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Targeting thromboinflammation in COVID-19 – A narrative review of the potential of C1 inhibitor to prevent disease progression

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is associated with a clinical spectrum ranging from asymptomatic carriers to critically ill patients with complications including thromboembolic events, myocardial injury, multisystemic inflammatory syndromes and death. Since the beginning of the pandemic several therapeutic options emerged, with a multitude of randomized trials, changing the medical landscape of COVID-19. The effect of various monoclonal antibodies, antiviral, anti-inflammatory and anticoagulation drugs have been studied, and to some extent, implemented into clinical practice. In addition, a multitude of trials improved the understanding of the disease and emerging evidence points towards a significant role of the complement system, kallikrein-kinin, and contact activation system as drivers of disease in severe COVID-19. Despite their involvement in COVID-19, treatments targeting these plasmatic cascades have neither been systematically studied nor introduced into clinical practice, and randomized studies with regards to these treatments are scarce. Given the multiple-action, multiple-target nature of C1 inhibitor (C1-INH), the natural inhibitor of these cascades, this drug may be an interesting candidate to prevent disease progression and combat thromboinflammation in COVID-19. This narrative review will discuss the current evidence with regards to the involvement of these plasmatic cascades as well as endothelial cells in COVID-19. Furthermore, we summarize the evidence of C1-INH in COVID-19 and potential benefits and pitfalls of C1-INH treatment in COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a pandemic leading to significant stress on healthcare systems worldwide with a massive human and economic toll.

The World Health Organization estimates SARS-CoV-2 to have led to almost 500'000'000 cases worldwide and over 6 million deaths globally.

The clinical spectrum of coronavirus disease 2019 (COVID-19) ranges from asymptomatic carriers to critically ill patients who require intensive care medicine support, mainly due to respiratory failure, but also due to associated complications including thromboembolic events, myocardial injury or multisystemic inflammatory syndromes (Yordanov et al., 2021). Early in this pandemic Siddiqi et al. suggested a disease stage model for COVID-19 (Fig. 1). Stage I (mild infection) is characterized by infection and replication of SARS-CoV-2 in the respiratory system. In stage II patients develop viral pneumonia which is characterized by a localized inflammatory response. About 20% of stage II patients have been described to progress to the most severe stage of illness (stage III), which is characterized by marked systemic inflammation leading to acute respiratory distress syndrome (ARDS). These patients usually require admission to the intensive care unit (Siddiqi and Mehra, 2020).

The exact reasons and factors promoting disease progression are not entirely understood. However, a systemic hyperinflammatory syndrome is a major driving factor for the development of severe pneumonia and detrimental outcomes. SARS-CoV-2 infection is associated with lymphopenia, a decrease in suppressor and regulatory T-cell counts and an extensive release of proinflammatory cytokines and markers of

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thromboinflammation such as interleukin (IL)– 1, IL-2, IL-6, ferritin, LDH and D-dimer (Giamarellos-Bourboulis et al., 2020; Qin et al., 2020; Wu et al., 2020; Zhou et al., 2020, 2020). Hyperactivation of the host immune system is only partially understood. Immune cells and inflammatory plasmatic cascades such as the complement (CS) and the contact activation system (CAS) are activated. In particular, the complement system has been implicated in both, localized and systemic inflammation after SARS-CoV-2 infection (Holter et al., 2020; Magro et al., 2020b). Local activation and injury of endothelial cells combined with hypercoagulability and involvement of the formerly mentioned cascades were linked to thromboembolic complications observed in many patients with COVID-19 (Tan et al., 2021).

A number of treatment options have been developed and are now recommended during different stages of the disease, based on large randomized controlled trials. These include antiviral, anti-inflammatory and anticoagulation drugs. Prophylactic anticoagulation is universally administered depending on the individual risk of thromboembolic complications. However, the majority of clinical trials assessing therapeutic anticoagulation and antiplatelet agents have failed to show a significant benefit in COVID-19 (Connors and Ridker, 2022). Lastly, the fact that broad anti-inflammatory agents such as systemic corticosteroids, JAK-inhibitors and interleukin-6-receptor-antagonist have been associated with improved survival in randomized controlled trials underscore the impact of an overreacting immune system after SARS-CoV-2 infection.

Despite their involvement in COVID-19, treatments targeting more specific components of plasmatic cascades such as proteins of the CS, kallikrein-kinin system (KKS) or CAS have been scarcely investigated. This narrative review provides an overview about the role of the plasmatic cascades in thromboinflammation after SARS-CoV-2 infection and discusses potential beneficial effects of C1 inhibitor (C1-INH), the natural multi-target inhibitor of the above mentioned cascades, in patients with moderate to severe COVID-19.

2. The role of the complement system in COVID-19 – marker or driver of severe disease?

The CS is an integral part of the innate immune system and consists of several distinct plasma proteins that act as a first line of defense triggering an inflammatory response after opsonization of pathogens and dying cells (Fig. 2) (Walport, 2001a,2001b). Inflammatory responses include the activation of macrophages, neutrophils, platelets and endothelial cells, interacting with other plasmatic cascades such as the coagulation cascade and direct cell injury, thereby increasing vascular permeability and tissue injury.

