; SN = serum neutralization.

the post-cell phase of the SARS-CoV-2 life cycle in vitro [97]. Therefore, we recommend that patients with COVID-19 take alisporivir to combat the virus and prevent immune storms, and that patients with SLE should continue to be treated with CNI, regardless of whether or not they have COVID-19.

5.9. Azathioprine

Due to findings that azathioprine-treated ferrets had prolonged infection times [98], there are concerns that the immunosuppressive function of azathioprine could increase the risk of infection [95]. Moreover, there is clinical evidence that azathioprine may be associated with increased risk of severe COVID-19 [99]. However, a review of 180 studies found no evidence that azathioprine increases the risk of respiratory viral infections [61]. Hence, the effect of azathioprine on the development of COVID-19 warrants further research. If a patient with SLE has stable clinical symptoms, there is currently insufficient evidence to change their treatment or destabilize them clinically [100].

5.10. Belimumab

Belimumab has been the first biologic agent approved for SLE therapy so far. Belimumab mainly acts by binding to and antagonizing soluble BAFF [101], so that it has a rapid and harmful effect on B lymphocytes in the early developmental stage, especially naive B cells [102]. In addition, studies have found that the extrafollicular pathways are also the pathways by which BAFF affects the activation and differentiation of naive B cells. Through the extrafollicular pathway, BAFF can strongly prevent naive B cells from producing antibody-secreting cells (ASC) [103–104]. And it has been proven that critically ill patients with COVID-19 displayed a robust activation of extrafollicular B cell responses and ASC expansions, which are similar to those previously reported in SLE [35,103]. Although there is still a lack of discussion and research on the performance of belimumab in COVID-19. But we may expect that Belimumab, which inhibits the differentiation of naive B cells into ASC, but not into regulatory B cells [105], will down-regulate the excessive inflammatory response in patients with severe COVID-19. And taht will be of great benefit to patients with comorbid SLE and COVID-19.

6. Conclusion

SLE interacts with COVID-19 through inflammatory factors, such as IL-6 and IFN-α, during pathophysiological processes. Each of the key links in these interactions is a potential target for patients with SLE and COVID-19. The specific mechanism underlying the pathogenic processes occurring in patients with SLE combined with COVID-19 warrant further exploration, with the aim of promoting the development of therapeutic drugs and providing a reliable scientific basis for the clinical diagnosis, treatment, and prognosis prediction in patients with SLE combined with COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The support of Southern Medical University is acknowledged.

Author contribution

WZJ and ZPD conceived the idea. ZBY, LSY and YJJ wrote the review article. All authors critically revised the manuscript and approved the final version for submission.

References

[1] S. Şimşek Yavuz, S. Ünal, Antiviral treatment of COVID-19. 2020. 50(Si-1): p. 611-619.
[2] D.A. Swan, C. Bracis, H. Janes, M. Moore, L. Matrajt, D.B. Reeves, E. Burns, D. Donnell, M.S. Cohen, J.T. Schiffer, D. Dimitrov, COVID-19 vaccines that reduce symptoms but do not block infection need higher coverage and faster rollout to achieve population impact, Sci. Rep. 11 (1) (2021), https://doi.org/10.1038/s41598-021-94719-y.
[3] A. Danza, G. Ruiz-Irastorza, Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies, Lupus 22 (12) (2013) 1286–1294.
[4] P. Gautret, et al., Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, Int. J. Antimicrob. Agents 56 (1) (2020), 105949.
[5] S.A. Meo, D.C. Klonoff, J. Akram, Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19, Eur. Rev. Med. Pharmacol. Sci. 24 (8) (2020) 4539–4547.
[6] A. Saxena, et al., Evaluation of SARS-CoV-2 IgG antibody reactivity in patients with systemic lupus erythematosus: analysis of a multi-racial and multi-ethnic cohort, Lancet. Rheumatol. 3 (8) (2021) e585–e594.
[7] Y. Slimani, R. Abbassi, F.-Z. El Fatoiki, L. Barrou, S. Chiheb, Systemic lupus erythematosus and varicella-like rash following COVID-19 in a previously healthy patient, J. Med. Virol. 93 (2) (2021) 1184–1187.
