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Review Article

COVID-19: Immunology and treatment options

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A B S T R A C T

The novel coronavirus SARS-CoV2 causes COVID-19, a pandemic threatening millions. As protective immunity does not exist in humans and the virus is capable of escaping innate immune responses, it can proliferate, unhindered, in primarily infected tissues. Subsequent cell death results in the release of virus particles and intracellular components to the extracellular space, which result in immune cell recruitment, the generation of immune complexes and associated damage. Infection of monocytes/macrophages and/or recruitment of uninfected immune cells can result in massive inflammatory responses later in the disease. Uncontrolled production of pro-inflammatory mediators contributes to ARDS and cytokine storm syndrome. Antiviral agents and immune modulating treatments are currently being trialled. Understanding immune evasion strategies of SARS-CoV2 and the resulting delayed massive immune response will result in the identification of biomarkers that predict outcomes as well as phenotype and disease stage specific treatments that will likely include both antiviral and immune modulating agents.

1. Introduction

Until the SARS outbreak (2002), during which coronaviruses (CoV) showcased their potential for epidemic spread and significant pathogenicity in humans, they were mainly known as causes of mild respiratory and gastrointestinal disease [1]. Over the last two decades, three novel *Betacoronaviruses*, Severe Acute Respiratory Syndrome (SARS)-CoV, Middle East Respiratory Syndrome (MERS)-CoV and SARS-CoV2, have crossed the species barrier and caused significant outbreaks characterized by high case-fatality rates in humans [2–4] . The latest addition to human pathogenic coronaviruses (hCoVs) is SARS-CoV2, the cause of COVID-19. At the time of submission of this review SARS-CoV2 has infected over 2.6 million people worldwide and claimed 185.000 lives, threatening many more (https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6). In the following, epidemiological and clinical features of COVID-19, pathophysiological mechanisms, and already available and future therapeutic options will be discussed based on limited evidence available, and extrapolation from related viral disease.

2. Epidemiology & clinical presentation

The first hCoVs were described in 1966, E229-CoV and OC43-CoV [5,6]. They are part of a group of currently four known seasonal hCoVs (shCoV) that also includes HKU1-CoV and NL63-CoV, which were only discovered in 2005 [7,8]. All shCoVs are globally endemic and frequently cause common colds, accounting for 2-18% of all respiratory tract infections [9–13]. By their fourth birthday, 75% of children show antibodies directed against at least one of the shCoVs [14,15]. Anti-shCoVs antibodies provide some cross-immunity and antibody-mediated protection against infection by other species within the group [16]. While their overall pathogenic potential is comparatively low, in the immunocompromised, infants, the elderly and those with pre-existing pulmonary disorders, shCoVs can cause severe respiratory or sepsis-like presentations [17–21]. OC43 displays some neurotropism and can cause demyelination and CNS infections in vulnerable patient groups [22,23]. While estimates of their contribution to annual respiratory illness vary, shCoVs remain asymptomatic in approximately 50% of cases [24–26].

This is in stark contrast to the clinical presentation encountered in infections with so-called “novel coronaviruses” SARS-CoV, MERS-CoV and SARS-CoV2, which are associated with morbidity and case-fatality ratios that far exceed the ones in shCoVs.

The SARS pandemic of 2002/3 originated in Foshan, Guangdong province, China and spread to South East Asia, Europe and North America [27]. Containment was declared by the end of 2003, with no re-emergence reported since. Overall, 8096 probable cases caused 774 deaths, resulting in a mortality rate of 9.6% (https://www.who.int/csr/sars/en/). Mortality strongly correlated with age, approaching 7% for those younger, and 55% for those older than 60 years [28]. Health care workers in contact with SARS patients demonstrated a very low seroconversion rate of 2% in asymptomatic individuals. Less than 5% of all affected were children, and post-containment seroprevalence among

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children considered high-risk for significant exposure was extremely low. This suggests that subclinical SARS among children had not occurred [29–31]. Approximately 20% of SARS patients required intensive care support for acute respiratory distress syndrome (ARDS), half of who died within the following 28 days [32].

The severe clinical phenotype of SARS was replicated during the emergence of MERS in 2012, which continues to circulate, albeit to a lesser extent [36]. To date, 2494 cases of MERS have occurred worldwide, presenting as severe pneumonia, and resulting in respiratory and multiorgan failure, with a case-fatality-ratio of 35%-45% [37]. Individuals with comorbidities, males, and the immunocompromised are considered at particularly high risk.

In both previous novel coronavirus outbreaks, the severity of the clinical manifestation has puzzled clinicians. Common features included massive inflammatory cell infiltration of the lungs resulting in acute lung injury (ALI) and ARDS, highly elevated inflammatory markers in the serum, evidence of monocyte/macrophage activation, activated coagulation and pro-inflammatory cytokine and chemokine profiles [33–38]. This soon led to the implication of the host response as an important factor in this fulminant disease process [38]. Animal models of SARS suggest that lung inflammation intensifies after viral clearance, peaking as late as 14 days after infection [39], and similar observations were made in human SARS patients. This suggests that clinical deterioration later in the disease course was likely not due to uncontrolled viral replication, but rather uncontrolled immune responses and associated damage [40,41].

Similar descriptions of clinical presentations in COVID-19 are now emerging. Presenting features of cough and fever subacutely progress to respiratory distress and acute respiratory distress sydrome (ARDS) in 8-19% of patients, with the elderly and those with underlying comorbidities especially cardiovascular disease, diabetes mellitus, chronic pulmonary disorders or renal disease especially at risk https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_24_marzo_eng.pdf [42–45]. It is estimated that about 14% of COVID-19 patients develop respiratory symptoms requiring supplemental oxygen, and approximately 5% develop a need for mechanical ventilation [44–46] The CDC reports an overall case-fatality rate of 2.3%, though higher at 14.8% in patients over 80 years of age and 49% among the critically ill requiring mechanical ventilation [46].

The pulmonary pathology in COVID-19 is characterized by diffuse alveolar damage, and focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration and evidence of intravascular thrombosis. Monocytes, macrophages, and lymphocytes infiltrate the pulmonary interstitium [47,48]. The severe pulmonary inflammatory infiltrate of pulmonary tissue impedes alveolar gas exchange. In addition, one fifth of hospitalized patients develop significant cardiovascular morbidity, characterized by troponin rise, tachyarrhythmias and thromboembolic events, which is strongly associated with mortality risk [49–51]. Common features of COVID-19 patients requiring hospitalization and intensive care level support therefore are severe pneumonia with hypoxic respiratory failure of subacute onset evolving into ARDS, with a clinical picture characterized by fevers, lymphopenia, highly elevated C-reactive protein, proinflammatory cytokines, serum ferritin, and D-Dimers. Histopathological evidence of a prominent pulmonary infitrate dominated by monocytes and macrophages, vasculitis and hypercoagulability is seen [52,53].

Based on current knowledge, clinical pictures, disease pathology and progression of SARS-CoV2 infections are similar causing significant morbidity and mortality that may be associated with hyperinflammatory responses in a subset of patients.

3. Viral structure, host range and cell entry mechanisms

Coronaviruses are highly prevalent animal pathogens with a wide host range. Overall, thousands of species of coronaviruses are known [54,55]. Currently, seven CoVs are recognized as human pathogens [1]. The family of Coronaviridae is divided into two subfamilies: Coronavirinae and Torovirinae. Coronavirinae include the genera Alpha-, Betacoronaviruses, infecting only mammals, and Gamma-, and Deltacoronaviruses which infect both mammals and birds. Human CoVs E229 and NL63 are human pathogenic alpha-, while OC43 and HKU1 and all novel CoVs (including SARS-CoV2) are betacoronaviruses. The potential of Toroviruses to cause disease is humans is unknown https://talk.ictvonline.org/ictv-reports/ictv_9th_report/positive-sense-rna-viruses-2011/w/posrna_viruses/222/coronaviridae .