The CS and particularly the lectin pathway of complement have been found to interact with several viruses and are involved in their clearance (Bermejo-Jambrina et al., 2018; Bibert et al., 2019; Kase et al., 1999; Schiela et al., 2018; Thielens et al., 2002). Some authors consider complement activation as beneficial during the early stage of infection but harmful at later stages (Swierzko and Cedzynski, 2020). While the CS is not critical for controlling corona virus (CoV) replication, unregulated complement activation – induced by viruses including influenza and CoV – plays a crucial role in the pathogenesis of acute lung injury (ALI). Indeed, the CS was identified as central mediator of SARS-CoV-induced lung disease and regulator of the proinflammatory response in experimental models. Mice deficient in complement C3 were affected less severely and showed a reduced lung involvement and lower local and systemic cytokine levels compared to control mice, when infected with SARS-CoV-1 (Gralinski et al., 2018). In line, inhibition of complement C5a signaling alleviated lung damage in experimental MERS-CoV and influenza H7N9 infections (Jiang et al., 2018; Sun et al., 2015). Similar results were reported with inhibition of complement protein C3a after avian influenza infection (Sun et al., 2013). Conversely, $C3^{-/-}$ mice had increased inflammation and morbidity after influenza infection underscoring the concept of complement contributing to the protection from influenza viruses (O'Brien et al., 2011). Regarding SARS-CoV-2, Holter et al. (2020) showed an association between systemic complement activation and respiratory failure in COVID-19 patients in a prospective cohort study. Of note, sustained complement activation throughout admission was demonstrated in these COVID-19 patients. Similarly, the RCI-COVID-19 study group demonstrated an association between increased complement activation and increased mortality and thromboembolic complications (de Nooijer et al., 2020).

Already prior to the COVID-19 era, C5a has been considered to play a significant role in ARDS and virus-induced ALI (Hammerschmidt et al., 1980). It attracts lymphocytes, mediates neutrophil extracellular traps, promotes the release of reactive oxygen species and mediates upregulation of adhesion molecules and histones (Wang et al., 2015). In

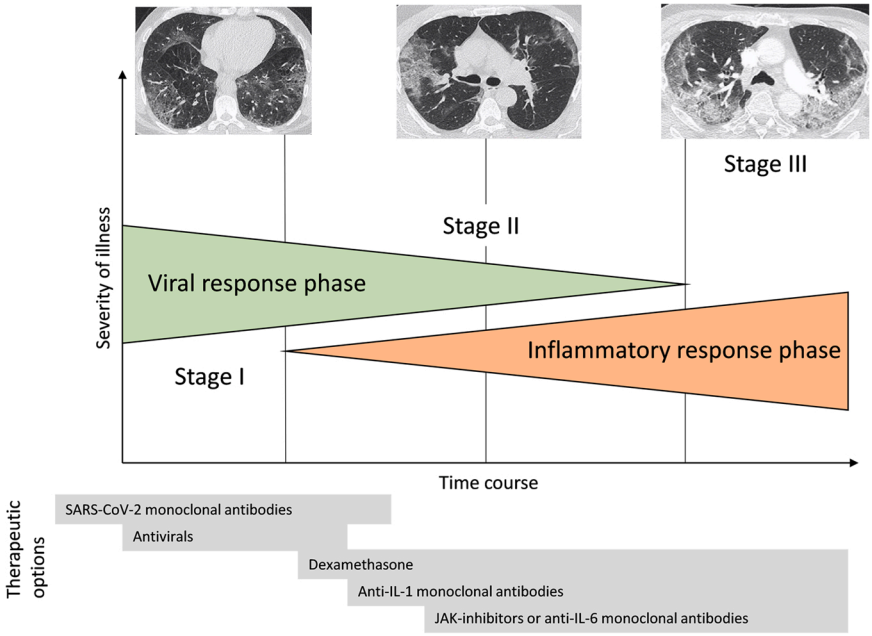

Fig. 1. Disease stages and established therapeutic options. Chest computed tomography scans showing ground-glass opacities and consolidations during different disease stages. While SARS-CoV-2 monoclonal antibodies and direct antivirals have demonstrated reduced hospitalization rates and improved outcomes during the early viral response phase and including moderately affected hospitalized patients, immunomodulatory drugs reduce the requirement of mechanical ventilation and death in moderate to severe disease and critically ill individuals. Scans from Urwyler P. et al. Treatment of COVID-19 With Conestat Alfa, a Regulator of the Comlement, Contact Activation and Kallikrein-Kinin System. Front Immunol. 2020.
Figure adapted from Siddiqi HK and Mehra MR. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. J Heart Lung Transplant. 2020. Abbreviations: IL, interleukin.

