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REVIEW

# Autoimmune and rheumatic musculoskeletal diseases as a consequence of SARS-CoV-2 infection and its treatment

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## Abstract

The coronavirus disease-2019 (COVID-19) pandemic is likely to pose new challenges to the rheumatology community in the near and distant future. Some of the challenges, like the severity of COVID-19 among patients on immunosuppressive agents, are predictable and are being evaluated with great care and effort across the globe. A few others, such as atypical manifestations of COVID-19 mimicking rheumatic musculoskeletal diseases (RMDs) are being reported. Like in many other viral infections, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection can potentially lead to an array of rheumatological and autoimmune manifestations by molecular mimicry (cross-reacting epitope between the virus and the host), bystander killing (virus-specific CD8 + T cells migrating to the target tissues and exerting cytotoxicity), epitope spreading, viral persistence (polyclonal activation due to the constant presence of viral antigens driving immune-mediated injury) and formation of neutrophil extracellular traps. In addition, the myriad of antiviral drugs presently being tried in the treatment of COVID-19 can result in several rheumatic musculoskeletal adverse effects. In this review, we have addressed the possible spectrum and mechanisms of various autoimmune and rheumatic musculoskeletal manifestations that can be precipitated by COVID-19 infection, its therapy, and the preventive strategies to contain the infection.

**Keywords** Coronavirus disease-2019 (COVID-19) · Rheumatic musculoskeletal diseases (RMDs) · Autoimmunity · Rheumatology

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## Abbreviations

| | |
|---|---|
| AAV | Anti-neutrophil cytoplasmic antibody-associated vasculitis |
| ACE2 | Angiotensin-converting enzyme 2 |
| ANA | Antinuclear antibodies |
| AIDS | Acquired immunodeficiency syndrome |
| APCs | Antigen-presenting cells |
| APS | Antiphospholipid antibody syndrome |
| ARDS | Acute respiratory distress syndrome |
| CAHA | Coronavirus-associated hemostatic lung abnormality |
| CAR-T | Chimeric antigen receptor T cell |
| CCL2 | Chemokine (C–C motif) ligand 2 |
| CK | Creatine kinase |
| COVID-19 | Coronavirus disease-2019 |
| CSF | Cerebrospinal fluid |
| CRS | Cytokine release syndrome |
| CXCL8 | C-X-C motif chemokine ligand 8 |
| DADA-2 | Deficiency of adenosine deaminase-2 |
| DIC | Disseminated intravascular coagulation |

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| | |
|---|---|
| ER | Endoplasmic reticulum |
| ERAP | Endoplasmic reticulum aminopeptidase |
| EULAR | European league against rheumatism |
| GBS | Guillain–Barré syndrome |
| GM-CSF | Granulocyte–macrophage colony-stimulating factor |
| HLA | Human leukocyte antigen |
| IFN | Interferon |
| IL | Interleukin |
| IRAK4 | Interleukin-1 receptor-associated kinase 4 |
| IRF | Interferon regulatory transcription factor |
| ISRE | Interferon-stimulated response element |
| IVIg | Intravenous immunoglobulin |
| JAK | Janus kinase |
| LAC | Lupus anti-coagulant |
| MAA | Myositis-associated autoantibodies |
| MAS | Macrophage activation syndrome |
| MRI | Magnetic resonance imaging |
| MDA-5 | Melanoma differentiation-associated protein-5 |
| MHC | Major histocompatibility |
| MSA | Myositis-specific autoantibodies |
| MVAS | Mitochondrial antiviral-signaling protein |
| MYD88 | Myeloid differentiation primary response-88 |
| NETs | Neutrophil extracellular traps |
| NF-κB | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| NIH-SS | National Institute of Health Stroke Score |
| PRR | Pattern recognition receptors |
| RA | Rheumatoid arthritis |
| RIG-1 | Retinoic acid-inducible gene-I |
| RMDs | Rheumatic musculoskeletal diseases |
| RNA | Ribonucleic acid |
| RNP | Ribonuclear protein |
| PCR | Polymerase chain reaction |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus-2 |
| SLE | Systemic lupus erythematosus |
| Sm | Smith |
| SJS-TEN | Steven Johnson syndrome-toxic epidermal necrolysis |
| STAT | Signal transducer and activator of transcription |
| TLR | Toll-like receptor |
| TNF | Tumor necrosis factor |
| vWF | Von Willebrand factor |

## Introduction

The coronavirus disease-2019 (COVID-19) pandemic has taken a heavy toll on the healthcare system across the world. With a global incidence of over six million, the mortality rate so far has been approximately 6.5% [1]. Though a few countries have succeeded in containing the spread of the virus, the overall incidence of fresh infections is still on the rise. Moreover, with no vaccine or definitive treatment in sight [2], the health care systems across the world are strained and are staring at an uncertain future and a long-term coexistence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with the human host has been anticipated.

From the perspective of a rheumatologist, there are concerns regarding compelling actions and future preparedness for facing COVID-19 and its after effects. We have always considered rheumatic musculoskeletal diseases (RMDs) as conditions that are precipitated when a genetically susceptible host encounters specific environmental triggers. Our firsthand knowledge of the host-environment interaction in RMD until now was limited to epidemiological studies related to small infectious outbreaks like the Chikungunya epidemic which has given us insights into various post-infectious RMD manifestations. The COVID-19 pandemic, in contrast to these relatively small occurrences, is a mammoth event in the history of humankind. The infection has spread across all large countries affecting people from all age groups. Such an infection is likely to have long-term consequences, and RMDs could be a major fallout given the quantum of immune dysregulation the virus is known to cause [3]. There are already reports of post-COVID-19 autoimmunity with an increase in the incidence of Kawasaki disease [4] and Guillain-Barré syndrome [5, 6]. In a global attempt to curb this pandemic, a variety of drugs with varying mechanisms of action are being tried. While some of these drugs are known to cause adverse effects mimicking RMDs and other autoimmune diseases, there is a lack of information for the majority of them. There are also concerns regarding the right approach to treat existing rheumatic diseases and about the outcome of infection among those on immunosuppressive agents. This and many more challenges faced by patients with RMDs and their care providers during the COVID-19 pandemic are being addressed by the Global Alliance Registry and the COVID-19 database of the European League Against Rheumatism (EULAR); mining these data will serve as a guide in the future for the management of patients with RMDs [7].

The COVID-19 pandemic has undoubtedly uncovered the strengths of global collaborations, effective communication, and dissemination of information. Unless we prepare and foresee the likely new set of RMDs and the possible mimics of RMDs [8] due to this pandemic, we are going to fail in delivering care to our patients. We have recently learned

the costs of being underprepared when challenged with the rheumatological manifestation [9] resulting from the use of immune checkpoint inhibitors in cancer treatment. The initial dilemma on the management plan and prognosis of these conditions set the rheumatology community on a backfoot [10]. Keeping this context in mind, it is time to pool all our existing knowledge and resources to prepare for any rheumatological fallout of COVID-19 and its treatment, which may have left behind its footprints even in the post-COVID-19 era.