[8] G.A. Ramirez, M. Gerosa, L. Beretta, C. Bellocchi, L.M. Argolini, L. Moroni, E. Della Torre, C. Artusi, S. Nicolosi, R. Caporali, E.P. Bozzolo, L. Dagna, COVID-19 in systemic lupus erythematosus: Data from a survey on 417 patients, Semin. Arthritis Rheum. 50 (5) (2020) 1150–1157.
[9] R. Bonometti, et al., The first case of systemic lupus erythematosus (SLE) triggered by COVID-19 infection, Eur. Rev. Med. Pharmacol. Sci. 24 (18) (2020) 9695–9697.
[10] X. Li, M. Geng, Y. Peng, L. Meng, S. Lu, Molecular immune pathogenesis and diagnosis of COVID-19, J. Pharm. Anal. 10 (2) (2020) 102–108.
[11] J. Nikolich-Zugich, K.S. Knox, C.T. Rios, B. Natt, D. Bhattacharya, M.J. Fain, SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes, Geroscience 42 (2) (2020) 505–514.
[12] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19, J. Infect. 80 (6) (2020) 607–613.
[13] L. Rönnblom, The importance of the type I interferon system in autoimmunity, Clin. Exp. Rheumatol. 34 (4 Suppl 98) (2016) 21–24.
[14] J. Hadjadj, N. Yatim, L. Barnabei, A. Corneau, J. Boussier, N. Smith, H. Péré, B. Charbit, V. Bondet, C. Chenevier-Gobeaux, P. Breillat, N. Carlier, R. Gauzit, C. Morbieu, F. Pène, N. Marin, N. Roche, T.-A. Szwebel, S.H. Merkling, J.-M. Treluyer, D. Veyer, L. Mouthon, C. Blanc, P.-L. Tharaux, F. Rozenberg, A. Fischer, D. Duffy, F. Rieux-Laucat, S. Kernéis, B. Terrier, Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients, Science 369 (6504) (2020) 718–724.
[15] C.S. Curran, S. Gupta, I. Sanz, E. Sharon, PD-1 immunobiology in systemic lupus erythematosus, J. Autoimmun. 97 (2019) 1–9.
[16] Y. Wu, et al., Clinical characteristics and immune injury mechanisms in 71 patients with COVID-19. 2020. 5(4).
[17] J. Major, S. Crotta, Type I and III interferons disrupt lung epithelial repair during recovery from viral infection. 369(6504) (2020) 712–717.
[18] U. Felgenhauer, A. Schoen, H.H. Gad, R. Hartmann, A.R. Schaubmar, K. Failing, C. Drosten, F. Weber, Inhibition of SARS-CoV-2 by type I and type III interferons, J. Biol. Chem. 295 (41) (2020) 13958–13964.
[19] A. Mahajan, M. Herrmann, L.E. Muñoz, Clearance deficiency and cell death pathways: a model for the pathogenesis of SLE, Front. Immunol. 7 (2016) 35.
[20] F. Yang, et al., Programmed cell death pathways in the pathogenesis of systemic lupus erythematosus 2019 3638562.
[21] G. Zandman-Goddard, Y. Shoenfeld, G. Zandman-Goddard, Y. Shoenfeld, Infections and SLE, Autoimmunity 38 (7) (2005) 473–485.
[22] A. Doria, M. Canova, M. Tonon, M. Zen, E. Rampudda, N. Bassi, F. Atzeni, S. Zampieri, A. Ghirardello, Infections as triggers and complications of systemic lupus erythematosus, Autoimmun. Rev. 8 (1) (2008) 24–28.
[23] G.C. Tsokos, M.S. Lo, P.C. Reis, K.E. Sullivan, New insights into the immunopathogenesis of systemic lupus erythematosus, Nat. Rev. Rheumatol. 12 (12) (2016) 716–730.
[24] A.C. Lundell, et al., IFN type I and II induce BAFF secretion from human decidual stromal cells, Sci. Rep. 7 (2017) 39904.
[25] R. Panchanathan, D. Choubey, Murine BAFF expression is up-regulated by estrogen and interferons: implications for sex bias in the development of autoimmunity, Mol. Immunol. 53 (1-2) (2013) 15–23.
[26] M. Shankar-Hari, et al., Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. Jama 326(6) (2021) 499–518.
[27] X. Yao, J. Huang, H. Zhong, N. Shen, R. Faggioni, M. Fung, Y. Yao, Targeting interleukin-6 in inflammatory autoimmune diseases and cancers, Pharmacol Ther 141 (2) (2014) 125–139.