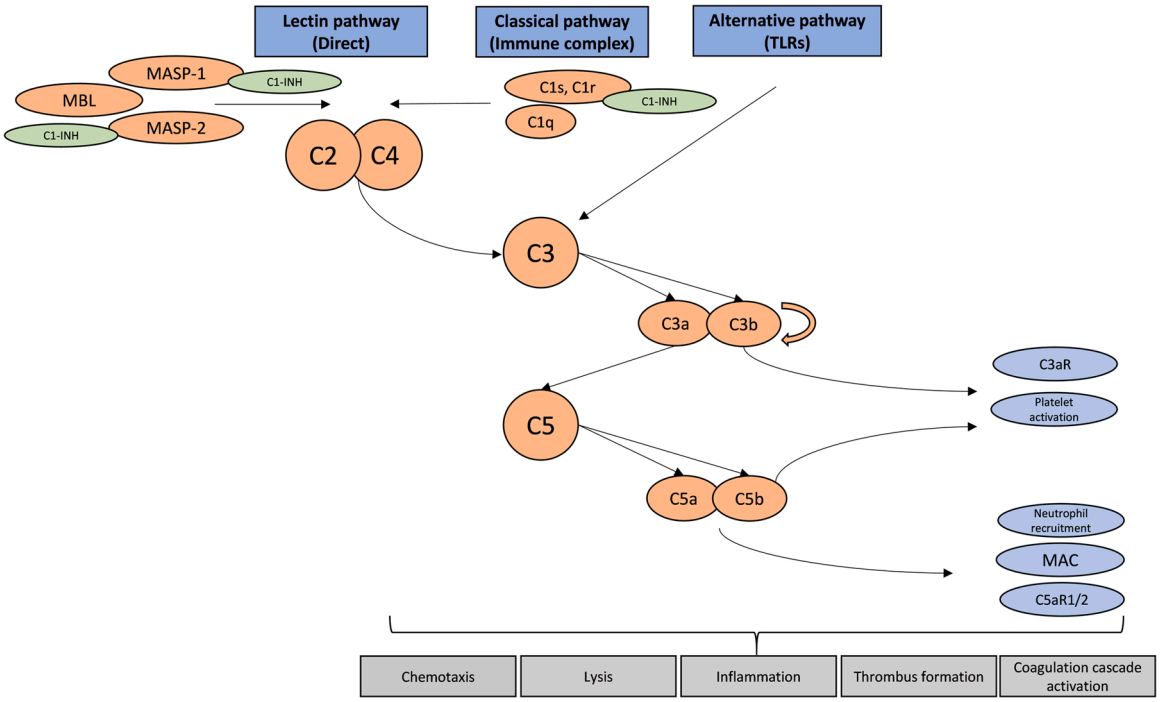

Fig. 2. Simplified illustration of key players of the complement system in COVID-19. Activation of the complement system is initiated by three distinct activation pathways via direct binding to pathogens/dying cells (lectin pathway), binding to immune complexes (classical pathway) and after toll-like receptor (TLR) activation, contact with various proteins, lipids and carbohydrate structures or spontaneous hydrolysis (alternative pathway). After binding, proteases of the classical and lectin pathway generate a common C3 convertase (C4b2a). The alternative pathway also acts as amplification pathway. Consequently, the C5 convertase cleaves C5 to bioactive fragments C5a and C5b. The latter forms the membrane-attack-complex (MAC), while C5a is involved in the recruitment of neutrophils and binding to its membrane bound receptors (C5aR). Abbreviations: C1-INH: C1 inhibitor; C3aR, complement component C3a receptor; C5aR1/2, complement component C5a receptor 1 and 2; MASP, mannose-binding lectin associated serine protease.

addition, interaction of C5a with its receptor C5aR1 was recently shown to induce endothelial dysfunction and a prothrombotic phenotype leading to platelet activation and aggregation (Aiello et al., 2022). Of note, serum from COVID-19 patients induced significant formation of the membrane attack complex on endothelia cells and had a strong prothrombotic effect in vitro in this study. Increased soluble C5a levels were associated with disease severity in patients with pneumonia ARDS due to SARS-CoV2 (Carvelli et al., 2020). Furthermore, increased C5aR1 expression in blood and pulmonary myeloid cells was identified and ALI prevented in human C5aR1 knock-in mice when treated with anti-C5aR1 monoclonal antibodies. Taken together inflammatory lung tissue damage in COVID-19 is at least partially mediated and aggravated by an activated complement system.

An obvious next question is which of the three complement pathways is primarily responsible for downstream complement activation. Binding of mannose-binding lectin (MBL), a pattern recognition protein of the lectin pathway, to SARS-CoV-2 with subsequent complement activation has been demonstrated first (Ali et al., 2021; Gao et al., 2020; Magro et al., 2020a; Malaquias et al., 2021; Stravalaci et al., 2022). MBL recognized the S protein of SARS-CoV-2 including of variants of concern in a glycan dependent manner and inhibited viral entry into lung epithelial cells (Stravalaci et al., 2022). The *MBL2* gene on chromosome 10 is characterized by a high frequency of single nucleotide polymorphisms in the promotor and exon 1 region which form seven common haplotypes as a consequence of linkage disequilibrium (Garred et al., 2006). These haplotypes are often grouped according to their associated MBL protein concentrations into high, medium and low activity haplotypes. Conflicting results regarding the association of MBL activity and SARS-CoV-2 outcome have been reported (Charitos et al., 2021; Hultstrom et al., 2022; Stravalaci et al., 2022). Recently, Hultström M et al. described a U-shaped association between MBL haplotypes and thrombotic complications/pulmonary embolism. They speculate, that high MBL activity may predispose to excessive complement activation and subsequent thrombosis (Eriksson et al., 2019; Hultstrom et al., 2022; Pavlov et al., 2015), whereas an increased thrombosis risk in individuals with low MBL activity is driven by the failure to remove SARS-CoV-2 and prevent subsequent endothelial cell activation and thrombosis. Along the same lines, an interaction of highly pathogenic CoVs (MERS-CoV, SARS-CoV-1 and SARS-CoV-2) with mannose-binding lectin associated serine protease-2 (MASP-2), the key activator of the lectin pathway of complement (Heja et al., 2012), was demonstrated leading to uncontrolled activation of the complement cascade (Gao et al., 2020). MASP-2 knock-out mice and mice treated with MASP-2 inhibitors including C1-INH showed significantly milder symptoms in a virus protein mouse pneumonia model. Mannose-binding lectin (MBL), the pattern recognition molecule of the lectin pathway, that activates MASP-2 upon binding to pathogens, was found to bind to SARS-CoV-1 spike glycoprotein (Zhou et al., 2010). In COVID-19 patients, MBL levels strongly correlated with D-Dimer levels indicating a potential link to activated coagulation (Eriksson et al., 2020). Interestingly, spike and nucleocapsid derived proteins have been reported to propagate inflammatory processes themselves. *In vitro,* Perico et al. (2022) showed SARS-CoV-2-derived spike protein 1 to induce a proinflammatory phenotype and lead to excessive C3 and C5b-9 deposition on endothelial cells alongside with C3a and C5a generation. Ali et al. (2021) furthermore showed a direct binding capability of the N-protein to the lectin pathway effector MASP-2 and subsequent complement activation. Interestingly, a MASP-2 inhibitory monoclonal antibody was able to block this LP-mediated complement activation. On the other hand, analyses of patient samples from our and other centers did not confirm an active role of the lectin pathway in disease progression to severe COVID-19 and pointed mainly towards an overactivated alternative pathway, at least in critically ill COVID-19 patients (Charitos et al., 2021; Sinkovits et al., 2021). In line, the S protein of SARS-CoV-2