## Objective and search strategy

Our objective was to narrate various autoimmune and rheumatic manifestations that are associated with COVID-19 and the drugs used in its treatment. We conducted a literature search for articles since inception and published until 20 May 2020 in the English language using the Medline database. The search terms used in various combinations were: "coronavirus disease-19", "COVID-19", "SARS-CoV-2", "rheumatic", "autoimmune", "musculoskeletal", "clinical", "manifestations", "antivirals", and "vaccines". Additionally, we performed a focused literature search in the same database for articles on drugs used in COVID-19. We included original research articles, reviews, viewpoints, opinions, commentaries, case series, and case reports as relevant to our objective. The search strategy was used to obtain the titles and the abstracts of the relevant studies which were initially screened, and if necessary, the full text was retrieved to determine the suitability. The references and related citations for the resulting articles were also reviewed for pertinence. Finally, the information was synthesized in a logical sequence with expert inputs from the senior authors.

## Clinical presentations of COVID-19

SARS-CoV-2 enters the cells through angiotensin-converting enzyme 2 (ACE2) receptors located on the nasopharyngeal and bronchial mucosa, and on alveolar pneumocytes in the lungs [11]. The smooth muscles of the arterial walls and endothelial cells of the veins in every organ of the body express ACE2 receptors explaining the ubiquitous distribution, and the possibility of multisystem involvement by the SARS-CoV-2 virus [12]. The spectrum of presentation of COVID-19 ranges from asymptomatic or mild symptoms to severe-critical illness which is categorized as mild, severe, and critical illness [13]. Patients with mild presentation have symptoms of fever, cough, nasal congestion, sore throat, malaise, headache, and myalgia without dyspnea. The severe presentation includes patients with respiratory distress as indicated by a respiratory rate of $\geq 30$/min, $SpO_2$ (blood oxygen saturation) of $\leq 93\%$, $PaO_2$ (partial pressure of oxygen)/$FiO_2$ (fraction of inspired oxygen) ratio of $< 300$, or presence of infiltrates in more than half of the lung fields in a radiograph or CT scan. Critical illness encompasses respiratory failure, septic shock, disseminated intravascular coagulation (DIC), and multiorgan dysfunction syndrome [13]. Besides respiratory symptoms, multiple cohorts have reported anosmia and dysgeusia, ranging from 34–87% of the patients [14, 15]. Gastrointestinal manifestations, including nausea, vomiting, and diarrhea have been reported in 11–24% of the cases and as presenting symptoms in a few reports of COVID-19 [16, 17]. In a case series from China, 32% of the patients had ophthalmological manifestations, mainly conjunctival redness and edema with increased eye discharge [18]. The other musculoskeletal, dermatological, neurological, and cardiovascular manifestations have been discussed in detail further in this review. The risk factors for severe disease and mortality include old age, immunocompromised status, and comorbidities, such as hypertension, diabetes mellitus, cardiovascular disease, chronic respiratory disorders, chronic kidney disease, liver diseases, cancer, and severe obesity [19]. Initial data from the COVID-19 Global Rheumatology Alliance provider registry suggests that the features and prognosis in patients with RMDs on immunosuppressive agents contracting SARS-CoV-2 are similar to those in the general population [20].

## Spectrum of rheumatic musculoskeletal manifestations of SARS-CoV-2 infection and antiviral drugs

With scientific literature pouring in from different parts of the world on the clinical presentations and complications of SARS-CoV-2 infections, atypical clinical and laboratory manifestations mimicking RMDs have been reported (Table 1). Musculoskeletal manifestations reported with COVID-19 include arthralgia, myalgia, and proximal weakness with elevated creatine kinase (CK) level [21, 22]. Some of these manifestations preceded respiratory symptoms of COVID-19. For instance, a patient who presented with proximal weakness with muscle edema on magnetic resonance imaging (MRI), turned negative for myositis-specific and associated antibodies but progressed to develop the symptoms of COVID-19 [22]. The spectrum of dermatological manifestations mimicking RMDs includes COVID toes/pseudo-chilblain, transient urticarial or maculopapular rash, livedoid/necrotic lesions, punctiform or diffuse purpura, and erythema elevatum diutinum-like rash [23]. COVID toes/pseudo-chilblain is reported predominantly in children and young adults and seems to be a relatively late feature of COVID-19. On the other hand, livedoid/necrotic lesions are seen in elderly patients with severe COVID-19 with no association with the duration of infection. Cases of young stroke involving large vessels, commonly evaluated in rheumatology clinics, have also been reported

**Table 1** Rheumatic musculoskeletal manifestations associated with SARS-CoV-2 infection

| | Reported with SARS-CoV-2 | Clinical characteristics | Refs. |
|---|---|---|---|
| Musculoskeletal manifestations | | | |
| Arthralgia-Myalgia | In 14.4–44% of the cases | Early and transient features<br>Resolves in 10–15 days | [21] |
| Acute Myositis | Case report | Symptom of myalgia and proximal muscle weakness preceded respiratory symptom of COVID-19<br>Elevate Creatine kinase (CK) level (25,384 IU/L)<br>MRI showed muscle edema<br>Negative MSA and MAAs | [22] |
| Dermatological manifestations | | | |
| COVID toes/pseudo-chilblain | In ~ 19–59% of the pediatric and young adults | Asymmetrical multiple red–purple pustular or vesicular lesions at distal extremities<br>Relatively late feature | [23] |
| Skin rash | In ~ 19% of the cases | Transient (6–9 days) urticarial or maculo-papular rash<br>Associated with severe disease | |
| Purpura | Rare | Punctiform or diffuse | |
| Livedoid/necrotic lesions | In 6% of the elderly with severe disease | Acral and truncal distribution with ischemic features in severe cases | |
| Erythema elevatum diutinum-like rash | Rare | Multiple red–purple papulo-nodular lesion over the dorsum of hands | |
| Neurological manifestations | | | |
| Large vessel stroke in young patients | Case reports | National Institute of Health Stroke Score range: 13–23<br>Probably secondary to endothelitis and coagulopathy secondary to COVID-19 | [24] |
| Cardiovascular manifestations | | | |
| Myocarditis in absence of previous comorbidities | Case reports | Likely to occur within 7 days of symptoms<br>Circumferential pericardial effusion, global hypokinesia, low ejection fraction and normal cardiac valves on echocardiography<br>Normal coronary angiography<br>Cardiac MRI: myocardial edema and pattern of late gadolinium-enhancement fulfilling Lake Louis criteria of acute myocarditis<br>Improved with supportive care, hydroxychloroquine, lopinavir/ritonavir, and intravenous methylprednisolone | [25, 26] |
| Multisystem autoinflammatory syndrome | | | |
| Cytokine storm/Secondary Hemophagocytic lymphohistiocytosis (sHLH) | Represents critical patients with SARS-CoV-2 infection | After 8–9 days of the symptom onset<br>Unremitting fever, cytopenia, and hyperferritinemia<br>Acute respiratory distress syndrome and multiple organ failure<br>Interplay of Interferons, interleukins, chemokines, colony-stimulating factors, and TNF-alpha<br>Hyperferritinemia and elevated serum IL-6, associated with mortality<br>H-score of > 169, 93% sensitivity and 86% specificity for the diagnosis of the sHLH<br>Report on improvement with IL-1 and IL-6 inhibitor | [27] |