[28] S. Yuan, C. Tang, miR-98 modulates cytokine production from human PBMCs in systemic lupus erythematosus by targeting IL-6 mRNA, 2019, p. 9827574.

[29] L. Pearce, S.M. Davidson, The cytokine storm of COVID-19: a spotlight on prevention and protection 24(8) (2020) 723-730.
[30] M.o. Liu, Y. Yang, C. Gu, Y. Yue, K.K. Wu, J. Wu, Y. Zhu, Spike protein of SARS-CoV stimulates cyclooxygenase-2 expression via both calcium-dependent and calcium-independent protein kinase C pathways, Faseb j 21 (7) (2007) 1586–1596.
[31] N. Raychaudhuri, R.S. Douglas, T.J. Smith, M. Ludgate, PGE2 induces IL-6 in orbital fibroblasts through EP2 receptors and increased gene promoter activity: implications to thyroid-associated ophthalmopathy, PLoS ONE 5 (12) (2010) e15296.
[32] M.Y. Abou-Ismail, A. Diamond, S. Kapoor, Y. Arafah, L. Nayak, The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management, Thromb Res 194 (2020) 101–115.
[33] W. Luo, Y.-X. Li, L.-J. Jiang, Q. Chen, T. Wang, D.-W. Ye, Targeting JAK-STAT signaling to control cytokine release syndrome in COVID-19, Trends Pharmacol. Sci. 41 (8) (2020) 531–543.
[34] P.C. Heinrich, I. Behrmann, S. Haan, H.M. Hermanns, G. Müller-Newen, F. Schaper, Principles of interleukin (IL)-6-type cytokine signalling and its regulation, Biochem. J. 374 (1) (2003) 1–20.
[35] M.C. Woodruff, R.P. Ramonell, D.C. Nguyen, K.S. Cashman, A.S. Saini, N. S. Haddad, A.M. Ley, S. Kyu, J.C. Howell, T. Ozturk, S. Lee, N. Suryadevara, J. B. Case, R. Bugrovsky, W. Chen, J. Estrada, A. Morrison-Porter, A. Derrico, F. A. Anam, M. Sharma, H.M. Wu, S.N. Le, S.A. Jenks, C.M. Tipton, B. Staitieh, J. L. Daiss, E. Ghosn, M.S. Diamond, R.H. Carnahan, J.E. Crowe, W.T. Hu, F.-H. Lee, I. Sanz, Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19, Nat. Immunol. 21 (12) (2020) 1506–1516.
[36] N. Kaneko, H.-H. Kuo, J. Boucau, J.R. Farmer, H. Allard-Chamard, V.S. Mahajan, A. Piechocka-Trocha, K. Lefteri, M. Osborn, J. Bals, Y.C. Bartsch, N. Bonheur, T. M. Caradonna, J. Chevalier, F. Chowdhury, T.J. Diefenbach, K. Einkauf, J. Fallon, J. Feldman, K.K. Finn, P. Garcia-Broncano, C.A. Hartana, B.M. Hauser, C. Jiang, P. Kaplonek, M. Karpell, E.C. Koscher, X. Lian, H. Liu, J. Liu, N.L. Ly, A.R. Michell, Y. Rassadkina, K. Seiger, L. Sessa, S. Shin, N. Singh, W. Sun, X. Sun, H.J. Ticheli, M.T. Waring, A.L. Zhu, G. Alter, J.Z. Li, D. Lingwood, A.G. Schmidt, M. Lichterfeld, B.D. Walker, X.G. Yu, R.F. Padera, S. Pillai, Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19, Cell 183 (1) (2020) 143–157.e13.
[37] V.D. Dang, E. Hilgenberg, S. Ries, P. Shen, S. Fillatreau, From the regulatory functions of B cells to the identification of cytokine-producing plasma cell subsets, Curr. Opin. Immunol. 28 (2014) 77–83.
[38] W. Hoepel, et al., High titers and low fucosylation of early human anti-SARS-CoV-2 IgG promote inflammation by alveolar macrophages, Sci. Transl. Med. 13 (596) (2021).
[39] N. Petrosillo, et al., COVID-19, SARS and MERS: are they closely related? Clin. Microbiol. Infect. 26 (6) (2020) 729–734.
[40] M.E. Colling, Y. Kanthi, COVID-19-associated coagulopathy: an exploration of mechanisms, Vasc. Med. 25 (5) (2020) 471–478.