was shown to directly activate the alternative pathway (Yu et al., 2020), and recent data from Canadian ICU patients suggested markers of the alternative pathway to correlate with hypoxemia and predict in-hospital mortality, and a history of macular degeneration (often associated with complement-activating genetic polymorphisms in alternative pathway genes) was identified as risk factors for SARS-Cov-2-associated mortality (Leatherdale et al., 2022; Ramlall et al., 2020). The S protein of SARS-CoV-2 was also shown to directly activate the alternative pathway (Yu et al., 2020), and circulating immune complexes may activate the classical pathway (Castanha et al., 2022) in line with results from autopsy studies (Macor et al., 2021).

Underscoring the close interplay between plasmatic cascades and cellular immunity, the CS induced activated CD16(+) cytotoxic T cells via C3a (Georg et al., 2022). Proteomic analyses from sera of COVID-19 patients showed increased levels of multiple proteins involved in the acute phase response, particularly in patients with increased IL-6 levels. Amongst others, increased levels of clusters of proteins related to the coagulation and complement cascade have been observed (D'Alessandro et al., 2020).

COVID-19 is not only a pulmonary inflammatory disease, but several organs are usually affected during moderate to severe disease. Apart from lung injuries cardiovascular inflammation due to high expression of ACE2 has been postulated in COVID-19. The CS was implicated in myocardial dysfunction via C5a and MAPK in a polymicrobial sepsis model (Fattahi et al., 2017). Multiorgan affection by the CS has also been shown in autopsies of patients who died of COVID-19 not only in lung tissue but also in specimens of the kidney and the liver. Lung deposits of C1q, C4, C3 and C5b-9 in this study showed similar distribution as IgG (Macor et al., 2021). Other autopsy findings from a subgroup of patients with severe COVID-19 infection revealed excessive complement activation in the lung tissue associated with complement mediated microthrombotic disease (Magro et al., 2020b). The lectin pathway of complement was implicated as major complement pathway in these patients. Data from our center confirm the presence of endothelial damage and pulmonary microthrombi (Menter et al., 2020). Findings from Brazil showed amongst others higher IL-6, TNF-alpha and MBL expression in COVID-19 lung tissue compared to patients with influenza H1N1 and control groups, suggesting a link to worse outcome (Malaquias et al., 2020). Importantly, MASP-1 and MASP-2 may interact with the coagulation cascade and have been shown to induce clot formation in humans, in particular in a prothrombotic environment (Jenny et al., 2018; Kozarcanin et al., 2016).

In summary, whilst activation of the CS may only be regarded as a potential surrogate marker of severe disease, we do believe, that the evidence indicates that an over-activated complement system contributes to ALI and generation of microthrombi in response to infection with SARS-CoV-2, leading to the clinical picture of severe COVID-19.

3. The role of the contact activation and kallikrein-kinin system in COVID-19

Since the beginning of the pandemic, bradykinin has been discussed as a potential driver of lung inflammation in COVID-19. The KKS is a plasmatic cascade that involves the cleavage of kininogen by kallikrein in response to the activation of this system (shear stress of vessels, e.g. during vascular inflammation) and is followed by the local (tissue) and systemic release of bradykinin. Bradykinin binds to B2 receptors on endothelial cells leading to capillary leakage and angioedema. After enzymatic cleavage bradykinin metabolites (e.g. des-Arg9-bradykinin) may also bind to B1 receptors on endothelial cells that are upregulated under proinflammatory conditions (e.g. sepsis (Tidjane et al., 2015) and ischemia (Raslan et al., 2010)) and have strong vasopermeable capacity (Schmaier, 2016). The CAS is another plasmatic cascade at the interface of coagulation, fibrinolysis, complement activation and pathogen defense. Although often considered synonymous to the KKS, it has a distinct role whilst at the same time overlapping and interacting with the KKS (e.g. prekallikrein and H-kininogen are part of both cascades (Schmaier et al., 2019)), particularly in the intravascular compartment (Meini et al., 2020). Activation of CAS leads to thrombin generation with fibrin clot formation and platelet activation, which is initiated by auto-activation of factor XII. Interestingly, factor XII deficient mice are protected from thrombosis while showing no signs of increased bleeding tendency. In addition, in experimental sepsis studies, inhibition of factor XIIa or downstream activation of the CAS improved outcomes after lethal *Escherichia coli* or *Staphylococcus aureus* challenge and was associated with a reduced CS activation and reduced levels of IL-6 (Jansen et al., 1996; Silasi et al., 2019).