Coronaviruses (CoVs) are large enveloped viruses with a single-stranded, nonsegmented, positive sense RNA genome that spans approximately 30 kilobases, making it the largest known genome of any RNA virus [56]. Being RNA viruses, CoVs readily evolve by mutation and homologous and non-homologous recombination, which expands their host range and facilitates crossing of species barriers. Extensive animal reservoirs, especially among bats, genetic recombination among CoVs, and their plasticity in terms of receptor use renders CoVs highly effective at host switching, sometimes across wide taxonomic distances [57,58].

All hCoVs are thought to be zoonoses. Novel coronaviruses SARS-CoV, MERS-CoV and SARS-CoV2 are comparatively poorly adapted to humans, which affects their pathogenic potential [55,59]. Their genomic proximity to animal CoVs may allow for ongoing interspecies recombination events, as observed in MERS [60]. MERS-CoV, SARS-CoV and SARS-CoV2 have a natural reservoir in bats. Infection of humans likely occurred through intermediate hosts, including dromedary camels (MERS), the masked palm civet (SARS) and the pangolin (SARS-CoV2) [61]. As wild palm civets do not carry SARS-CoV, it must be assumed that the proximity of animals in markets facilitates recombination events and the emergence of novel viruses that may be pathogenic in humans [62,63].

Coronaviruses are spherical in shape. Their most prominent feature are club-like projections on the virus surface which are referred to as “spikes”. The virus membrane contains four structural components, the spike (S), envelope (E), membrane (M) and nucelocapsid (N) protein [56] (Fig. 1). For SARS-CoV and SARS-CoV2, the S protein is the primary determinant for host tropism and pathogenicity. It is the main target for neutralizing antibodies and therefore of great interest in terms of immunological response and vaccine design [64]. The spike structure is formed by homotrimers of S-glycoproteins, each of which

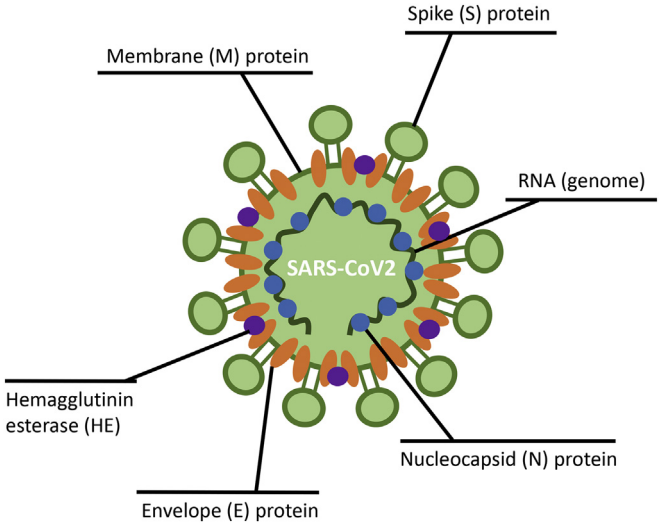

Fig. 1. Structure of SARS-CoV2. The spike protein (S) facilitates binding to the trans-membrane ACE2 host receptor; the envelope (E) protein together with the membrane (M) protein form the viral envelope and determine its shape; the hemagglutinin esterase (HE) protein may resemble another cell entry mechanism of novel CoVs; the nucleocapsid (N) protein in bound to the RNA genome of the virus to form the nucleocapsid.

consists of two subunits, whereby S1 forms the part involved in receptor recognition, and S2 is highly conserved, anchors the protein in the viral membrane and facilitates viral fusion [65–67]. S1 contains a hypervariable loop which differs greatly between betacoronaviruses on both size and sequence. Viral entry requires the proteolysis of the S protein in two locations, a process that utilizes host proteases, and results in irreversible conformational changes of the S protein [64,67]. Some anti-SARS-CoV antibodies in humans mimic receptor engagement, thus modeling conformational S protein changes upon antigen-antibody interaction [67]. The amino acid sequence of receptor binding sites of SARS-CoV2 is 74% homologous to that of SARS- CoV suggesting similar or even identical cell entry mechanisms for both viruses [68].

NL63, SARS-CoV and SARS-CoV2 all use the transmembrane angiotensin converting enzyme (ACE)2 as host receptor, whereas MERS CoV utilizes dipetidylpeptidase-4 (DPP4) [65]. Both receptors are transmembrane ectoenzymes that are highly conserved among mammals, thus facilitating interspecies transfer. However, their enzymatic activity in itself is not necessary for successful binding and fusion [69–71].

Binding affinity of the S protein of SARS-CoV2 and ACE2 is high. High sequence and conformational conservation of the S protein observed across SARS-CoV2 and SARS-CoV allows for some level of cross neutralization of the two viruses *in vitro* [64,68].

Hemagglutinin residues enhance binding by allowing interactions with sialic acid residues on host cell surfaces. *Betacoronaviruses* feature yet another structural protein, hemagglutinin-esterase (HE) which binds sialic acid on cell surfaces [72] (Fig. 1). This may enhance the virus' ability to bind and invade host cell surfaces and may constitute a virulence factor in novel hCoVs.

4. Immune pathology of COVID-19

While an estimated 80% of SARS-CoV2 infections are asymptomatic or result in mild disease, the remaining 20% of patients are severely or critically unwell [73,74]. Currently, limited information is available on host factors affecting individual outcomes in COVID-19.

4.1. Mechanisms of infection and immune evasion

While data on SARS-CoV2 are still sparse, aforementioned parallels with SARS-CoV and MERS-CoV may (for now) allow extrapolation of knowledge to understand how SARS-CoV2 escapes the host's immune response. Notably, SARS-CoV2 shares almost 80% RNA sequence homology with SARS-CoV, and 50% with MERS-CoV [75], with SARS-CoV2 exhibiting additional genomic regions when compared to SARS-CoV. In particular, the viral spike protein, which binds to the host cell receptor, is 20-30 amino acids longer than SARS-CoV, and other closely related coronaviruses [75]. Thus, it is possible, even likely, that SARS-CoV2 uses similar immune evasion strategies to other coronaviruses, but additional as yet undiscovered mechanisms may also be utilized by SARS-CoV2 [76].

As mentioned above, SARS-CoV and SARS-CoV2 both use ACE2 as their host cell receptor to establish infection (Fig. 2A) [77]. ACE2 is expressed in almost all organs in the body. ACE2 has been shown to be highly expressed on surfactant producing type 2 alveolar cells, and on ciliated and goblet cells in the airways; these cells likely provide a portal of entry for the virus in humans [78–80]. High ACE2 expression is also observed on the intestinal epithelium [81]. Furthermore, ACE2 is expressed on cardiac cells and vascular endothelia, which may explain cardiovascular complications in some patients [53]. For SARS-CoV, infection of immune cells including monocytes/macrophages and T cells has been observed. It is not clear to date whether and to what extent SARS-CoV-2 can also infect these cell types. ACE2 is also, but at lower levels and not ubiquitously, expressed on monocytes and macrophages, so this may also provide an entry mechanism into immune cells for SARS-CoV-2. However, other receptors and/or phagocytosis of virus containing immune complexes may also be involved (Fig. 1B) [76,82,83].