**Table 1** (continued)

| | Reported with SARS-CoV-2 | Clinical characteristics | Refs. |
|---|---|---|---|
| Post-viral autoimmunity | | | |
| Guillain-Barré syndrome (GBS) | Case reports | The interval from COVID symptoms to GBS symptoms was 5–10 days<br>Axonal or demyelinating variant<br>Negative PCR for SARS-CoV-2 from CSF<br>One of the patients succumbed to respiratory complications, and the other recovered with IVIg/plasmapheresis | [5, 6] |
| Kawasaki-like disease | 30-fold increased incidence as compared to the pre-COVID time in Italy | Higher mean age (7.5 years)<br>More cardiac involvement, shock syndrome, and macrophage activation syndrome as compared to pre-COVID-19 Kawasaki disease | [4] |
| Laboratory findings | | | |
| Positive Antinuclear antibodies (ANA) | Reported in 35% of the patients | Single-center report<br>No impact on outcome with positive ANA | [28] |
| Anti-Ro52 | Reported in 4.4% of the patients | | |
| Antiphospholipid antibodies | Case series ($n=56$)<br>LAC positive ($n=25$)<br>Anticardiolipin or anti-β2-glycoprotein I antibodies IgG/IgM ($n=5$)<br>Case reports ($n=3$)<br>Anticardiolipin or anti-β2-glycoprotein I antibodies IgA | Epiphenomenon rather than autoimmunity<br>Expert opinion favoring to start heparin in patients with antiphospholipid test positivity | [29, 30] |
| Increased D-Dimer without DIC | > 0.5 mg/L in 46% of the patients | Higher chance for ICU admission<br>> 1 mg/L on admission has 18-times increased mortality (95% CI, 2·6–128·6; $p=0·0033$) | [31] |

*COVID-19* coronavirus disease-2019, *CSF* cerebrospinal fluid, *DIC* disseminated intravascular coagulation, *IL* interleukin, *LAC* lupus anti-coagulant, *MAA* myositis-associated autoantibodies, *MSA* myositis-specific autoantibodies, *RA* rheumatoid arthritis, *PCR* polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2

with COVID-19 [24]. A couple of cases of Guillain-Barré syndrome (GBS) has been described as a consequence of post-viral autoimmune phenomenon. Out of the two reported cases, one succumbed to respiratory complications, and the other recovered with intravenous immunoglobulin (IVIg)/plasmapheresis [5, 6]. Myocarditis related to COVID-19 in young patients without any prior cardiac morbidity has been reported with early onset of cardiac symptoms. They present with intact coronaries in cardiac echo and MRI showing the classical features of myocarditis. Improvement of myocarditis was noticed following treatment with hydroxychloroquine, lopinavir/ritonavir, and intravenous methylprednisolone [25, 26]. An increase in the incidence of Kawasaki disease has been reported from Italy as a post-SARS-CoV-2 phenomenon. As compared to the classical Kawasaki disease, these children were older (mean age, 7.5 years) and reported to have more cardiac involvement, shock syndrome, and macrophage activation syndrome (MAS) [4]. Cytokine storm or secondary hemophagocytic lymphohistiocytosis (sHLH), yet another entity encountered in rheumatology practice, is reported with COVID-19. The clinical manifestations start 8–9 days after the onset of respiratory symptoms and range from unremitting fever, cytopenia, to hyperferritinemia ultimately resulting in multiorgan failure. Hyperferritinemia and elevated serum interleukin (IL)-6 are often associated with mortality in these patients [27]. There are reports of improvement with therapy targeting IL-1 and IL-6, and there are multiple ongoing clinical trials to evaluate the role of immunosuppressive therapy for this cytokine storm reported with COVID-19. In addition to these clinical manifestations mimicking RMDs, laboratory reports of positive antinuclear antibodies (ANA) [28], antiphospholipid antibodies, lupus anti-coagulant assay [29, 30] and increased level of D-dimer [31] have been reported with COVID-19. All these reports of COVID-19 mimicking or precipitating RMDs points towards a possibility of persisting intermediate to long-term immune dysregulation.

Based on evidence from in-vitro studies and experience from other viral infections, several antiviral therapies are currently in trial/practice in different parts of the world [32]. There are reports of rheumatic musculoskeletal adverse reactions following the use of these drugs. Table 2 depicts the list of the major anti-SARS-CoV-2 drugs with their mechanisms of action and the important rheumatological adverse events. Of these, some adverse events

**Table 2** Anti-SARS-CoV-2 drugs and its rheumatic musculoskeletal adverse effects

| Drugs | Antiviral mechanisms | Rheumatic musculoskeletal adverse events | Refs. |
|---|---|---|---|
| Chloroquine and hydroxychloroquine | Inhibit pH-dependent internalization and fusion of the virus with lysosomes | Myopathy and neuromyopathy | [33] |
| Favipiravir | Inhibit viral RNA-dependent RNA polymerase | Hyperuricemia | [34] |
| Remdesivir | | Not reported | |
| EIDD-2801 | | Not reported | |
| Lopinavir-ritonavir | Protease inhibitor | Hyperuricemia (≤5%), musculoskeletal pain (6%), arthralgia (<2%), osteonecrosis, vasculitis, SJS-TEN | [35] |
| Umifenovir | Block the virus-cell membrane fusion as well as virus-endosome fusion | Not reported | |
| Galidesivir | Antiviral adenosine nucleoside analog | Not reported | |
| Ribavirin | Interfere with polymerases, RNA capping, and inosine monophosphate dehydrogenase | Arthralgia (> 10%), musculoskeletal pain (> 10%), backache (1–10%),<br>gout (< 1%), myositis (< 1%),<br>Exacerbation of sarcoidosis (higher incidence in combination with interferon α) | [36] |
| Camostat mesylate | Serine protease inhibitor | Not reported | |
| Interferon α and β | Inhibit replication | Interferon α2b:<br>Myalgia (16–75%), musculoskeletal pain (1–21%), arthralgia (3–19%), backache (1–19%), amyotrophy (< 5%),<br>Arthritis (< 5%) including RA,<br>Other autoimmune disease (< 1%) including sarcoidosis, myositis, rhabdomyolysis, SJS, SLE, vasculitis<br>Interferon β1a and β1b:<br>Myalgia (25–29%),<br>Backache (23–25%),<br>Autoimmune hepatitis,<br>Immune thrombocytopenia, SLE, osteonecrosis, Sjogren syndrome | [37] |
| Convalescent plasma | | Chance of transfusion-related adverse events: urticaria, anaphylaxis, transfusion-related acute lung injury<br>Latent risk of hyperimmune attacks:<br>Possibly via antibody-dependent enhancement of tissue damage and blunting of endogenous immunity to the virus | |

*RNA* ribonucleic acid, *SJS-TEN* Steven Johnson syndrome-toxic epidermal necrolysis, *SLE* systemic lupus erythematosus

deserve special mention. Myopathy and neuromyopathy can rarely occur following long-term treatment with chloroquine and hydroxychloroquine [33]. Favipiravir can lead to hyperuricemia [34]. Lopinavir-ritonavir-related rheumatic adverse events include arthralgia, back pain, osteonecrosis, and vasculitis [35]. Ribavirin can cause arthralgia, back pain, myositis, and exacerbation of sarcoidosis [36]. Musculoskeletal pain and myalgia have been reported in up to half of the patients on interferon therapy. Additionally, in rare cases, interferon therapy can lead to drug-induced RMDS, such as rheumatoid arthritis, lupus, Sjogren syndrome, myositis, sarcoidosis, and vasculitis [37]. With the increased use of these drugs, there is a possibility of a rise in these adverse drug reactions necessitating active pharmacovigilance. Moreover, it must be noted that some of the frontrunner drugs like remdesivir have limited clinical data making it even more important to be vigilant.