Several facts argue for kallikrein-kinin induced inflammation and involvement of bradykinin in pulmonary edema as observed in COVID-19. ACE2 is not only a cell membrane bound protein that is utilized by SARS-CoV-2 to enter the cells (Daly et al., 2020) but also possesses enzymatic activity inactivating B1 receptor ligands of systemic and tissue-derived bradykinin thereby preventing the activation of B1 receptor on endothelial cells. Interestingly, expression of ACE2 and its enzymatic activity is decreased in SARS-CoV and inflammatory conditions (Guy et al., 1992; Kuba et al., 2005; Sodhi et al., 2018) and hence one may speculate that the interaction of SARS-CoV-2 with ACE2 may impair the function of ACE2 leading to a relative abundance of active bradykinin metabolites with subsequent B1 receptor activation, local pulmonary edema and exacerbated lung injury (Sodhi et al., 2018). Indeed, a reduced ACE2 expression in hamster lungs after SARS-CoV-2 infection was recently demonstrated (Yamaguchi et al., 2021). In a recently published study, a soluble ACE2 protein with increased binding to the spike protein has shown protective capabilities with regards to lung and kidney injury (Hassler et al., 2022). In COVID-19 patients, several groups reported strong systemic KKS activation in severely affected patients demonstrated by e.g. consumption of prekallikrein, increased levels of kallikrein/C1-INH complexes (Busch et al., 2020; Lipcsey et al., 2021) and decreased levels of bradykinin (Alfaro et al., 2022). KKS activation was also linked to organ dysfunction including ARDS and mechanical ventilation (Lipcsey et al., 2021). Gene expression analysis from cells in bronchoaveolar lavage fluid (BALF) from COVID-19 and control patients revealed an increase in kininogen and kallikreins but also B1- and B2 receptors with decreased expression of bradykinin inactivating enzymes at the same time (Garvin et al., 2020). Viral proteins were shown to bind to kininogen with subsequent generation of bradykinin (Savitt et al., 2021). Lastly, bradykinin and tissue kallikrein activity was increased in BALF of COVID-19 compared to control patients pointing to a dysregulated KKS in the lungs Martens et al. (2021).

The role of the CAS has not yet been fully elucidated in COVID-19. However, dysregulated coagulation is commonly observed in critically-ill patients with COVID-19, and thromboembolism has been reported more frequently compared to other diseases causing severe sepsis (Helms et al., 2020; Poissy et al., 2020). This may be a consequence of over-activation of the CAS since sepsis and ARDS are prototypic states that strongly activate the CAS (Carvalho et al., 1988; Schmaier, 2016). Although binding and direct activation of CAS proteins to other viruses has not been shown, recombinant SARS-CoV-2 proteins were able to bind factor XII (Savitt et al., 2021). In addition, several factors associated with viral infections may contribute to indirect activation of CAS proteins such as the release of neutrophil extracellular traps (NETs) from neutrophils (Oehmcke et al., 2009) in response to viral infection or the interaction of CAS proteins with viral infected cells (Taylor et al., 2013). Contact system activation has been shown in COVID-19 and in particular factor XIa is thought to correlate with adverse outcomes (Henderson et al., 2022). Busch et al. (2020) characterized the activation of the intrinsic pathway of coagulation in COVID-19 and analyzed 228 consecutive patients with mild, moderate and severe SARS-CoV-2. Apart from the activation of neutrophils, NETs and complement they report increased concentrations of factors XIa complexes that correlated with severity of the disease and underscore

the CAS as potential driver of thromboinflammation in COVID-19. Increased levels of factor XI and XII at presentation were observed in another study in COVID-19 patients compared to healthy control (Ceballos et al., 2021). Interestingly, patients with lower levels on admission had a higher mortality risk and this association was more pronounced in men. Finally, factor XIIa activation was not only present in plasma from COVID-19 patients but expression and activity also increased in postmortem lung tissue (Englert et al., 2021). Factor XIIa colocalized with NETS in lung parenchyma which may indicate activation of factor XII as a consequence of NET accumulation. Bioinformatic investigations of the cytokine profile of SARS-CoV-2 infected lung epithelial cells have even suggested, that the large number of NETs are the most important factor for vascular injury, thrombosis and organ damage (Maxwell et al., 2020). In our view, microthrombi observed in COVID-19 autopsy series are more likely the result of over-activation of several pathways involved in thromboinflammation including the CS, CAS and NETosis.