[41] Y. Jin, H. Yang, W. Ji, W. Wu, S. Chen, W. Zhang, G. Duan, Virology, epidemiology, pathogenesis, and control of COVID-19, Viruses 12 (4) (2020) 372, https://doi.org/10.3390/v12040372.
[42] Y. Gartshteyn, A.D. Askanase, N.M. Schmidt, E.J. Bernstein, L. Khalili, R. Drolet, R.J. Broderick, L. Geraldino-Pardilla, T. Kapoor, COVID-19 and systemic lupus erythematosus: a case series, Lancet. Rheumatol. 2 (8) (2020) e452–e454.
[43] R. Fernandez-Ruiz, J.L. Paredes, T.B. Niewold, COVID-19 in patients with systemic lupus erythematosus: lessons learned from the inflammatory disease, Transl. Res. 232 (2021) 13–36.
[44] T. Sawada, D. Fujimori, Y. Yamamoto, Systemic lupus erythematosus and immunodeficiency, Immunol. Med. 42 (1) (2019) 1–9.
[45] A. Ballesteros-Tato, A. Papillion, Mechanisms of action of low-dose IL-2 restoration therapies in SLE, Curr. Opin. Immunol. 61 (2019) 39–45.
[46] M. Wang, et al., Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. 30(3) (2020) 269–271.
[47] M.J. Vincent, et al., Chloroquine is a potent inhibitor of SARS coronavirus infection and spread, Virol J. 2 (2005) 69.
[48] J. Fantini, C. Di Scala, H. Chahinian, N. Yahi, Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection, Int. J. Antimicrob. Agents 55 (5) (2020) 105960, https://doi.org/10.1016/j.ijantimicag.2020.105960.
[49] N. Hussain, E. Chung, J. Heyl, B. Hussain, M. Oh, C. Pinon, S. Boral, D. Chun, B. Babu, A meta-analysis on the effects of hydroxychloroquine on COVID-19, Cureus 12 (8) (2020), https://doi.org/10.7759/cureus.10005.
[50] M.F. Marmor, COVID-19 and chloroquine/hydroxychloroquine: is there ophthalmological concern? Am. J. Ophthalmol. 213 (2020) A3–A4.
[51] R. Kurd, M. Zuckerman, E. Ben-Chetrit, Hydroxychloroquine-related rash in COVID-19 infected patient, Isr. Med. Assoc. J. 22 (8) (2020) 525.
[52] O. Mitjà, et al., A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19, N Engl J Med 384(5) (2021) 417–427.
[53] L. Trefond, E. Drumez, M. Andre, N. Costedoat-Chalumeau, R. Seror, M. Devaux, E. Dernis, Y. Dieudonné, S. El Mahou, A. Lanteri, I. Melki, V. Queyrel, M. Roumier, J. Schmidt, T. Barnetche, T. Thomas, P. Cacoub, A. Belot, O. Aumaitre, C. Richez, E. Hachulla, Impact of hydroxychloroquine used as DMARD on SARS-CoV-2 tests and infection evolution in a population of 871 patients with inflammatory rheumatic and musculoskeletal diseases, Joint Bone Spine 88 (6) (2021) 105226, https://doi.org/10.1016/j.jbspin.2021.105226.
[54] W. Xiong, R.G. Lahita, Pragmatic approaches to therapy for systemic lupus erythematosus, Nat. Rev. Rheumatol. 10 (2) (2014) 97–107.
[55] M. Østensen, P.M. Villiger, Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus, Lupus 10 (3) (2001) 135–139.
[56] J.S. Chen, Cyclooxgenase-2 is induced by SARS-CoV-2 infection but does not affect viral entry or replication. 2020.
[57] G.M. Verrall, Scientific rationale for a bottom-up approach to target the host response in order to try and reduce the numbers presenting with adult respiratory distress syndrome associated with COVID-19. Is there a role for statins and COX-2 inhibitors in the prevention and early treatment of the disease? Front. Immunol. 11 (2020) 2167.
[58] J.S. Chen, M.M. Alfajaro, R.D. Chow, J. Wei, R.B. Filler, S.C. Eisenbarth, C. B. Wilen, T. Gallagher, Non-steroidal anti-inflammatory drugs dampen the cytokine and antibody response to SARS-CoV-2 infection, J. Virol. 95 (7) (2021), https://doi.org/10.1128/JVI.00014-21.