## Coagulopathy as a consequence of inflammation COVID-19 cases

One of the factors leading to mortality in COVID-19 patients is the presence of coagulopathy [38]. The autopsy findings of COVID-19 death from a majority of the cases show the presence of coagulopathy either in the form of deep venous thrombosis, pulmonary embolism, or multiple pulmonary thrombi coexisting with acute respiratory distress syndrome (ARDS) changes in the lungs [39]. The laboratory markers of COVID-19 coagulopathy include increased D-dimer

level, borderline thrombocytopenia, and prolonged prothrombin time [40]. Though the exact mechanism underlying coagulopathy is unclear, a possibility of local lung-TMA as a coronavirus-associated hemostatic lung abnormality (CAHA) is proposed, linking inflammation and endothelial cell activation [41]. Endothelial cell activation results in the production of von Willebrand factor (vWF) in excess to the clearance capacity of ADAMTS-13. This leads to local thrombotic microangiopathy and perpetuates lung damage [42].

The association of netosis has also been proposed with coagulopathy in COVID-19 patients requiring further therapeutic exploration [43]. Moreover, the presence of lupus anti-coagulant and antiphospholipid antibodies may point towards the autoimmune contribution rather than just an epiphenomenon. Thus, linking inflammation to coagulopathy which is not a common occurrence in other viral infections suggests the role of immune activation at the vessel wall. This phenomenon warrants serious consideration of the anecdotal evidence supporting the role of immunosuppressants in addition to anticoagulants in severe COVID-19 cases [44].

## SARS-CoV-2 infection and autoimmunity

The interplay of various genetic, hormonal, immunological, and environmental factors constitutes the mosaic of autoimmunity [45]. Viral infections play a substantial role in the development of several autoimmune diseases in individuals with underlying immune dysregulation [46]. Follow up data from survivors of viral outbreaks like influenza, Zika, Ebola, and Chikungunya have shown development of autoimmune phenomenon within weeks to months after recovery. While GBS, fulminant type1 diabetes, IgA vasculitis, APS have been observed after a previous outbreak of influenza [47], transverse myelitis, arthralgia, myalgia, and arthritis were reported following Zika [48], Chikungunya [49] and Ebola infections [50]. Besides overt clinical manifestations, long-term persistence of autoreactive cells and autoantibodies (against antiphospholipid with influenza and ds-DNA and heat shock protein-60 with Ebolavirus) have also been demonstrated with some of these infections [47, 49]. The mechanisms by which viruses disrupt self-tolerance include molecular mimicry, epitope spreading, bystander activation, persistence of the latent virus, and poly/oligoclonal immune activation in the background of autoimmunity mosaic [51]. Table 3 enlists known viral infections and associated autoimmune diseases with the possible mechanisms as elaborately described by Smatti et al. [52]. Similar mechanisms may lead to autoimmunity following SARS-CoV-2 infection. We herein describe some of the possible mechanism of autoimmunity following SARS-CoV-2 infection as follows:

### Molecular mimicry

Molecular mimicry, as a result of the cross-reacting epitope between the virus and the host, leads to both humoral and cellular autoreactivity (Fig. 1a) [53]. This mechanism plays a vital role in the pathogenesis of prototype systemic rheumatological diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, and Sjogren syndrome [54]. SARS-CoV-2 proteins displayed at least one match with the human protein on a comparative peptidome analysis comprising of 37 viral proteins [55]. These similarities potentially can lead to loss of tolerance to self-peptides and result in autoimmunity. Recently, an epitope mapping analysis has identified immunogenic linear epitopes, 2′-O-ribose methyltransferase, RNA-dependent RNA polymerase and 3′-to-5′ exonuclease proteins from autoimmune dermatomyositis patients matching with the SARS-CoV-2 peptides [56].

In addition to the presence of cross-reactive epitopes, activation of antigen-presenting cells (APCs) either by an adjuvant or infectious stimulus is essential to increase the expression of co-receptors [51]. Viral RNA of the SARS-CoV-2 activates dendritic cells through cytosolic RIG like receptors and endosomal TLRs, as well as by the release of interferon α/β and γ enhancing antigen-presenting capacity (Fig. 1b) [57]. Such activation by the virus can result in precipitation of inflammatory cascade in the presence of an already existing cross-reactive antigen. The clinical phenomenon of initial asymptomatic to mild symptoms followed by severe autoinflammatory syndrome in COVID-19 is proposed to be due to a similar autoreactive adaptive response with SARS-CoV-2 infection [3].

The role of genetic susceptibility should also be considered while evaluating the role of cross-reactive epitopes in precipitating autoimmunity. Human leukocyte antigen (HLA) susceptibility map for SARS-CoV-2 has shown that HLA-B*15:03 efficiently presents highly conserved SARS-CoV-2 peptides that are shared among the common human coronaviruses [58]. The association of HLA-B*15 with primary Sjogren's syndrome [59] and Bechet's diseases [60] is well documented, and the consequence of its association with SARS-CoV-2 peptide presentation needs to be carefully followed up.

Following molecular mimicry with the dominant epitope, diversification in epitope specificity commences resulting in the neo-epitopes presentation. Immune response to these neo-epitopes differs from that to the dominant epitope and involves newer targets for autoimmunity [61]. The sequential appearance of various autoantibodies in RA and SLE follows the theory of epitope spreading [62, 63]. In SLE, before clinical disease onset, autoantibodies are targeted against Ro, La, and phospholipid antigens. In contrast, the clinical manifestations commence with the appearance of autoantibodies

**Table 3** Mechanisms of autoimmune manifestation following different viral infections

| Molecular mechanisms | Viruses | Autoimmune diseases |
|---|---|---|
| Molecular mimicry | Coxsackievirus | Type 1 diabetes mellitus |
| | Cytomegalovirus | Multiple sclerosis, type 1 diabetes mellitus, anti-β2 glycoprotein-1 antibody |
| | Enterovirus | Type 1 diabetes mellitus |
| | Epstein-Barr virus | Grave's disease, Hashimoto's disease, multiple sclerosis |
| | Hepatitis C virus | Immune thrombocytopenia, autoimmune hepatitis, polyarthritis |
| | Herpes simplex virus | Human herpes encephalitis |
| | Human T-lymphotropic virus-1 | Myelopathy/tropical spastic paraparesis |
| | Influenza | Acute disseminated encephalomyelitis |
| | Measles virus | Multiple sclerosis |
| | Theiler's virus | Multiple sclerosis |
| | Varicella-Zoster virus | Multiple sclerosis |
| | West Nile virus | Myasthenia gravis |
| | Zika virus | Guillain-Barré syndrome |
| | Chikungunya virus | Symmetric polyarthritis |
| | Cytomegalovirus | Rheumatoid arthritis, SLE |
| | Epstein-Barr virus | Rheumatoid arthritis |
| | Hepatitis C virus | SLE, porphyria cutanea tarda |
| Bystander effect | Hepatitis C virus | Vasculitis, cryoglobulinemia, Sjogren Syndrome, thrombocytopenia |
| | Enteroviruses | Type 1 diabetes mellitus |
| | Herpes simplex virus | Stromal keratitis |
| | Human Herpesvirus 6A | Thyroiditis |
| | Human immunodeficiency virus | Autoantibodies in AIDS |
| | Influenza | Acute disseminated encephalomyelitis |
| Persistent infection and polyclonal activation | Epstein-Barr virus | Lymphoproliferation |
| | Hepatitis C virus | Mixed cryoglobulinemia |

*AIDS* acquired immunodeficiency syndrome, *SLE* systemic lupus erythematosus

to ds-DNA, Smith (Sm), and ribonuclear protein (RNP) antigens [64]. Although with SARS-CoV-2 infection, epitope diversification is not reported, it would be worthwhile to closely follow those patients with positive autoantibodies.