The host response and clearance of viral infections heavily relies on type I interferon (T1IFN) expression [84]. Expression of T1IFN and down-stream signals modulate cell responses and reprogram cells into an "anti-viral state", subsequently promoting infection control and pathogen clearance [85]. As a first step, immune cells sense viral infection through identification of virus derived pattern associated molecular patterns (PAMPs), such as viral RNA. These bind to and activate pattern recognition receptors (PRRs) in/on immune cells and result in immune cell activation (Fig. 2). RNAs viruses, such as SARS-CoV, SARS-CoV2 and MERS-CoV are detected by endosomal RNA PRRs, including Toll-like receptors (TLR-)3 and 7 and/or cytoplasmic RNA sensors, namely retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) (Fig. 2). Usually, TLR3/7 activation results in nuclear translocation of the transcription factors NFκB and IRF3, while RIG-1/MDA5 activation result in activation of IRF3. In turn, this triggers increased expression of T1IFN (through IRF3) and other innate pro-inflammatory cytokines (IL-1, IL-6, TNF-α through NFκB) [76,86]. In this context, T1IFN and other innate pro-inflammatory cytokines promote their own expression through auto-amplification: T1IFN activate the IFN-α receptor complex (IFNAR) which results in the phosphorylation/activation of STAT family transcription factors 1 and 2 (Fig. 2), while IL-1, IL-6, and TNF receptor activation feeds into pro-inflammatory cytokine expression though the transcription factor NFκB (Fig. 2) [85–87]. Activation and priming of innate and adaptive immune responses should result in pathogen clearance and recovery.

However, in a proportion of infected individuals, SARS-CoV, MERS-CoV and likely SARS-CoV2 evade immune system recognition through suppression of these mechanisms, a phenomenon associated with more severe disease and poorer prognosis [38,88,89](Fig. 2, red symbols). SARS-CoV has been shown to alter ubiquitination and degradation of RNA sensors (RIG-I and MDA5). It inhibits activation of mitochondrial antiviral-signaling protein (MAVS), which are essential for the activation and nuclear translocation of IRF3 in response to cytoplasmic RNA sensor activation. Furthermore, SARS-CoV, and likely SARS-CoV2, inhibit the TNF receptor-associated factors (TRAF) 3 and 6, which are central for the induction of IRF-3/7 in response to TLR3/7 and/or RIG-I and MDA-5 ligation as well as NFκB signalling pathways (which are usually activated in response to TLR3/7 ligation or cytokine receptor signaling) [88]. Lastly, novel coronaviruses can counteract T1IFN signaling through inhibition of STAT family transcription factor phosphorylation [86]. Taken together, suppression of innate immune mechanisms in infected epithelial cells and, to some extent, infected monocytes/macrophages allow novel coronaviruses to proliferate without triggering the innate anti-viral response machinery of these cells.

However, at a later stage, infected cells undergo cell death and release virus particles together with intracellular components that trigger innate inflammatory mechanisms through their recognition by PRRs in/on innate immune cells. As a result of this innate immune activation and resultant expression of pro-inflammatory cytokines (including IL-1β, IL-6, TNF-α, etc.), adaptive immune cells become involved in the host's defense against viral infections. T lymphocytes play a central role in this anti-viral response, including $CD4^+$ T cell derived cytokines, $CD8^+$ T cell mediated cytotoxicity, and B cell activation resulting in antibody production. Novel coronaviruses may also (partially) escape these mechanisms through the induction of T cell apoptosis [90]. However, lymphocytes may also become depleted due to the expression of pro-inflammatory cytokines by (not infected) innate immune cells that become recruited to the lungs and trigger hyper-inflammation, seen during the development of a "cytokine storm" [91].

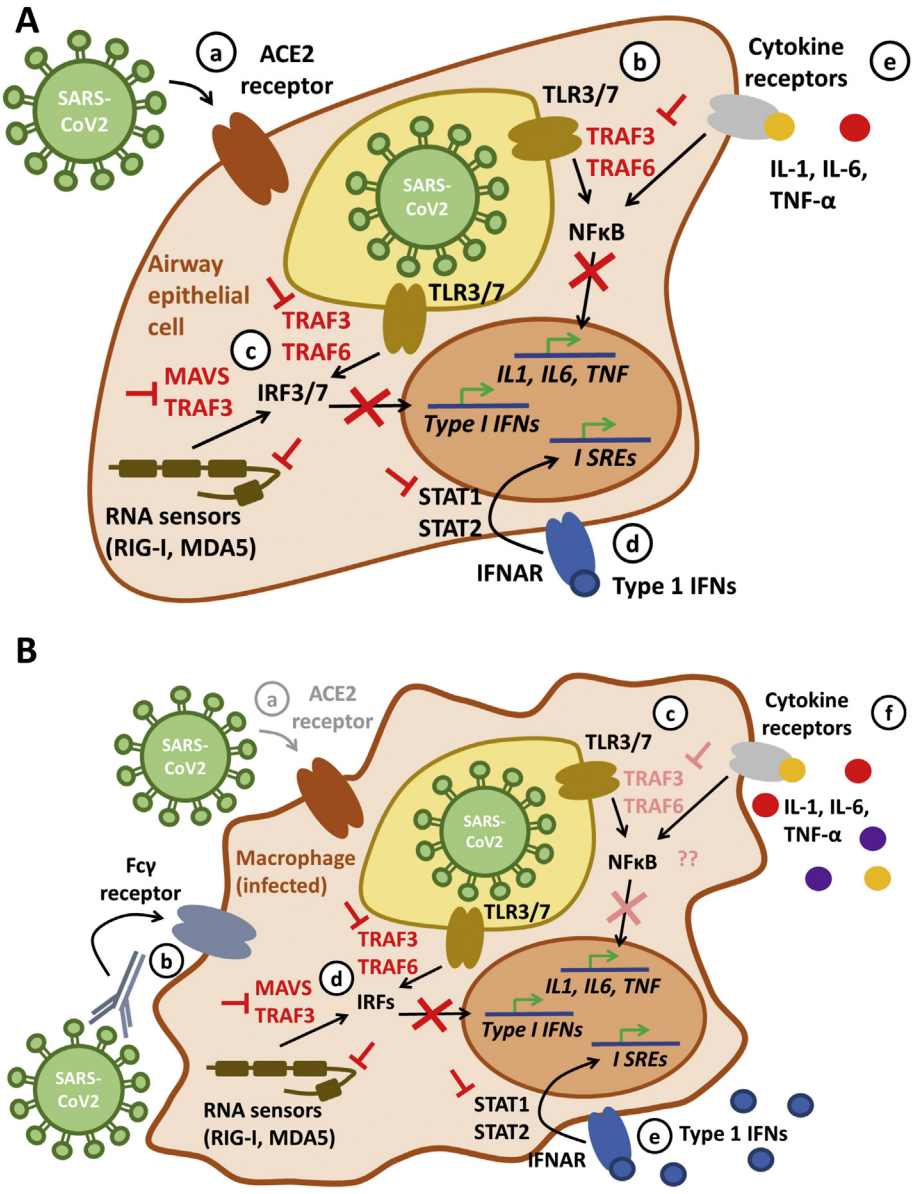

Fig. 2. Immune evasion strategies of SARS-CoV2. A) SARS-CoV2 infects airway epithelial cells through interactions with the trans-membrane enzyme ACE2 (a). While RNA viruses usually activate TLR3 and/or 7 in endosomes (b) and cytosolic RNA sensors RIG-I and MDA-5 (c), SARS-COV2 effectively suppresses the activation of TNF receptor-associated factors (TRAF) 3 and 6, thereby limiting activation of the transcription factors NFκB and IRF3 and 7, thereby suppressing early pro-inflammatory responses through type I interferons (IFN) and pro-inflammatory effector cytokines IL-1, IL-6 and TNF-α (red symbols). Furthermore, novel CoVs inhibit the activation of STAT transcription factors (d) in response to type I IFN receptor activation, which further limits antiviral response mechanisms. Altogether, this prohibits virus containment through activation of anti-viral programs and the recruitment of immune cells. B) Tissue monocytes/macrophages express ACE2 to a significantly lower extent, making infection through this route less likely (a). However, immune complexes consisting of ineffective antibodies against e.g. seasonal CoVs and virus particles may be taken up by macrophages through Fcγ receptors resulting in their infection (b). In a process referred to as antibody directed enhancement (ADE), virions inhibit type I IFN signaling in infected macrophages while allowing pro-inflammatory IL-1, IL-6 and TNF-α expression, which may contribute to hyperinflammation and cytokine storm syndrome (c,d). Inhibited type 1 IFN signaling suppresses anti-viral programs, while increased IL-1, IL-6 and TNF-α expression auto-amplifies itself through positive feedback loops (f).