[59] L.C. Lund, K.B. Kristensen, Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study. 2020. 17(9): p. e1003308.
[60] M. Gianfrancesco, et al., Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. 79(7) (2020) 859-866.
[61] A. Kilian, Y.P. Chock, I.J. Huang, E.R. Graef, L.A. Upton, A. Khilnani, S.D. S. Krupnikova, I. Almaghlouth, L.C. Cappelli, R. Fernandez-Ruiz, B.A. Frankel, J. Frankovich, C. Harrison, B. Kumar, K. Monga, J.A.R. Vega, N. Singh, J. A. Sparks, E. Sullo, K.J. Young, A. Duarte-Garcia, M. Putman, S. Johnson, R. Grainger, Z.S. Wallace, J.W. Liew, A. Jayatilleke, Acute respiratory viral adverse events during use of antirheumatic disease therapies: a scoping review, Semin. Arthritis Rheum. 50 (5) (2020) 1191–1201.
[62] M. Pagnesi, et al., Determinants of the protective effect of glucocorticoids on mortality in hospitalized patients with COVID-19: Insights from the Cardio-COVID-Italy multicenter study, Int. J. Infect Dis 108 (2021) 270–273.
[63] M.Z. Tay, C.M. Poh, L. Rénia, The trinity of COVID-19: immunity, inflammation and intervention. 20(6) (2020) 363-374.
[64] L.F. García, Immune response, inflammation, and the clinical spectrum of COVID-19, Front. Immunol. 11 (2020) 1441.
[65] F. He, Q. Luo, M. Lei, L. Fan, X. Shao, K. Hu, S. Qin, N.a. Yu, J. Cao, L. Yang, Successful recovery of recurrence of positive SARS-CoV-2 RNA in COVID-19 patient with systemic lupus erythematosus: a case report and review, Clin. Rheumatol. 39 (9) (2020) 2803–2810.
[66] P.M. Sauñe, et al., Methylprednisolone pulse therapy: An alternative management of severe COVID-19, Respir. Med. Case Rep. 31 (2020), 101221.
[67] A. Orieux, P. Khan, R. Prevel, D. Gruson, S. Rubin, A. Boyer, Impact of dexamethasone use to prevent from severe COVID-19-induced acute kidney injury, Crit. Care 25 (1) (2021), https://doi.org/10.1186/s13054-021-03666-7.
[68] S. Akerstrom, et al., Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus, J. Virol. 79 (3) (2005) 1966–1969.
[69] F. Oroojalian, A. Haghbin, B. Baradaran, N. Hemmat, M.-A. Shahbazi, H.B. Baghi, A. Mokhtarzadeh, M.R. Hamblin, Novel insights into the treatment of SARS-CoV-2 infection: an overview of current clinical trials, Int. J. Biol. Macromol. 165 (2020) 18–43.
[70] J.A.C. Sterne, S. Murthy, J.V. Diaz, A.S. Slutsky, J. Villar, D.C. Angus, D. Annane, L.C.P. Azevedo, O. Berwanger, A.B. Cavalcanti, P.-F. Dequin, B. Du, J. Emberson, D. Fisher, B. Giraudeau, A.C. Gordon, A. Granholm, C. Green, R. Haynes, N. Heming, J.P.T. Higgins, P. Horby, P. Jüni, M.J. Landray, A. Le Gouge, M. Leclerc, W.S. Lim, F.R. Machado, C. McArthur, F. Meziani, M.H. Møller, A. Perner, M.W. Petersen, J. Savovic, B. Tomazini, V.C. Veiga, S. Webb, J. C. Marshall, Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis, JAMA 324 (13) (2020) 1330, https://doi.org/10.1001/jama.2020.17023.
[71] Y. Fu, Y. Cheng, Y. Wu, Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools 35(3) (2020) 266-271.
[72] F. Moeinzadeh, et al., Newly diagnosed glomerulonephritis during COVID-19 infection undergoing immunosuppression therapy, a case report, Iran J. Kidney Dis. 14 (3) (2020) 239–242.
[73] S. Revannasiddaiah, et al., A potential role for cyclophosphamide in the mitigation of acute respiratory distress syndrome among patients with SARS-CoV-2, Med. Hypotheses 144 (2020), 109850.
[74] F. Kato, et al., Antiviral activities of mycophenolic acid and IMD-0354 against SARS-CoV-2. 64(9) (2020) 635–639.