## Bystander activation and damage

Pre-clinical studies of diabetes and experimental autoimmune encephalomyelitis suggest the role of bystander activation as one of the mechanisms predisposing to autoimmunity [65, 66]. The bystander damage starts with the virus-specific $CD8^+$ T cells migrating to the infected target tissues and exerting perforin and granzyme-mediated cytotoxicity. The target cell death in the inflammatory milieu activates the surrounding macrophages to release reactive oxygen species and nitric oxide resulting in bystander killing of surrounding uninfected cells [67]. The $CD4^+$ T cells contribute to this bystander damage through the release of proinflammatory cytokines and enhancing phagocytic activities of macrophage [68]. Ineffective clearance of these killed cells exposes autoantigen to antigen-presenting cells, resulting in the generation of autoreactive cells (Fig. 2) [51]. The association of hepatitis C virus and Sjogren syndrome serves a classical example among RMDs explaining the bystander activation and damage theory [69]. Hepatitis C, primarily a hepatotropic virus, also exhibits sialotropism and lymphotropism leading to bystander activation of the salivary gland epithelium and lymphocytes, respectively [70]. The activation of salivary epithelial cells and resultant antiviral defense in the salivary gland result in bystander damage manifesting as sicca symptoms and parotidomegaly. Bystander activation and dysregulated proliferation of the lymphocytes result in cryoglobulinemic vasculitis, generation of rheumatoid factor, autoantibodies (ANA, anti-SSA, anti-SSB), and low complements.

Lymphopenia due to reduced $CD4^+$ T cells and $CD8^+$ T cells is well documented in severe cases of SARS-CoV-2. The reduction is possibly secondary to functional exhaustion and preferential accumulation of the primed lymphocytes at the site of viral infection [71]. These preferentially accumulated lymphocytes exhibit increased activity as confirmed by the expression of HLA-DR, CD69, CD38, and CD44. Activated lymphocytes, along with activated macrophages at the target tissue lead to bystander killing

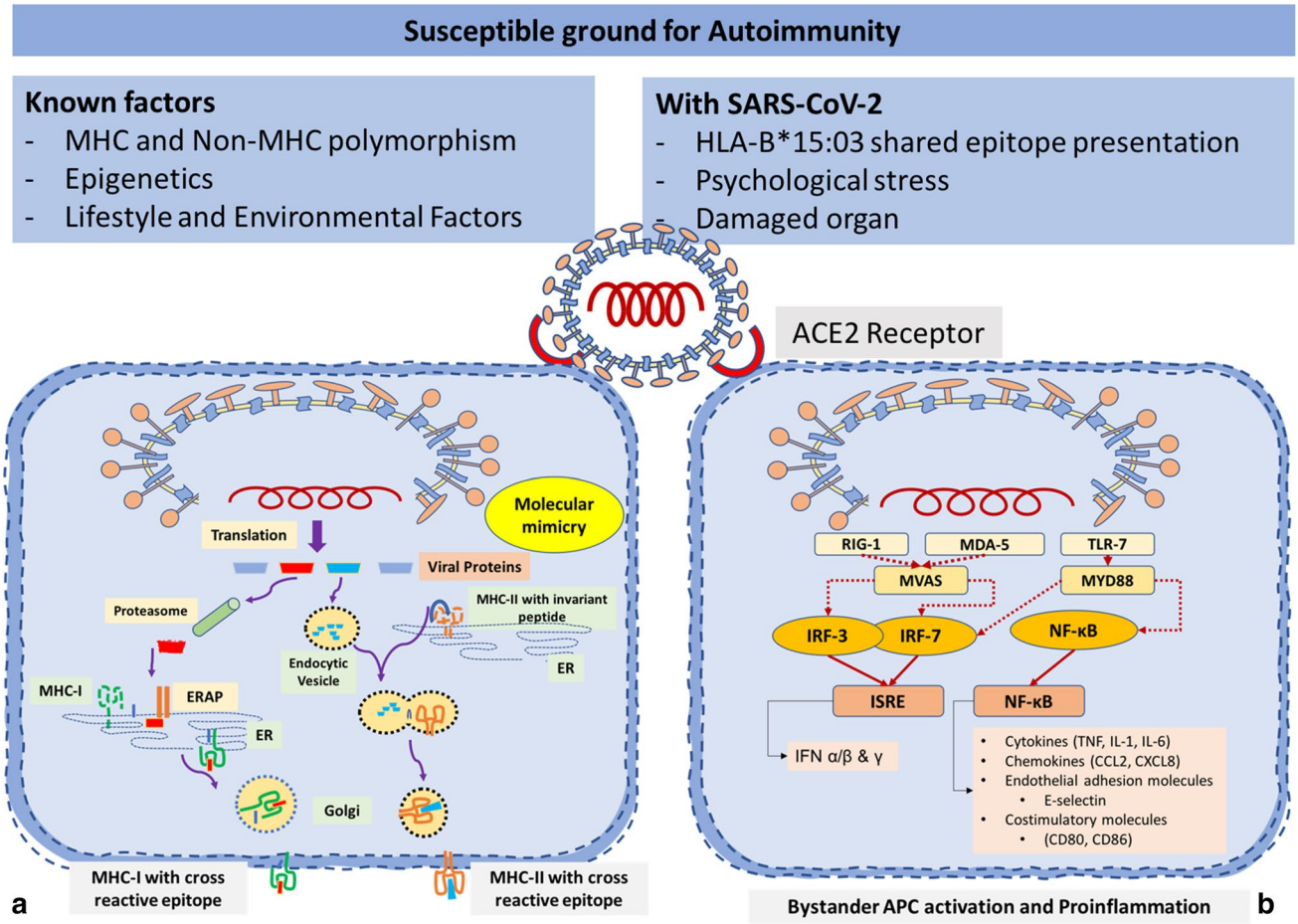


**Fig. 1** Mechanism of autoimmunity through molecular mimicry and bystander activation of antigen-presenting cells and proinflammation. **a** Molecular mimicry: The processing of cross-reactive peptide and presentation via MHC1 and MHC2 to T cells lead to the generation of autoreactive cells. *ACE2* angiotensin-converting enzyme 2, *ER* endoplasmic reticulum, *ERAP* endoplasmic reticulum aminopeptidase, *MHC* major histocompatibility. **b** Bystander activation of antigen-presenting cells and proinflammation: The cytoplasmic pattern recognition receptors after identifying viral RNA phosphorylates downstream IRF-3, IRF-7, and NFκB leading to the secretion of interferons as well as proinflammatory cytokines. *CCL2* chemokine (C–C motif) ligand 2, *CXCL8* C-X-C motif chemokine ligand 8, *IL* interleukin, *IRF* interferon regulatory transcription factor, *ISRE* interferon-stimulated response element, *MDA-5* melanoma differentiation-associated protein-5, *MVAS* mitochondrial antiviral-signaling protein, *MYD88* myeloid differentiation primary response-88, *RIG-1* retinoic acid-inducible gene-I, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells), *TLR* toll-like receptor, *TNF* tumor necrosis factor