4.2. Hyperinflammation and cytokine storm

While symptoms of COVID-19 disease may be (sometimes only slightly) milder in comparison to infections with SARS-CoV or MERS-CoV, several key pathogen-associated and clinical features of disease are similar and we can extrapolate knowledge from what is already known about the pathophysiology of SARS and MERS .

In COVID-19, as in SARS or MERS, several key findings were associated with poor outcomes in cohort studies, and suggest hyper-inflammation may be linked to more severe disease. Three early studies from Wuhan linked cytopenia and/or significantly elevated inflammatory parameters with severe disease and unfavorable outcomes. One study, involving 99 patients reported neutrophilia (38%), lymphopenia (35%), and increased systemic inflammatory proteins (IL-6 in 52%, and CRP in 84%) as common symptoms in COVID-19 disease [72]. Another study involving 41 individuals, linked severe disease culminating in ICU admission and mortality, with neutrophilia and lymphopenia [4]. The third study reported significant leukopenia (11.8%), lymphopenia (77.6%), thrombopenia (41.2%), anemia (48.2%), hypofibrinogenemia (22.4%), and hypo-albuminemia (78.8%) in a cohort of 85 patients who died from COVID-19 [83,92]. These observations are in line with findings in severe or lethal cases of SARS and MERS, in which increased numbers of neutrophils and monocytes/macrophages are present in the airways [83,93]. Other groups reported severe clinical phenotypes and ICU dependency of patients to be associated with increased plasma levels of innate chemokines, specifically C-X-C motif chemokine 10 (CXCL10)/Interferon gamma-induced protein 10 (IP-10), chemokine (C-C motif) ligand 2 (CCL2)/monocyte chemoattractant protein 1 (MCP-1), Macrophage Inflammatory Protein (MIP-)1A/CCL3, and the pro-inflammatory cytokine TNF-α [2]. This, indeed, is similar to the situation reported in SARS and MERS in which uncontrolled inflammation centrally contributes to poor outcomes [94–96].

Though seemingly contradictory to mechanisms of immune evasion discussed above, enhanced innate immune activation, including increased T1IFN, IL-1β, IL-6, and TNF-α expression centrally contributes to morbidity and mortality in COVID-19, MERS and SARS. One possible explanation is the induction of endothelial and vascular cell damage and cell death as a result of viral replication. Virus-induced inflammatory cell death, including necrosis or pyroptosis result in pro-inflammatory cytokine expression, (uninfected) immune cell recruitment and activation [97]. Mice infected with SARS-CoV exhibit

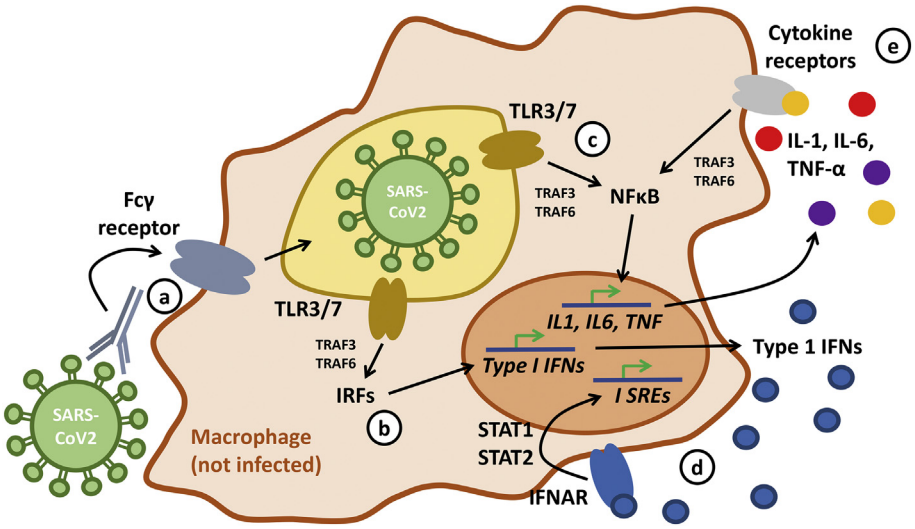

Fig. 3. Inflammatory response through monocytes macrophages. Uninfected monocytes/macrophages from the blood stream invade the lungs where they detect virus particles and/or cytoplasmic and nuclear components. Within immune complexes, these particles are taken up into the cell (a) where they are presented to TLRs, activating NFκB and/or IRF dependent pro-inflammatory pathways (b,c). As a result, uninfected monocytes/macrophages produce significant amounts of pro-inflammatory cytokines (d,e) which recruit additional innate and adaptive immune cells and cause additional tissue damage.

excessive T1IFN secretion from myeloid cells in infected tissues. Indeed, immune evasion through the suppression of anti-viral responses and T1IFN expression in respiratory epithelia results in high viral loads [38]. From this, it is hypothesized that (not infected) monocytes/macrophages and neutrophils recruited to the site of infection exhibit strong and poorly controlled inflammatory responses, resulting in tissue damage and systemic inflammation, both of which contribute to morbidity and mortality [53](Fig. 3).

Another factor thought to contribute to organ damage and poor outcomes is the early production of neutralizing antibodies against coronaviruses. Antibody-dependent enhancement (ADE) is a phenomenon shown to contribute to damage accrual during viral infections. It has been shown to promote cellular uptake of virus particles bound in immune complexes, through their binding to Fcγ receptors (FcγR). This may contribute to aforementioned persistent viral replication in immune cells (including newly infected antigen-presenting cells), but also immune complex mediated inflammatory responses (Figs. 2,3,4), that contribute to tissue and organ damage, including acute respiratory distress syndrome (ARDS) [98–100]. Indeed, a subset of COVID-19 patients reportedly develop vasculitic lesions, blood vessel occlusion and infarctions. Histopathologic reports from tissue sections suggests features associated with immune complex mediated vasculitis, including infiltration of monocytes and lymphocytes within and around blood vessels, wall thickening, and focal hemorrhage [53,101–103].

As is true for a number of systemic autoimmune/inflammatory conditions, uncontrolled activation of immune responses is (likely) not limited to the innate mechanisms. As a result of pro-inflammatory cytokine expression and the presence of nuclear antigens (from cell and tissue damage), adaptive immune cells may become activated and trigger a “second wave” of inflammation (potentially in those patients who deteriorate after 7-10 days of infection). Indeed, adaptive immune cells, namely T lymphocytes, which are observed in lung tissue sections of COVID-19 patients with ARDS and/or cytokine storm, may drive inflammation at later disease stages. Similar mechanisms have been reported in influenza and other viral infections [104,105]. Overall, severely ill COVID-19 patients experiencing cytokine storm exhibit lymphopenia and sometimes atrophy of the lymphatic tissues, namely lymph nodes and spleen [51,106,107]. This is in line with reports in primary and secondary forms of Hemophagocytic lymphohistiocytosis (HLH) and associated cytokine storm, which result in inflammatory cell death and hypo-cellularity of lymphatic organs [108–110].