[75] K.-W. Cheng, S.-C. Cheng, W.-Y. Chen, M.-H. Lin, S.-J. Chuang, I.-H. Cheng, C.-Y. Sun, C.-Y. Chou, Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus, Antiviral Res. 115 (2015) 9–16.
[76] D. Shin, R. Mukherjee, Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. 587(7835) (2020) 657-662.
[77] Q.-K. Lv, J.-X. Liu, S.-N. Li, Y.-J. Gao, Y. Lv, Z.-P. Xu, B.-X. Huang, S.-Y. Xu, D.-X. Yang, Y.-L. Zeng, D.-F. Liu, W. Wang, Mycophenolate mofetil modulates differentiation of Th1/Th2 and the secretion of cytokines in an active Crohn's disease mouse model, Int. J. Mol. Sci. 16 (11) (2015) 26654–26666.
[78] K.M. Andersen, H.B. Mehta, N. Palamuttam, D. Ford, B.T. Garibaldi, P. G. Auwaerter, J. Segal, G.C. Alexander, Association between chronic use of immunosuppresive drugs and clinical outcomes from coronavirus disease 2019 (COVID-19) hospitalization: a retrospective cohort study in a large US health system, Clin. Infect Dis. (2021), https://doi.org/10.1093/cid/ciaa1488.
[79] S. Thomas, K.H. Fisher, J.A. Snowden, S.J. Danson, S. Brown, M.P. Zeidler, A. N. Antoniou, Methotrexate Is a JAK/STAT Pathway Inhibitor, PLoS ONE 10 (7) (2015) e0130078.

[80] D.Y. Chen, et al., SARS-CoV-2 desensitizes host cells to interferon through inhibition of the JAK-STAT pathway. 2020.
[81] K.M. Stegmann, et al., The folate antagonist methotrexate diminishes replication of the coronavirus SARS-CoV-2 and enhances the antiviral efficacy of remdesivir in cell culture models, Virus Res 302 (2021), 198469.
[82] Y. Zhang, R. Guo, S.H. Kim, H. Shah, S. Zhang, J.H. Liang, Y. Fang, M. Gentili, C. N.O'. Leary, S.J. Elledge, D.T. Hung, V.K. Mootha, B.E. Gewurz, SARS-CoV-2 hijacks folate and one-carbon metabolism for viral replication, Nat. Commun. 12 (1) (2021), https://doi.org/10.1038/s41467-021-21903-z.
[83] A. Caruso, et al., Methotrexate inhibits SARS-CoV-2 virus replication "in vitro". 2020.
[84] F. Schälter, K. Dürholz, L. Bucci, G. Burmester, R. Caporali, C. Figuereido, J. F. Cobra, B. Manger, M.M. Zaiss, G. Schett, Does methotrexate influence COVID-19 infection? Case series and mechanistic data, Arthritis Res Ther 23 (1) (2021), https://doi.org/10.1186/s13075-021-02464-4.
[85] A. Yousaf, et al., Clinical outcomes of CoVid-19 in patients taking tumor necrosis factor inhibitors and/or methotrexate: a multi-center research network study, J. Am. Acad. Dermatol. (2020).
[86] E.Y. Senchenkova, J. Russell, A. Yildirim, D.N. Granger, F.N.E. Gavins, Novel role of T cells and IL-6 (Interleukin-6) in angiotensin II-induced microvascular dysfunction, Hypertension 73 (4) (2019) 829–838.
[87] J. Meletiadis, S. Tsiodras, P. Tsirigotis, Interleukin-6 blocking vs. JAK-STAT inhibition for prevention of lung injury in patients with COVID-19, Infect. Dis. Ther. 9 (4) (2020) 707–713.
[88] M. Levi, J. Thachil, T. Iba, J.H. Levy, Coagulation abnormalities and thrombosis in patients with COVID-19, Lancet. Haematol. 7 (6) (2020) e438–e440.
[89] E.M. Frohman, I.I. Part, et al., high-dose methotrexate with leucovorin rescue for severe COVID-19: An immune stabilization strategy for SARS-CoV-2 induced 'PANIC' attack, J. Neurol. Sci. 415 (2020), 116935.
[90] R. Xiong, L. Zhang, S. Li, Novel and potent inhibitors targeting DHODH are broad-spectrum antivirals against RNA viruses including newly-emerged coronavirus SARS-CoV-2. 2020. 11(10): p. 723-739.