of adjacent, non-infected healthy cells via proinflammatory cytokine and reactive oxygen species [72]. With SARS-CoV-2 infection, the multisystem inflammatory syndrome appears after the peak of viral load. This suggests a build-up of inflammatory cytokine and bystander activation of the macrophages by SARS-CoV-2 through pattern recognition receptors (PRR). It also suggests bystander killing of the cells devoid of ACE2 receptors by free oxygen radicals released in the inflammatory milieu [73]. Bystander damage can be one of the mechanisms responsible for the manifestations like ARDS, myocarditis, and neurological involvement reported with SARS-CoV-2 infection. Autopsy reports of COVID-19 patients show diffuse infiltration of lymphocytes in the lungs and focal infiltration in the heart, kidney, liver, pancreas, and adrenal gland, suggesting bystander damage by cytotoxic $CD8^+$ T cells [74]. Besides, in patients surviving SARS-CoV-2 infection, bystander activation may lead to sequestered autoantigen presentation leading to the emergence of neoepitope and autoimmune manifestations, as seen in SLE [75].

## Persistent immune activation

The third theory of persistent viral infection and oligo/polyclonal activation can be explained by the constant presence of viral antigens driving immune-proliferation resulting from the ineffective clearance of viruses [76]. Such mechanisms are commonly encountered with the Epstein-Barr virus

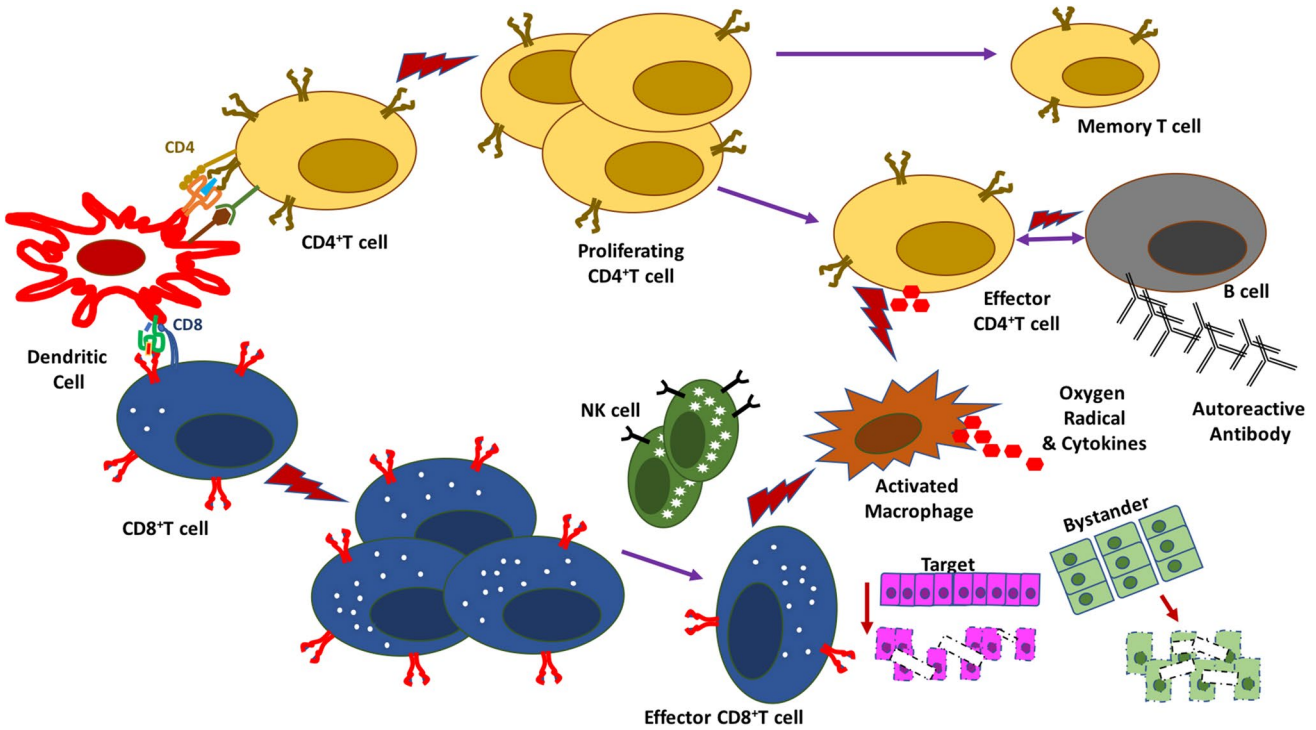


**Fig. 2** Bystander killing: virus-specific $CD8^+$ T cells migrating to the infected target tissues and exerting perforin and granzyme-mediated cytotoxicity. The $CD4^+$ T cells contribute to this bystander killing by the release of proinflammatory cytokines and enhancing phagocytic activities of the macrophages. The free oxygen radicals and cytokines secreted from the activated macrophages result in bystander killing off the surrounding non-infected cells. Ineffective clearance of these killed cells exposes autoantigen to the antigen-presenting cells, resulting in the generation of autoreactive cells in the presence of the costimulatory molecules

which resides in autoreactive B cells imparting immortality to the cells. These long-living autoreactive B cells cause lymphoproliferation and polyclonal activation culminating in chronic autoimmunity [77]. As the possibility of the persistence of the SARS-CoV-2 virus cannot be completely ruled out, this may add to an additional mechanism of autoimmunity. On a brighter side, complete clearance is reported in cases of other members of the coronavirus family following the development of specific antibodies [78], making the possibility of persistent immune activation due to SARS-CoV-2 chronicity less likely.

## Netosis

Knight et al. noted the formation of neutrophil extracellular traps (NETs) by demonstrating elevated serum levels of cell-free DNA, myeloperoxidase-DNA complexes, and citrullinated histone H3 among patients with COVID-19 compared to healthy controls [79]. NETs consist of extracellular webs of nuclear chromatin materials and supporting histones along with antibacterial proteins and oxidant enzymes from neutrophilic granules. The principal role of this transient phenomenon is to trap the microorganisms to resolve the infection. However, sustained netosis may beget inflammation and thrombosis [80]. In the past decade, researchers have established the role of netosis in autoimmune disease including but not limited to, SLE, RA, anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), antiphospholipid antibody syndrome (APS), and an autoinflammatory syndrome, deficiency of adenosine deaminase-2 (DADA-2) [81].