4.3. Host factors affecting individual risk and outcomes

Poor outcomes are associated with age; indeed, children appear to contract SARS-CoV2 and usually do not develop severe symptoms or

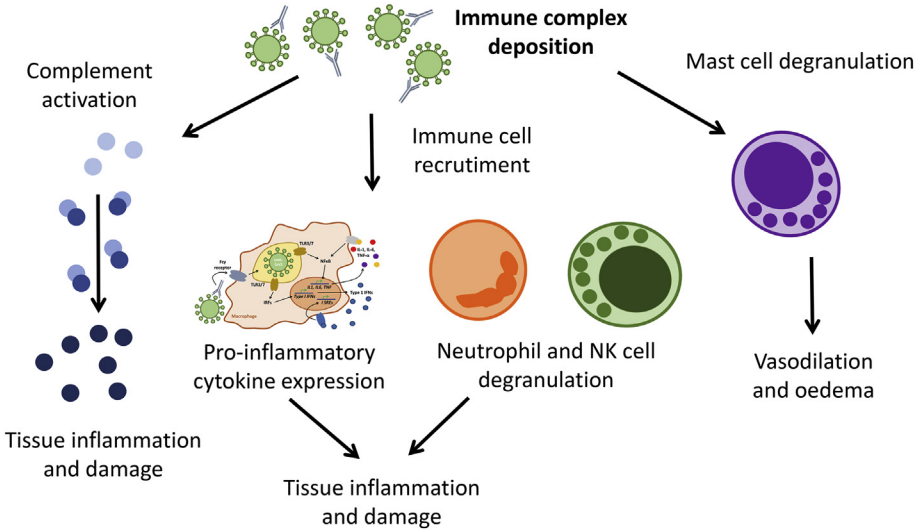

Fig. 4. Inflammatory mechanisms in immune complex vasculitis.

complications. This is surprising as children are prone to viral infections including severe manifestations. More than 75% of children get exposed to seasonal coronaviruses before their 4th birthday and seroconverts. However, antibody titres wane over time, most obvious in those over 60 years [110]. This may reduce immune response to SARS-CoV2 in the elderly as (limited) cross-reactivity between anti-seasonal coronavirus and anti-SARS antibodies exists, but also contribute to increased inflammation and complications. Immunological recall effects exist as anti-seasonal coronavirus titres increase in sera of convalescent SARS patients [111] which may influence immune pathology. As mentioned above, antibody-bound virions can enter susceptible cells, such as macrophages through Fcγ receptor ligation in a process termed antibody-dependent enhancement (ADE) [112]. In other viral infections (e.g. Dengue fever), ADE allows immune cell infection and reduces type I IFN dependent antiviral responses while promoting pro-inflammatory IL-6 and TNF-α expression [113,114]. Furthermore, massive recall antibody production in individuals with a history of exposure to seasonal coronaviruses but waning titres, such as the elderly, can result in immune complex deposition and promote inflammation and damage, including immune complex vasculitis [110].

Another age-dependent disease mechanism may be associated with live vaccinations (e.g. measles or BCG). Vaccines protect beyond their target antigen through induction of innate immune mechanisms termed non-specific heterologous effects. Individuals who received BCG vaccination produce increased levels of pro-inflammatory IL-1β and TNF-α in response to *S. aureus* or *Candida spp.*, and BCG vaccinated infants exhibit reduced infection-related mortality [115]. However, heterologous immune responses to unrelated antigens may also contrite to inflammation-related complications. Frequently, adults exhibit memory T cells that are specific to antigens they were never exposed to, and cross-reactive memory T cells can narrow the T cell response by favoring “high affinity” clones. Indeed, limited memory T cell repertoires are a feature of immune senescence and associated with disease progression and T cell mediated damage in other viral infections, such as virus hepatitis and infective mononucleosis [116].

As mentioned above, ACE2 acts as transmembrane cellular receptor for SARS-CoV2 allowing cell infection [117]. Variable ACE2 expression patterns affect disease susceptibility between tissues (e.g. respiratory epithelia vs immune cells), but potentially also between individuals (men vs women, children vs adults) thereby determining disease progression and outcomes. Recently, it has been suggested that ACE2 expression is highest in children and young women, that its expression decreases with age, and is lowest in individuals with chronic disease, including diabetes and hypertension, inversely correlating with risk for severe disease and unfavorable outcomes [118]. While ACE2 facilitates viral entry into cells, it also plays a role in controlling infection and inflammation. ACE2 is part of the ACE2/angiotensin- [1–7]/MAS system as it counteracts the pro-inflammatory effects of the angiotensin-2. It catalyzes angiotensin-2 processing into angiotensin-1-7, which counteracts vasoconstriction, modulates leukocyte migration, cytokine expression, and fibrogenic pathways [119]. Thus, ACE2 contributes to limiting tissue inflammation while favoring repair mechanisms. Furthermore, “high“ ACE2 expression may be of benefit as SARS-CoV2 virus particles may compete with angiotensin-2 for cell surface binding sites and cellular uptake. Thus, relatively increased ACE2 expression may explain why children and young adults, especially young women, are relatively protected from COVID19 and associated complications.

Taken together, novel coronaviruses, such as SARS-CoV2, may effectively suppress early T1IFN responses, which contributes to uncontrolled virus replication resulting in delayed and potentially increased cytokine responses at later stages. Early and sufficient control of virus replication and pathogen clearance may be altered in individuals at risk, such as the elderly, patients with diabetes or metabolic syndrome, etc. [74,75]. Healthy children and young people, on the other hand, may effectively control viral load at early stages of infection and less frequently develop severe disease and life-threatening complications. Lastly, early antibody production may result in integration of viable virus into immune cells and increased viral replication, resulting in immune complex mediated pathology, which may contribute to pathology in young patients with no obvious risk factors [100].

5. Treatment

The rapid spread of SARS-CoV2 infection globally, has led to the immediate need for a vaccine or therapeutic intervention to prevent or treat COVID-19 disease. Due to the speed at which the virus has spread globally there are few studies on potential therapeutics interventions or vaccine candidates. Further, due to the minimal severity of the SARS (774 deaths globally) and MERS (866 deaths globally) epidemics, few studies to generate a vaccine or therapeutic for other closely related coronaviruses have been undertaken, which could have efficacy for COVID-19 disease. Clinical trials testing treatments for COVID-19 are being undertaken, results from large randomized studies though remain outstanding at this stage. As a result, the following sections are not to be mistaken as evidence based treatment recommendations, but reflect (mostly) anecdotal experience with experimental treatment, extrapolation of data from related conditions, and expert opinion (Fig. 4).

5.1. Anti-viral treatment

5.1.1. (Hydroxy-)Chloroquine

Medical use of Chloroquine dates back decades. Its phosphate and sulphate derivatives are administered as antimalarials, and hydroxychloroquine is widely used as immunomodulatory agent in systemic lupus erythematosus. In addition, chloroquine has antiviral activity against Influenza, Chikungunya virus, seasonal CoVs, and SARS [120–123]. As for these viruses, cell entry and replication of SARS-CoV2 depends on pH-dependent internalization by endocytosis and lysosomal fusion (Fig. 2). Itself being a weak base, hydroxychloroquine follows the cellular pH gradient and accumulates in the acid environment of endolysosomes and other acidic cell organelles, thereby alkalinizing endosomes. In addition, hydroxychloroquine interferes with the terminal glycosylation of ACE2, interfering with virus binding [123].

Antiviral activity of chloroquine derivatives against SARS-CoV2 was identified *in vitro* early on [124]. Based on this, the drug was rapidly introduced into clinical use, and preliminary reports suggested improved viral clearance and clinical outcomes in COVID-19 patients receiving a 10-days course of Hydroxychloroquine [125]. A small French pilot study, randomizing 36 patients with COVID-19 suggested accelerated viral clearance in patients treated with a combination of hydroxychloroquine and azithromycin [126]. However, others have challenged results and found no benefit in either disease outcome or viral clearance [127] . Disappointingly, the largest (also retrospective) study to date assessing Hydroxychloroquine on its own or in combination with azithromycin found no benefit, but indeed an increased mortality risk among patients receiving hydroxychloroquine [128]. A study exploring chloroquine diphosphate in two dosing regimens was forced to terminate early for concerns over increased mortality in the high dose arm. The authors conclude that treatment with high dose chloroquine for 10 days is not sufficiently safe and should no longer be used in severe SARS-CoV2 patients [129].