[91] K.e. Hu, M. Wang, Y. Zhao, Y. Zhang, T. Wang, Z. Zheng, X. Li, S. Zeng, D. Zhao, H. Li, K.e. Xu, K.e. Lan, A Small-scale medication of leflunomide as a treatment of COVID-19 in an open-label blank-controlled clinical, Trial. 35 (6) (2020) 725–733.
[92] P. Guisado-Vasco, et al., Clinical characteristics and outcomes among hospitalized adults with severe COVID-19 admitted to a tertiary medical center and receiving antiviral, antimalarials, glucocorticoids, or immunomodulation with tocilizumab or cyclosporine: A retrospective observational study (COQUIMA cohort), EClinicalMedicine 28 (2020), 100591.
[93] A.H. de Wilde, V.S. Raj, D. Oudshoorn, T.M. Bestebroer, S. van Nieuwkoop, R.W. A.L. Limpens, C.C. Posthuma, Y. van der Meer, M. Bárcena, B.L. Haagmans, E. J. Snijder, B.G. van den Hoogen, MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment, J. Gen. Virol. 94 (8) (2013) 1749–1760.
[94] L.S. Belli, C. Fondevila, P.A. Cortesi, S. Conti, V. Karam, R. Adam, A. Coilly, B. G. Ericzon, C. Loinaz, V. Cuervas-Mons, M. Zambelli, L. Llado, F. Diaz-Fontenla, F. Invernizzi, D. Patrono, F. Faitot, S. Bhooori, J. Pirenne, G. Perricone, G. Magini, L. Castells, O. Detry, P.M. Cruchaga, J. Colmenero, F. Berrevoet, G. Rodriguez, D. Ysebaert, S. Radenne, H. Metselaar, C. Morelli, L.G. De Carlis, W.G. Polak, C. Duvoux, Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with Covid-19: results from the ELITA/ELTR multi-center European study, Gastroenterology 160 (4) (2021) 1151–1163.e3.
[95] A.S. Karadag, M. Aslan Kayıran, Immunosuppressive and immunomodulator therapy for rare or uncommon skin disorders in pandemic days, 2020, p. e13686.
[96] A. Suehiro, A. Sawada, Y. Hasegawa, H. Takatsuka, S. Higasa, E. Kakishita, Enhancement by cyclosporine A and tacrolimus of serotonin-induced formation of small platelet aggregation, Bone Marrow Transplant 29 (2) (2002) 107–111.
[97] L. Softic, R. Brillet, F. Berry, N. Ahnou, Q. Nevers, M. Morin-Dewaele, S. Hamadat, P. Bruscella, S. Fourati, J.-M. Pawlotsky, A. Ahmed-Belkacem, Inhibition of SARS-CoV-2 Infection by the Cyclophilin Inhibitor Alisporivir (Debio 025), Antimicrob Agents Chemother 64 (7) (2020), https://doi.org/10.1128/AAC.00876-20.
[98] S.J. Park, et al., Antiviral efficacies of FDA-approved drugs against SARS-CoV-2 infection in ferrets. 11(3) (2020).
[99] R.C. Ungaro, E.J. Brenner, R.B. Gearry, G.G. Kaplan, M. Kissous-Hunt, J.D. Lewis, S.C. Ng, J.-F. Rahier, W. Reinisch, F. Steinwurz, F.E. Underwood, X. Zhang, J.-F. Colombel, M.D. Kappelman, Effect of IBD medications on COVID-19 outcomes: results from an international registry, Gut 70 (4) (2021) 725–732.
[100] M.C. Dalakas, Guillain-Barré syndrome: The first documented COVID-19-triggered autoimmune neurologic disease: more to come with myositis in the offing, Neurol. Neuroimmunol. Neuroinflamm. 7 (5) (2020) e781, https://doi.org/10.1212/NXI.0000000000000781.
[101] T. Möckel, F. Basta, J. Weinmann-Menke, A. Schwarting, B cell activating factor (BAFF): Structure, functions, autoimmunity and clinical implications in Systemic Lupus Erythematosus (SLE), Autoimmun. Rev. 20 (2) (2021) 102736, https://doi.org/10.1016/j.autrev.2020.102736.