In COVID-19, a rise in neutrophil counts during early infection is a poor prognostic factor. The migration of these neutrophils towards virally infected sites follows the IL-8 gradient [82]. The production of free oxygen radicals and IL-1β by macrophages and pyroptosis of virally infected cells stimulate and maintain netosis of the migrated neutrophils [83]. Exposure of chromatin, histones, and neutrophil granules with sustained netosis, serve as a source of autoantigens. This may lead to the recognition of self-peptides by antigen-presenting cells and result in the expansion of autoreactive cells (Fig. 3).

## Population behavioral modification with COVID-19

In addition to the interaction of virus and host, the environmental factors play an important role in susceptibility and protection to autoimmune disease [45]. A paradigm

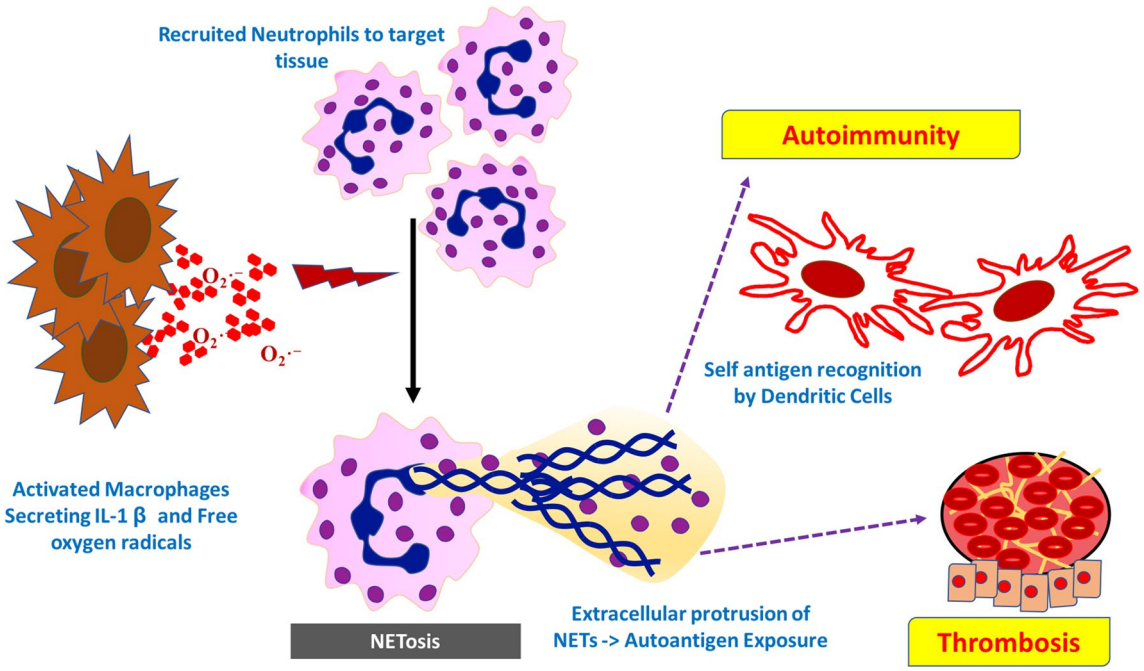


**Fig. 3** NETosis: Neutrophils recruited to the target tissues following chemokine IL-8 gradient gets activated by IL-1β and free oxygen radicals leading to a sustained generation of NETosis. NETs carrying autoantigen, which gets recognized by dendritic cells, leads to the activation of autoreactive T cells. *IL* interleukin, *NET* neutrophil extracellular traps

shift has taken place in the human behavior with advocacy of social distancing, handwashing, use of mask and gloves, and movement restrictions in an attempt to contain the spread of COVID-19 [21]. This shift is a double-edged sword in the mosaic of autoimmunity. The positive side is reflected by a reduction in airborne infectious disease with a documented shortening of the influenza season in the northern hemisphere by about six weeks [84]. This may reduce the occurrence of subsequent effects of influenza infection on RMDs. Diseases like acute rheumatic fever, where overcrowding plays an essential role in familial predisposition may also reduce with these hygienic measures [85]. At the negative spectrum of these hygienic measures, an increase in autoimmune disease should be born in mind as proposed by the proponents of the hygiene hypothesis. During the second half of the twentieth century, with the improvement in lifestyle especially in the developed world, the burden of infectious disease reduced with a parallel increase in autoimmune diseases like type1 diabetes mellitus, inflammatory bowel disease, and multiple sclerosis [86].

One of the key influencers to hygiene hypothesis is the microbiome of an individual which plays a protective role against autoimmune diseases. The mechanisms conferring protections by microbiome include antigenic competition, the role of lymphocyte homeostasis against pathogens, and the effect on immune regulatory pathway favoring the anti-inflammatory milieu with IL-10 and TGF-β secretion from the regulatory cells and TLR mediated receptor desensitization [87]. Disturbance in this microbiome is evident in the pathogenesis of autoimmune disorders including RA, SLE, and inflammatory bowel disease [88]. Over practice of distancing and antimicrobial sanitizers may lead to dysbiosis triggering autoimmunity. Additionally, the psychological stress caused by isolation, the anxiety of contracting the infection, and the economic burden along with its numerous adverse short- and long-term socio-economic consequences can turn as a trigger of various autoimmune diseases [89]. In summary, understanding the immune consequences of SARS-Cov-2 interaction with the host along with the environmental changes may explain the basis of rheumatic musculoskeletal manifestations.

## Preventive therapy against SARS-CoV-2 and the risk of autoimmunity

Currently, a multitude of vaccines for the prevention of SARS-CoV-2 infection is under investigation [90]. Except for the nucleocapsid, all immunogenic epitopes have been reported to have at least one match with human proteins [55]. This homology between the human and viral proteins is an established factor in vaccine-induced autoimmunity with the mechanism of molecular mimicry, as discussed

above. Furthermore, there is a theoretical possibility of the involvement of pathogenic priming in re-infection by COVID-19, triggering the release of proinflammatory cytokines leading to cytokine storm [55]. Similar instances have been experienced with H1N1 influenza [91], MERS [92], and SARS [93]. Thus, while developing vaccines, these epitopes should be carefully excluded to minimize unintended autoimmunity due to the risk of pathogenic priming.