Immunomodulatory effects of hydroxychloroquine are well established, and may enhance its therapeutic effect in COVID-19 complicated by macrophage activation and cytokine storm [130]. Alkalization of endosomes reduces proteolysis, chemotaxis, phagocytosis, receptor recycling, and interferes with processing of epitopes displayed by antigen-presenting cells [131]. This overall contributes to decreased production of IL-1, IL-6 and prostaglandins, and alters intracellular calcium and TLR dependent signaling. Furthermore, preventing the acidification of lysosomes, hydroxychloroquine impairs cellular autophagy, a critical step for innate and adaptive immunity activation [132]. Finally,

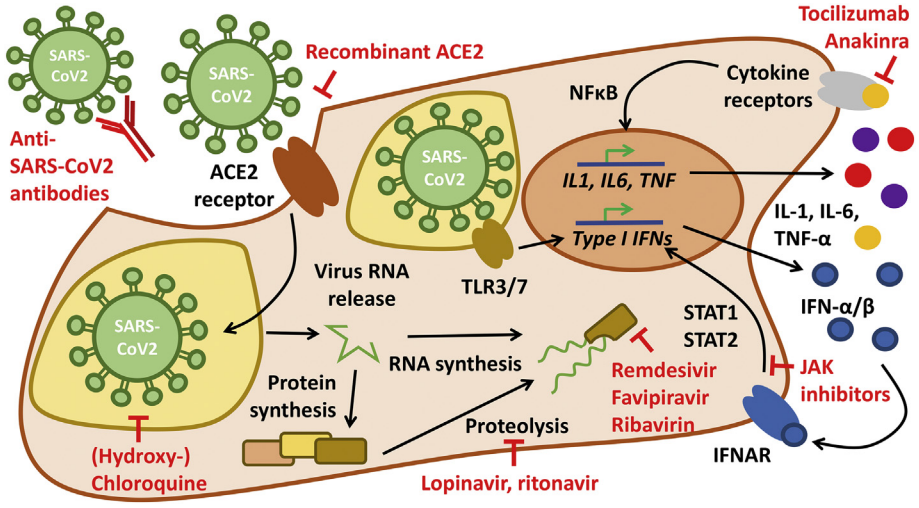

Fig. 5. Potential therapeutic targets in COVID-19. While no approved and evidence-based treatments are available for COVID-19, a number of treatments promise potential. Virus particles may be caught and inactivated using antibodies from convalescent patients. Recombinant soluble ACE2 protein may bind SARS-CoV2 and/or mediate anti-inflammatory effects to prevent pulmonary damage and hyper-inflammation. (Hydroxy-)chloroquine, potentially in combination with azithromycin), can change the pH of endosomes and reduce virus entry and replication. Furthermore, both medications have immune-modulating effects that may control pro-inflammatory cytokine expression. Anti-viral treatment with protease inhibitors (lopinavir, ritonavir, etc.) and/or nucleoside analogues (remdesivir, etc.) can limit virus replication. As SARS-CoV2 suppresses antiviral cytokine production, virus clearance may also be supported by the substitution of type 1 interferons, which activate their cytokine receptor (IFNAR) and induce anti-viral cellular programs. Hyperinflammation and resulting tissue damage may be prevented through immune modulation. Blocking IL-1 signaling (e.g. through recombinant IL-1 receptor antagonist anakinra) or IL-6 signaling (e.g. through IL-6 receptor antibody tocilizumab) may limit further immune activation, tissue damage and cytokine storms. Additional, less specific effects may be mediated through corticosteroids, immunoglobulins, hydroxychloroquine and/or azithromycin.

hydroxychloroquine has antithrombotic effects, which may be beneficial in COVID-19, where inflammatory stimuli and endothelial injury activate coagulation and promote micro-thrombus formation [133,134].

While generally deemed safe when administered at correct dosing and under close monitoring, the therapeutic range of chloroquine and its derivatives is narrow. Side effects include conduction defects, cardiomyopathy, retinopathy and hypoglycemia [135,136].

5.1.2. Azithromycin

As mentioned above, synergistic effects of azithromycin and hydroxychloroquine against SARS-CoV2 have been observed *in vitro,* which appeared to translate into clinical practice [126,137,138]. Interestingly, azithromycin is also a weak base, and also accumulates in endosomes, with an alkalinizing effect at least equivalent to Hydroxychloroquine. In addition to its antimicrobial properties, azithromycin is sometimes used for its immunomodulatory properties, especially in patients with chronic pulmonary disorders. Azithromycin polarizes macrophages towards an anti-inflammatory M2 phenotype, and inhibits pro-inflammatory STAT1 and NFκB signaling pathways [139,140]. In the context of anti-inflammatory effects, it is of particular interest that azithromycin is used in patients requiring intensive care for non-COVID-19 related ARDS and is associated with a significant reduction in mortality and shorter time to extubation [141–143].

Adverse cardiac effects and proarrhythmogenic properties of hydroxychloroquine, especially in combination with macrolide antibiotics, such as Azithromycin, deserves particular mention [144]. Hydroxychloroquine, azithromycin and, to a lesser extent, lopinavir have been associated with prolongation of the QTc interval and increase the risk for tachyarrhythmias and sudden cardiac death. Careful consideration of patient risk profile, pre-treatment ECG assessment and monitoring of pharmacokinetics, fluid and electrolyte status and polypharmacy are essential for the management of critically ill COVID 19 patients [145].

5.1.3. Remdesivir and other nucleoside analogues

Nucleoside analogues are explored as treatment options for COVID-19. Candidates include favipiravir, geldesivir, ribavirin, and remdesivir, with the latter having received the most attention. Remdesivir, a prodrug to adenosine [146], was originally developed for the treatment of hemorrhagic fever viruses, namely Ebola (EBOV) and Marburg viruses, but underperformed in EBOV treatment compared to antibody strategies. Both have antiviral *in vitro* activity in MERS and SARS [147,148]. Competing with ATP and substituting for adenosine during RNA synthesis, remdesivir inhibits the viral RNA dependent RNA polymerase (RdRp) [149]. Human mitochondrial RdRp show significantly lower affinity to remdesivir as compared to their viral counterparts, mitigating side effects for the host cell [150].

The presence of CoV-specific, proof-reading exonucleases capable of removing phosphorylated remdesivir from the RNA chain could present a potential for development of resistance. Remdesivir treatment for murine hepatitis virus in a mouse model showed that, while conferring resistance, the trade-off in viral fitness was of a magnitude sufficient to significantly attenuate viral pathogenicity [147]. The timing of administration in animal models of EBOV and MERS was crucial for remdesivir's efficacy, with most benefit achieved when given early [148]. This is in keeping with aforementioned phases of the disease with highest virus replication rates early in disease, and host-mediated damage through immune responses at later stages. A recent case report, however, highlights persisting benefits also if late administration [151].

Remdesivir underwent *in vitro* testing at the Wuhan Virus Research Institute early during the SARS-CoV2 outbreak [124], and was identified as potently inhibiting viral infection in cell cultures at concentrations readily achievable *in vivo*. It was first used successfully in a COVID-19 patient in January 2020 [152]. Since, remdesivir has been employed on a compassionate use basis, and results for its use as a 10 day course reported for 53 patients with SARS-CoV2, 34 of whom required ECMO [4] or mechanical ventilation [30] at baseline [153]; significantly reducing mortality. Assessment in randomized controlled trials is needed, two of which had been in place in China for the treatment of moderate to severe COVID-19, with recruitment terminated in March following declaration of containment (NCT04257656; NCT04252664). Trials are currently ongoing in Europe and North America. With effective reduction of pulmonary viral load in animal models, an acceptable safety profile in Ebola patients and a small group of COVID-19 patients, remdesivir may offer an effective and viable future treatment option.