Interestingly, there is a strong interaction between the CS and both, the KK and CAS system. For example, MASP-1, the amplifier of lectin pathway activation, was found to upregulate B2-receptors on endothelial cells (Debreczeni et al., 2019). Moreover, bradykinin release by MASP-1 mediated cleavage of kininogen was demonstrated (Dobo et al., 2011) and the enzyme that inactivates bradykinin is identical to the inactivator of the complement anaphylatoxins C3a and C5a (Kaplan and Ghebrehiwet, 2010). Conversely, factor XII and XI may trigger complement activation (Mossanen Parsi et al., 2021). Key elements of the KKS, the renin-angiotensin system and the coagulation system have been found to be co-expressed with ACE2 in human alveolar cells (Campbell and Kahwash, 2020). Proteomic analyses from severely ill COVID-19 patients showed a significant increase over time in inflammatory proteins in patients with fatal outcome, whilst anti-inflammatory proteins decreased (Demichev et al., 2022). Interestingly an increase in kallikrein was associated with survival in this study.

Key driving factors for capillary leakage, vascular inflammation and the prothrombotic state in COVID-19 still have to be identified along with potential therapeutic targets. Uncontrolled and imbalanced activation of the KKS and CAS in concert with an overactivated CS most likely contribute to thromboinflammation and increased vascular permeability (Fig. 3). We do believe, that in analogy to complement associated pathologies inhibition of these plasmatic cascades with single-target or even multiple-action inhibitors should be explored in appropriately powered clinical trials.

4. Hypercoagulability and the potential role of the endothelium in COVID-19

Hypercoagulability is commonly observed in patients with COVID-19, and various studies reported high rates of thromboembolic events in COVID-19 patients (Ahmed et al., 2020) as well as microthrombotic disease (Magro et al., 2020b; Menter et al., 2020). The presence of venous thromboembolism significantly increases the risk of mortality (Middeldorp et al., 2020) and as a surrogate marker of hypercoagulability, D-dimer levels are associated with a poor prognosis in COVID-19 (Li et al., 2020; Tang et al., 2020; Zhang et al., 2020, 2020). Recently published data from Sweden indicate a prolonged risk for bleeding events, deep vein thrombosis and pulmonary embolism for up to 6 months after COVID-19 recovery (Katsoularis et al., 2022).

Aid et al. (2020) demonstrated a similar lung pathology with regards to vascular disease and thrombosis after SARS-CoV-2 infection in a Rhesus Macaques model and in human lungs from COVID-19 patients. Their disease model, supported by histopathological, transcriptomic and proteomic analyses, implies upregulation of inflammatory and complement pathways, with subsequent recruitment of macrophages and neutrophils, activation of platelets and triggering of the coagulation cascade. Apart from the likely involvement of the CS, CAS and NETs in thromboembolic events in COVID-19, there is increasing evidence for endothelialitis (Ackermann et al., 2020) and COVID-19-associated coagulopathy (CAC) (Iba et al., 2020).

Besides the inflammatory state itself with activation of the innate immune system including activation of the complement system (which