## Targeted immunosuppressive therapy for SARS-CoV-2 infection

The clinical outcome of the patients relies on the fate of interaction between the SARS-CoV-2 virus and immune cells of the host [94]. Modulation of this virus-host cell interaction and its aftereffects can be possibly achieved with immunomodulatory therapies repurposed from drugs used in autoimmune diseases. The potential drug targets for COVID-19 has been reviewed extensively by Misra et al. [8]. In the early asymptomatic or mild symptomatic stage, antiviral therapy is likely to have maximum efficacy, and the addition of interferon therapy at this stage may theoretically benefit from augmenting the innate antiviral response. In the next stage of pulmonary and systemic hyper-inflammation, early initiation of immunosuppressant, including IVIg, corticosteroids, IL-6, or IL-1 inhibitors may help to halt the immune-mediated damage [95]. We have summarized the plausible role of targeted immunosuppressive therapy in Fig. 4. The role of IL-1 and IL-6 in particular is worth noticing as they are significant drivers of proinflammation in the cytokine release syndrome (CRS) of COVID-19. The IL-1 receptor antagonist, anakinra, has proven its beneficial effects in the MAS in

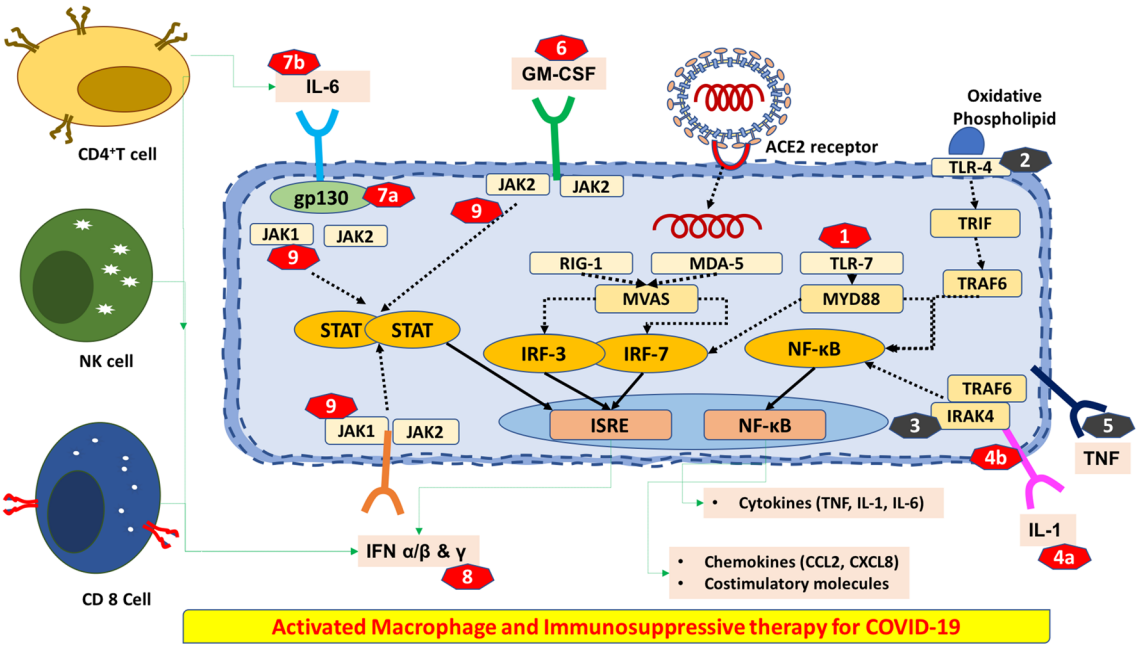


**Fig. 4** Targeted immunosuppressive therapy for COVID-19: Macrophages play a significant role in cytokine release syndrome associated with SARS-CoV-2 infection. The cells get activated directly by viruses as well as bystander activation with autocrine and paracrine actions of the proinflammatory cytokines mainly derived from the macrophages, NK cells, and T cells. The target of immunosuppressive therapy is denoted by the numbered boxes as described below. The red color box denotes the drugs for which clinical trials are ongoing and the grey color box denotes the drugs for which there is no ongoing clinical trial registered at present for the treatment of COVID-19. (1) TLR7 mediated viral signaling at the endosomal level—> chloroquine and hydroxychloroquine. (2) TLR4-TRIF signaling—> plausible therapeutic target, no approved drug. (3) IRAK4 inhibitor—> PF-06650833, CA-4948. (4) (a) Anti IL-1β—> canakinumab, (b) IL-1 receptor antagonist-> anakinra. (5) TNF inhibitors—> infliximab, adalimumab, etanercept. (6) GM-CSF signaling inhibition—> lenzilumab. (7) (a) Anti IL-6—> siltuximab, clazakizumab (b) Anti IL-6 receptor > tocilizumab, sarilumab. (8) Anti IFN γ—> emapalumab. (9) JAK inhibitor—> baricitinib, ruxolitinib, tofacitinib (multi-cytokine targeted therapy). *CCL2* chemokine (C–C motif) ligand 2, *CXCL8* C-X-C motif chemokine ligand 8, *ACE2* angiotensin-converting enzyme 2, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *IFN* interferon, *IL* interleukin, *IRAK4* interleukin-1 receptor-associated kinase 4, *IRF* interferon regulatory transcription factor, *ISRE* interferon-stimulated response element, *JAK* Janus kinase, *MDA-5* melanoma differentiation-associated protein-5, *MVAS* mitochondrial antiviral-signaling protein, *MYD88* myeloid differentiation primary response-88, *RIG-1* retinoic acid-inducible gene-I, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *STAT* signal transducer and activator of transcription, *TLR* toll-like receptor, *TNF* tumor necrosis factor

rheumatic diseases, as well as in chimeric antigen receptor T cell (CAR-T)-mediated severe CRS [96, 97]. Data from uncontrolled or historically controlled case series are encouraging for anakinra showing its safety and benefit on mortality, especially in critically ill patients with COVID-19 [98]. The high level of IL-6 in COVID-19 patients results from the secretion through viral infected respiratory cells, as well as from the infiltrating lymphocytes and monocytes [99]. The anti-IL-6 treatment strategy has shown efficacy in a similar CRS-like phenomenon observed with MAS in rheumatic diseases and has become an attractive target for COVID-19 critical cases [100]. To date, the supporting evidence for the beneficial effects of tocilizumab (a monoclonal antibody against the IL-6 receptor) is limited to observational studies [101]. The results of ongoing randomized controlled trials with IL-1 and IL-6 targeted therapy may clarify the role of tocilizumab in COVID-19. The downstream effects of IL-6 and its receptor are mediated via cytosolic Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling, a common pathway for multiple proinflammatory cytokines. Trials with baricitinib, which targets JAK-STAT signaling, are also ongoing in critically ill patients with COVID-19 [102].

## Conclusion

In this review, we primarily aimed at understanding the potential pathways and manifestations leading to autoimmunity and other RMD-like illnesses that could be triggered due to COVID-19 or the treatment for the same. This information may help the rheumatology community to tackle the threat of novel RMDs, RMD mimics, and other manifestations, including cytokine storm, Kawasaki disease, and coagulopathy. The immune consequences of SARS-CoV-2-host interaction along with the environmental changes, explain the basis of rheumatic musculoskeletal manifestations of COVID-19. There is a need for preparedness for a possible surge in diverse autoimmune diseases following the pandemic. The rheumatology community is already joining hands to treat, support, and inform our existing patient partners during this pandemic with the advantage of accessibility to cutting edge technology at our disposal. With a likely long-term coexistence of SARS-CoV-2 and the human host and the use of numerous therapeutic strategies, this preparedness may help in the effective management of the rheumatic manifestations of SARS-CoV-2 infection in the post-COVID-19 era.

**Author contributions** SS, VSN, and DD have initially conceptualized the review; SS, CKG, SD, and AMB were involved in drafting and critically revising the review; SS prepared all the figures with inputs from CKG and VSN; VSN and DD have provided expert inputs and updated the final review. All authors have provided substantial contributions to the conception and design of the work along with the interpretation. All authors have substantially contributed in drafting the manuscript and revising it critically for important intellectual content. All authors have approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work related to accuracy and integrity.

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**Conflicts of interest** The authors declare that they have no conflict of interest.

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