5.1.4. Protease inhibitors Lopinavir/ritonavir (LPV/r)

The combination of lopinavir and ritonavir (LPV/r), better known by tradenames Aluvia® and Kaletra®, is a frequently used antiretroviral treatment for HIV. Combining two protease inhibitors limits otherwise extensive CYP3A4 activation and drug metabolism, thereby resulting in much improved bioavailability of LPV [154]. Proteases are critical for

viral replication, as they cleave both structural and functional proteins from precursor viral polypeptides (Fig. 5), thus enabling maturation into an infectious virion particle. LPV/r is mainly metabolized in the liver, and thus pre-existing hepatic impairment is considered a relative contraindication [154].

In SARS, LPV/r in combination with Ribavirin was associated with a significant reduction in unfavorable outcomes (ARDS and death) as compared to ribavirin alone (2.4% versus 28.8%) [155]. Similar observations were made in a retrospective cohort study involving > 1000 SARS patients, where LPV/r was associated with significantly reduced mortality and need for intubation [73,156]; and it is currently being investigated by the WHO for use in MERS patients in an ongoing randomized clinical trial. Early use of LPV/r was recommended, based on aforementioned pathophysiological considerations rather than clinical data.

In view of the *in vitro* activity against both SARS and MERS and the limited clinical data available for LPV/r in treatment of critically ill SARS-CoV2 patients, a randomized open-label trial was undertaken in Wuhan, China [157]. It recruited almost 200 COVID-19 patients, randomized to either standard treatment or added LPV/r for 14 days. Whilst confirming safety of LPV/r use in COVID-19, no significant differences were seen between groups in relation to survival or time to recovery; thus leaving the authors question whether a combination of LPV/r with a nucleoside analogue, such as ribavirin, would have resulted in improved outcomes. Trials exploring the therapeutic potential for LPV/r are currentlyongoing (https://www.remapcap.org/coronavirus; https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments).

5.1.5. Recombinant soluble ACE2

As ACE2 has been identified as a key molecule for cell invasion (see above), its therapeutic blockade to control disease and aid viral clearance has been suggested [158]. However, unselective ACE blockade with currently available agents may be problematic as it could alter angiotensin-1 through -7, which have anti-inflammatory and anti-fibrotic properties [159]. Indeed, depletion of ACE2 by SARS-CoV2 may potentially contribute to increased disease activity in critically ill COVID-19 patients. In animal studies, ACE2 protects from ARDS [160–162], while angiotensin II contributes to pulmonary pathology, including edema and fibrosis [163]. Thus, accumulation of angiotensin II in the absence of ACE2 may aggravate disease and organ damage. Consequently, ACE2 induction has recently been suggested for COVID-19 treatment [85,159,164,165] . However, effects of ACE2 may vary between tissues and environments. Intestinal epithelia produce much higher levels of ACE2 than bronchial epithelia which is notable as not all patients develop gastrointestinal symptoms and when they do, symptoms tend to be mild, and some patients remain SARS-CoV2 positive in stool samples long after respiratory specimen became negative [78,166–168] . Based on these observations, one could suggest that high-level ACE2 expression such as that seen in the intestine and in contrast to the respiratory tract, or in children and young people as compared to individuals at risk (the elderly, especially when obese or chronically ill), may protect from inflammation and tissue damage. However, additional factors, such as the immunological micro-environment or regionally variable microbiomes may significantly affect virus uptake, replication and/or clearance. Thus, the exact role(s) of ACE2 in the context of COVID-19 remains to be unveiled and may be complex.

The administration of recombinant human ACE2 to neutralize virions prior to their attachment to the host cells is also being explored as a therapeutic option in the future. In the attempt of exploiting the anti-inflammatory effect of the ACE2/ Ang- [1–7]/Mas axis in non-COVID-19 related ARDS, first pilot trials in humans have been published [169], and whilst data supporting its efficacy as an ARDS treatment option remains outstanding, the treatment appeared safe and was well tolerated.

5.1.6. Type 1 interferons

As mentioned above, SARS-CoV2 effective inhibits the expression of type 1 interferons [38]. Resulting tissue damage and expression of pro-inflammatory cytokines and chemokines from infected monocytes/macrophages promote excessive immune cell infiltration and cytokine responses [114]. More recently, also abortive infection in T lymphocytes with SARS-CoV2 has been suggested [170], but detailed characterization remains outstanding. Altogether, unaltered virus replication in the presence of tissue damage and inflammatory cytokine expression can explain ARDS and cytokine storms in COVID-19. Overcoming immune evasion and enhancing antiviral activity may be a logical treatment strategy.

In SARS and MERS patients, recombinant interferons have been used with varying success. While antiviral activity of recombinant IFN-α2a, IFN-α2b, IFN-β1a and IFN-β1b was shown *in vitro* for MERS, SARS and SARS CoV2, neither mortality nor viral clearance were affected by recombinant interferons in MERS [171,172]. However, the time of administration may be critical, as suggested by a mouse model of IFN I treatment for MERS [173], therefore human patients may have received treatment too late to be fully effective.

5.1.7. Plasma from convalescent patients

Convalescent plasma, i.e. plasma from individuals following COVID-19 resolution and rich in immunoglobulins directed against SARS-CoV2, is being entertained as possible treatment option [174,175]. Anecdotal use in SARS, MERS, Ebola and Influenza patients supports its use as a neutralizing and/or immunomodulatory agent [176,177]. However, a larger randomized controlled assessment of hyperimmune intravenous immunoglobulin use for severe influenza [178,179] and Ebola [180] showed this intervention to not be superior to placebo. Similarly, rigorously evaluated data for its use in coronaviral infections is lacking - not only for its use in SARS-CoV2 [181], and a feasibility study exploring its use in MERS found that in many survivors, antibody titres were not high enough, thus further limiting the donor pool [182]. Variable dosing, issues surrounding donor recruitment in times of rapidly increasing patient numbers, and drawbacks regarding safety of widespread use of human blood products all limit the availability and utility as widely available treatment option.

Finally, in viruses that are subject to ADE (such as SEARS-CoV2, see above) by non-neutralizing antibodies, the option of plasma therapy also holds significant risks. This complication has recently been exemplified by anti-Zika virus antibodies enhancing Dengue virus infection [183]. Thus, the administration of hyperimmune/convalescent plasma may carry the risk of significant illness upon future exposure to related or yet-to-emerge coronaviruses.

5.2. Calming the cytokine storm through immune modulation

As mentioned above, current management of COVID-19 is mainly supportive and approved treatments based on scientific evidence are not available. Main causes of death include ARDS and cytokine storm syndrome (also referred to as macrophage activation syndrome, MAS or secondary Hemophagocytic histiocytosis, HLH) [74,92,106,107]. Indeed, ARDS occurs in 50% of patients with cytokine storm syndrome [184]). Considering impressively rapid development of systemic and pulmonary inflammation in a subset of patients with COVID-19, early identification and control of derailed immune responses is of utmost importance. Based on data from Chinese cohorts, markers associated with cytokine storm in other conditions may be predictive of poor outcomes in COVID-19, which include leukopenia, lymphopenia, thrombopenia, hypoalbuminemia, significantly elevated CRP and IL-6, hyperfibringenemia, and prolongedthrombin time [74,185,186]. However, this needs to be tested prospectively, and other more sensitive and specific biomarker may be identified.