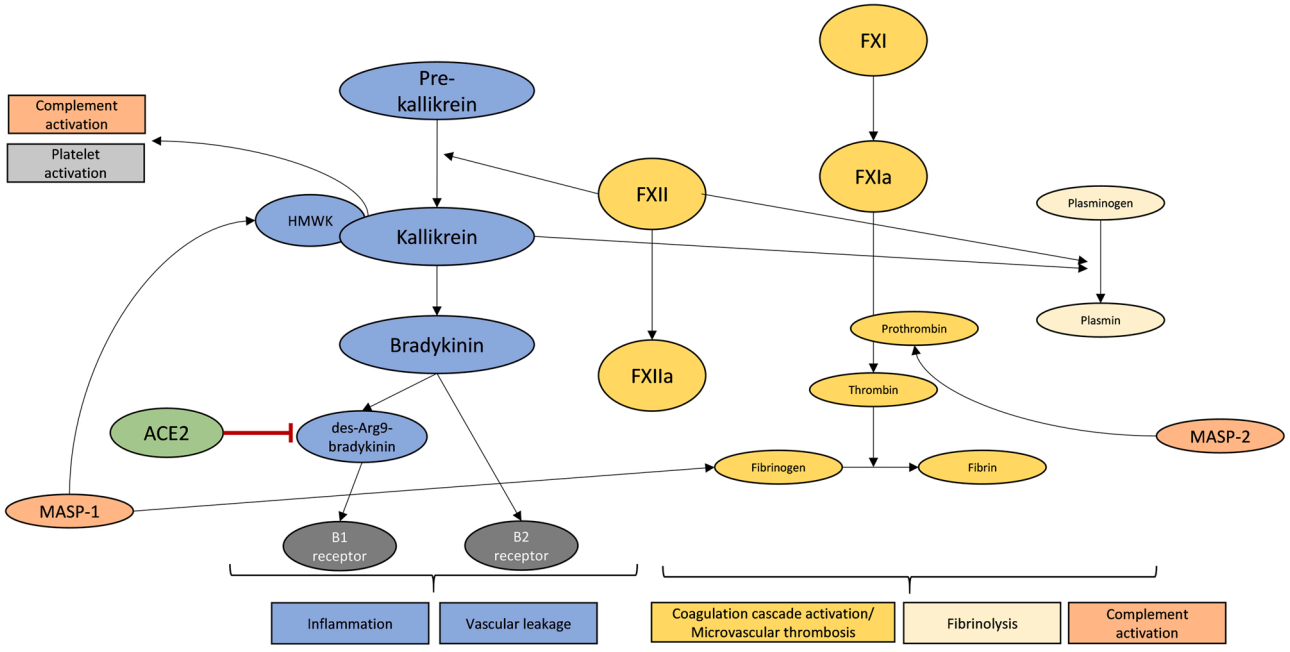

Fig. 3. Simplified illustration of key players of the CS/CAS/KKS in COVID-19. The KKS is activated in COVID-19, and bradykinin generation may contribute to increased inflammation and vascular leakage, in particular in the lungs. ACE2 inactivates bradykinin metabolites, and hence its reduced activity after SARS-CoV-2 infection may contribute to increased KKS activity. Activation of CAS has been demonstrated in COVID-19 including factor XIIa and XIa leading to thromboinflammation and potentially thrombosis. Lastly, the CS interacts with both, the CS and KKS. MASP-1 of the lectin pathway of complement may mediate cleavage of kininogen, and MASP-2 is a weak activator of prothrombin. Abbreviations: ACE2, angiotensin-converting enzyme 2; CAS, contact activation system; CS, complement system; HMWK, high-molecular weight kininogen; KKS, kallikrein-kinin system; MASP, mannose-binding lectin associated serine protease.

is closely linked with the coagulation system and endothelial cells) other procoagulatory factors might play a role, too. Coagulation analyses including thromboelastometry profiles confirmed a state of severe hypercoagulability rather than consumptive coagulopathy in COVID-19 patients with acute respiratory failure (Spiezia et al., 2020). They suspected SARS-CoV-2 to directly promote fibrin formation and deposition, which may explain high D-dimer levels. Interestingly, hypercoagulable profiles were described in a small cohort of critically ill COVID-19 patients despite therapeutic anticoagulation administered (Tsantes et al., 2020). Buijsers et al. (2020) observed increased heparanase activity and heparan sulfate levels in plasma of COVID-19 patients, which may compromise the endothelial glycocalyx. Furthermore, there is evidence of direct viral infection of endothelial cells. Mid-regional proAdrenomedullin, an established marker for endothelial damage, correlated with ARDS and mortality (Spoto et al., 2020). Similarly, Smadja et al. (2020) described angiopoietin-2 as a marker of endothelial activation to be a good predictor for ICU admission of COVID-19 patients). A recent study confirmed the presence of elevated markers of endothelial damage (endothelial stress products and glycocalyx degeneration), complement activation (sC5b9 and C5b9 deposits on endothelial cells) and fibrinolytic dysregulation in COVID-19 patients, with a distinct pattern from other septic syndromes (Fernandez et al., 2022). Indeed, histopathologic findings support the hypothesis of C5b-9-mediated endothelial dysfunction in COVID-19, induced by C5b-9 pore formation on endothelial membrane (Farkas et al., 2002). Further supporting the concept of SARS-CoV-2 related endothelial dysfunction markers of endothelial cell activation have been consistently linked to COVID-19 outcome (de Nooijer et al., 2021; Holter et al., 2020; Kristensen et al., 2021; Ma et al., 2021; Spadaro et al., 2021; Vassiliou et al., 2021).

Endothelial cells are a main target of SARS-CoV2 due to expression of ACE-2 leading to direct damage and inflammation. If antigen-antibody complex formation occurs, binding to C1q can lead to complement activation. MBL of the lectin pathway is well known to interact with activated/ischemic endothelial cells promoting a pro-inflammatory phenotype (Neglia et al., 2020; Orsini et al., 2018). Attraction of neutrophils by C5a may further compromise endothelial cell integrity. The damaged endothelium also releases von Willebrand Factor (VWF), which is reflecting in high plasma levels of VWF in COVID-19 patients, and may interact with C1q of the CS inducing platelet rolling and adhesion (Donat et al., 2019; Kolm et al., 2016; Middleton et al., 2020). However, inflammatory states itself are also known to promote a dysbalance between VWF and its protease ADAMTS-13, and hence not surprisingly, Bazzan et al. (2020) found patients who died from COVID-19 to have lower levels of ADAMTS-13 and higher levels of VWF. A study of 148 patients with COVID-19 showed not only increased VWF but also increased levels of other indicators for endothelial dysfunction such as tissue-type plasminogen activator (t-PA) and plasminogen activator-inhibitor 1 (PAI-1) (Cugno et al., 2020).

A potential role of the renin angiotensin system (RAS) has been discussed extensively elsewhere (Del Turco et al., 2020). In short, ACE2 downregulation (after its use by the virus to enter host cells) and high Angiotensin II levels lead to vasoconstriction and are thought to increase pro-inflammatory and pro-coagulant effects. It remains to be determined if endothelial dysfunction might be improved by widely used drugs such as RAS inhibitors or new compounds such as recombinant ACE2 that act as a soluble receptor trap in order to prevent SARS-CoV-2 infection and internalization (Krishnamurthy et al., 2021; Nagele et al., 2020).