[102] D. Ramsköld, I. Parodis, T. Lakshmikanth, N. Sippl, M. Khademi, Y. Chen, A. Zickert, J. Mikeš, A. Achour, K. Amara, F. Piehl, P. Brodin, I. Gunnarsson, V. Malmström, B cell alterations during BAFF inhibition with belimumab in SLE, EBioMedicine 40 (2019) 517–527.
[103] C.M. Tipton, C.F. Fucile, J. Darce, A. Chida, T. Ichikawa, I. Gregoretti, S. Schieferl, J. Hom, S. Jenks, R.J. Feldman, R. Mehr, C. Wei, F.-H. Lee, W.C. Cheung, A. F. Rosenberg, I. Sanz, Diversity, cellular origin and autoreactivity of antibody-secreting cell population expansions in acute systemic lupus erythematosus, Nat. Immunol. 16 (7) (2015) 755–765.
[104] S.W. Jackson, A. Davidson, BAFF inhibition in SLE-Is tolerance restored? Immunol. Rev. 292 (1) (2019) 102–119.
[105] C.M. Fehres, et al., APRIL induces a novel subset of IgA(+) regulatory B cells that suppress inflammation via expression of IL-10 and PD-L1, Front. Immunol. 10 (2019) 1368.
[106] M.E. Hassan, et al., Dexamethasone in severe COVID-19 infection: a case series, Respir. Med. Case Rep. 31 (2020), 101205.
[107] H. Liaquat, B. Shupp, S. Kapoor, A. Matin, High-dose prednisone for treatment of autoimmune pancreatitis in a patient with coronavirus disease 2019 (COVID-19) due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Am. J. Case Rep. 21 (2020), https://doi.org/10.12659/AJCR.926475.
[108] Z. Liu, X. Li, G. Fan, F. Zhou, Y. Wang, L. Huang, J. Yu, L. Yang, L. Shang, K.e. Xie, J. Xu, Z. Huang, X. Gu, H. Li, Y.i. Zhang, Y. Wang, Z. Huang, B. Cao, Low-to-moderate dose corticosteroids treatment in hospitalized adults with COVID-19, Clin. Microbiol. Infect. 27 (1) (2021) 112–117.
[109] C. Ding, X. Feng, Y. Chen, J. Yuan, P. Yi, Y. Li, Q. Ni, R. Zou, X. Li, J. Sheng, L. Li, K. Xu, Effect of corticosteroid therapy on the duration of SARS-CoV-2 clearance in patients with mild COVID-19: a retrospective cohort study, Infect. Dis. Ther. 9 (4) (2020) 943–952.
[110] M.A. Schramm, et al., COVID-19 in a severely immunosuppressed patient with life-threatening eosinophilic granulomatosis with polyangiitis, Front. Immunol. 11 (2020) 2086.
[111] A. von Borstel, W.H. Abdulahad, G. Dekkema, A. Rutgers, C.A. Stegeman, J. Veldman, P. Heeringa, J.S. Sanders, H.M. Ashour, Mycophenolic acid and 6-mercaptopurine both inhibit B-cell proliferation in granulomatosis with polyangiitis patients, whereas only mycophenolic acid inhibits B-cell IL-6 production, PLoS ONE 15 (7) (2020) e0235743.
[112] M. Wang, et al., Treatment of COVID-19 Patients with Prolonged Post-Symptomatic Viral Shedding with Leflunomide – a Single-Center, Randomized, Controlled Clinical Trial, Clin. Infect. Dis. (2020).
[113] A. Pizzorno, et al., In vitro evaluation of antiviral activity of single and combined repurposable drugs against SARS-CoV-2, Antiviral Res 181 (2020), 104878.
[114] A. Strangfeld, M. Schäfer, M.A. Gianfrancesco, S. Lawson-Tovey, J.W. Liew, L. Ljung, E.F. Mateus, C. Richez, M.J. Santos, G. Schmajuk, C.A. Scirè, E. Sirotich, J.A. Sparks, P. Sufka, T. Thomas, L. Trupin, Z.S. Wallace, S. Al-Adely, J. Bachiller-Corral, S. Bhana, P. Cacoub, L. Carmona, R. Costello, W. Costello, L. Gossec, R. Grainger, E. Hachulla, R. Hasseli, J.S. Hausmann, K.L. Hyrich, Z. Izadi, L. Jacobsohn, P. Katz, L. Kearsley-Fleet, P.C. Robinson, J. Yazdany, P. M. Machado, Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry, Ann. Rheum. Dis. 80 (7) (2021) 930–942.