First data on cytokine storm syndrome and its catastrophic effects on tissues and organs was generated in patients with familial HLH, in which mutations in associated genes (including *PRF1, UNC13D, STX1, STXP2, LYST, XIAP*, and others) result in systemic inflammation and, if not controlled, death [109]. Standard treatment in these conditions include high-dose corticosteroids (dexamethasone), the calcineurin inhibitor cyclosporine A, chemotherapy with etoposide, and ultimately stem cell transplantation [187]. While the underlying molecular causes of familial HLH are different to COVID-19 associated cytokine storm syndrome, clinical (fevers, organomegaly in some patients) and laboratory features (cytopenias, massively elevated inflammatory parameters including CRP, ESR and ferritin, hypalbuminemia, hyperfibrinogenaemia, etc.) and consequences (tissue and organ damage, death) overlap. Furthermore, based on observations in the H1N1 influenza pandemic in 2009, a significant proportion of individuals developing disease-associated secondary cytokine storm syndrome may have mutations in one or more genes associated with familial HLH (in H1N1 36% of fatalities were associated with mutations in genes associated with the perforin pathway [188].Thus, clinical management of COVID-19 associated cytokine storm syndrome may, to some extent, be informed by what we know from familial HLH. However, treatment of COVID-19 associated cytokine storm should be more targeted and not include cytotoxic drugs and/or stem cell transplantation, as it is secondary to an infection, which will hopefully be cleared.

Corticosteroids are used in primary and secondary forms of HLH, and can control inflammation in ARDS [91,189]. First preliminary data from SARS and COVID-19 suggest that high-dose steroids did not have beneficial effects on lung injury [190,191]. Instead, high-dose corticosteroids are associated with complications in other forms of ARDS, including avascular osteonecrosis [192]. Short courses of low- or medium-dose corticosteroids, however, have been suggested to be of benefit in a Chinese cohort of critically ill COVID-19 patients [193]. Taken together, the limited data on the efficacy and safety of corticosteroids in ARDS are anecdotal and not conclusive; controlled trials do not exist. As their use is associated with widely variable effects on pathogen clearance, and evidence for their efficacy is lacking, high-dose corticosteroids cannot be generally recommended for the treatment of COVID-19 [194], and the use of low dose regimens must be trialed in formal and controlled studies.

Intravenous immunoglobulins (IVIG) are used in systemic autoimmune/inflammatory conditions to control systemic inflammation through several mechanisms, including the capture of activated complement factors, blockade of Fcγ receptors, inhibition of B and T lymphocyte differentiation and activation, neutralisation of cytokines and antibodies, etc. [195]. As mentioned above, immune complexes containing viable virus may mediate infection, activate Fcγ receptors, and/or be deposited in tissues and organs, lastly resulting in pro-inflammatory responses [196]. Of note, ARDS and cytokine storm in SARS coincided with serum conversion in a majority of patients supporting these arguments. Furthermore, patients who ultimately died, seroconverted significantly earlier when compared to individuals who recovered from infection [40,197]. Based on these observations, IVIG may be of benefit to some patients by inhibiting Fcγ receptors and limiting antibody-dependent enhancement (discussed above). Furthermore, aforementioned “classical” anti-inflammatory effects may limit systemic inflammation, and anti-pathogen properties may be supportive in cases with bacterial superinfection or in patients who previously cleared SARS-CoV2 and developed specific antibodies [186,198].

The blockade of cytokines associated with hyper-inflammation during COVID-19 is a more targeted approach when compared to the use of systemic corticosteroids, and is a promising therapeutic avenue. Indeed, first anecdotal reports suggest efficacy at least in some patients.

The IL-6 receptor antagonist tocilizumab has been used successfully in patients with secondary cytokine storm syndrome [199], including COVID-19 [200,201]. Several studies have started or are about to be launched, investigating efficacy and safety of tocilizumab in patients with secondary cytokine storm syndrome in COVID-19 (including ChiCTR2000029765 in China) [202].

The recombinant IL-1 receptor antagonist anakinra was originally developed to control cytokine storm and associated tissue damage in sepsis patients [203]. Subsequently, anakinra has successfully been used in patients with cytokine storm syndrome secondary to autoimmune/inflammatory [204,205] infectious or malignant disease [206]. Anakinra may have significant potential at controlling hyperinflammation in severe COVID-19 disease, considering the absence of severe side-effects in aforementioned sepsis trials [203], and reduced frequency of neutropenia and hepatotoxicity when compared to tocilizumab. Currently, anakinra is being trialled in a randomised placebo-controlled study in children and adults with COVID-19 associated cytokine storm syndrome in China (NCT02780583) [91].

Inhibition of Janus kinases (JAK) with small molecules is a relatively new concept used in systemic autoimmune/inflammatory conditions. JAKs are involved in cytokine receptor signaling, including (but not limited to) the IL-6 receptor, as well as type 1 and type 2 IFN receptors [91,207]. They mediate the phosphorylation of STAT family transcription factors which are, in turn, involved in pro-inflammatory cytokine expression. Thus, JAK inhibitors efficiently limit cytokine expression, and may aid in controlling cytokine storms [91]. However, JAKs are also centrally involved in controlling the expression of T1IFN, which plays a key role in limiting virus replication and initiating pathogen clearance [208]. At least in the initial stages of COVID-19 disease, when virus replication and infection may be limited to the epithelium, SARS-CoV2 likely limits T1IFN expression (see above). Therefore, additional inhibition of JAK through small molecules may be counterproductive as they further limit pathogen containment and clearance, and may cause unforeseeable complications. Thus, JAK inhibition may not be the most suitable “target-directed” treatment option in COVID-19 associated cytokine storm syndrome and/or ARDS. To our knowledge, at least two clinical trials are ongoing to test efficacy and safety of JAK inhibitors in severe COVID-19 (ChiCTR2000030170, ChiCTR2000029580).

6. COVID-19 in patients receiving immune modulating treatment

The previously discussed mechanisms of infection, immune evasion, and dysregulation of innate and adaptive immune responses cause significant concern for and among patients on systemic immune modulating treatments, including patients with malignant or systemic autoimmune/inflammatory diseases. Based on previous coronavirus outbreaks (SARS and MERS) and first small observational studies in COVID-19 cohorts, risk factors for poor outcomes include old age, presence of comorbidities (diabetes, metabolic syndrome, etc.), obesity, male sex, coronary heart disease, chronic obstructive pulmonary disease, and kidney disease [209]. Of note, immune modulation or suppression was not identified as a risk factor for poor prognosis in China or Italy [186,210]. While this could generally be considered “good news”, immune suppression and associated altered immune function may predispose patients to infection and potentially prolong virus spreading. Furthermore, as COVID-19 is associated with lymphopenia, patients receiving immune modulating treatment may be prone to secondary infections, such as bacterial pneumonia.

As discussed above, some immune modulating drugs may protect from viral infections. Antimalarial drugs (chloroquine, hydroxychloroquine) may inhibit tissue infection and viral replication [53,103]. Furthermore, immune modulating medications (anti-malarial drugs, classical as well as biologic DMARDs, and others) may prevent or control cytokine storm syndromes.

Uncontrolled discontinuation of immune modulating treatment may result in disease flares in autoimmune/inflammatory conditions, organ rejection in transplant patients, or reoccurrence of malignancies, which (on top of obvious effects) may also all increase the risk for viral infection. Thus, national and international societies, including the ACR

and EULAR, recommend continuation of treatment in the absence of symptoms and alterations to existing treatment regimens only in agreement with and under close monitoring by the responsible clinical service [211,212]. International collaboration is needed and under way to safely assess individual risk in these vulnerable patient groups. Until reliable data is available, close clinical monitoring and social distancing should be prioritized.

7. Conclusions

As immunity does not exist and a significant proportion of humans develop severe disease, the novel coronavirus SARS-CoV2 is a threat to millions globally. SARS-CoV2 has the capacity to escape innate immune responses, which allows the pathogen to produce large copy numbers in primarily infected tissues, usually airway epithelia. Through the infection of innate immune cells and/or the recruitment of uninfected cells from the circulation to the primary site of infection, massive immune reactions induce hyperinflammation that can result in a cytokine storm and life-threatening complications. We are only beginning to understand host factors, such as differential expression of cell surface proteins that may determine infection risk, disease presentation and outcomes. Unveiling tissue and stage specific factors contributing to pathology will result in new, effective and disease stage specific therapeutic approaches that control virus replication while limiting inflammatory damage until vaccinations become available.

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