Similarities to some extent between CAC and various other entities such as antiphospholipid syndrome, hemophagocytic syndrome and thrombotic microangiopathy (TMA) have been discussed. Antiphospholipid antibodies have been detected in some patients in China with clinically significant coagulopathy, whilst lupus anticoagulant was not found (Y. Y. Zhang et al., 2020; X. Zhang et al., 2020). Hemophagocytic syndrome is defined by a set of clinical and laboratory criteria, of which usually only hyperferritinemia is observed in COVID-19, although cytokine storms may be observed in both entities. TMA is characterized by thrombus formation in microvessels along with microangiopathic hemolytic anemia and thrombocytopenia. Increased LDH and bilirubin are indeed observed in TMA and COVID-19 (Jhaveri et al., 2020). Interestingly, transcriptome analyses in transplant-associated TMA suggest significant upregulation of the classical, alternative and lectin complement pathways and increased STAT1 and STAT2 signaling. All those pathways normalized after eculizumab therapy (Jodele et al., 2020). In a recent trial, the MASP-2 inhibitor narsoplimab improved TMA laboratory markers and organ function in the majority of patients with transplant associated TMA (Khaled et al., 2022).

In summary, hypercoagulability observed in COVID-19 is probably the result of a complex interplay between activation of several plasmatic cascades including the CS and CAS and endothelial cells that have lost their regulatory role amongst other factors. Given the link between the complement system, the CAS, the coagulation cascade and endothelial cells (Conway, 2018; Foley, 2016), one might speculate, that complement inhibition in particular might reduce thromboembolic events in COVID-19 (Campbell and Kahwash, 2020).

5. Potential therapeutic targets in the complement cascade

The importance of the CS has been established for the pathophysiology of several diseases (e.g. hereditary angioedema, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome and C3 glomerulopathy). However, the potential relevance of the complement cascade has been discussed in a multitude of additional diseases such as autoimmune, degenerative, ischemia-reperfusion and acute injuries (Morgan and Harris, 2015). Given the potentially significant role of the CS in severe COVID-19 various case reports and series as well as case-control studies have examined and reported beneficial effects of compounds inhibiting the complement system (Fodil and Annane, 2021). Attractive targets in complement inhibition are C3 and its activation fragments (C3a and C3b) as well as C5 and its activation fragments and receptors (e.g. C5a, C5aR1). Furthermore, a more upstream inhibition of MASP-1/− 2 is promising as well as inhibition via C1-INH, which will be discussed in more detail below.

Whilst the inhibition of MASPs (e.g. with narsoplimab) mainly prevents lectin pathway activation, it is unclear, if the major role of ficolins and MASPs in the defense of Gram-negative (and Gram-positive) bacteria will increase the susceptibility to bacterial infection, in particular in the lungs during COVID-19 (Matsushita, 2010). As a central molecule of the complement cascade at the level where all pathways converge, C3 is considered to be an attractive target in complement over-activation (e.g. with experimental medications such as AMY-101 and APL-9). However, a lack of C3 may be associated with severe infections, an inherent risk of C3-blockade (Ram et al., 2010). C5 blockade (e.g. with eculizumab, ravulizumab, zilucoplan and other compounds) or more specifically blockade of its activation fragments (e.g. with vilobelimab) is attractive because of a more downstream inhibition of the complement cascade, inhibiting the most potent of the anaphylatoxins, i.e. C5a (Guo and Ward, 2005). Furthermore, a pharmacologic interaction with C5a can also occur on a cellular level with the C5aR-blocking medication avdoralimab (Carvelli et al., 2020). Therapeutic experience is greatest with monoclonal antibodies targeting C5 which includes the awareness of an increased risk for infections with encapsulated bacteria such as unusual *Neisseria spp*. (Crew et al., 2019). However, safety data from the global atypical hemolytic uremic syndrome registry was reassuring when safety measures are implemented (Rondeau et al., 2019).

There are still very few randomized trials assessing compounds interacting with the complement cascade in COVID-19. Results of a randomized phase II/III trial (PANAMO) assessing vilobelimab in patients with severe COVID-19 pneumonia plus best supportive care compared with best supportive care (phase II) or placebo (phase III) were reported for the phase 2 part including 30 patients. All patients of the vilobelimab group received one to seven doses of 800 mg vilobelimab i.v., treatment was stopped if patients were discharged. 26.7% of

the control group died compared to 13.3% of the vilobelimab group. In addition, serious pulmonary embolisms occurred in only 2 (13%) vs. 6 (40%) of the vilobelimab and best supportive care group, respectively. The authors postulate that C5a inhibition may improve micro-angiopathy and microthrombosis and that an observed increase of D-dimers from baseline after C5a inhibition could be a sign of increased fibrinolysis (Vlaar et al., 2020). Results of the much larger phase III and placebo controlled trial of vilobelimab including more than 350 critically-ill COVID-19 patients will be reported soon (ClinicalTrials.gov Identifier: NCT04333420). A large (n = 80) but non-randomized trial assessing eculizumab in patients with COVID-19 admitted to a single ICU found a significant difference in mortality by day 15 (82.9% survival with standard of care plus eculizumab and 62.2% survival with standard of care alone). A total of 35 patients did receive eculizumab in this trial (Annane et al., 2020). However, both trials recruited their patients in spring 2020 when corticosteroids were not part of standard of care for severe COVID-19 yet.

Trials examining compounds targeting the KKS and CAS are scarce. Mansour et al. (2021b) reported the results of a pilot study of icatibant, a B2 receptor competitive antagonist on endothelial cells in COVID-19. The rationale is that icantibant may influence the increased vascular permeability and resulting pulmonary edema in COVID-19 as a consequence of a decrease in ACE2 activity and subsequent increase in local and systemic bradykinin products. Patients with moderate to severe COVID-19 were randomized to icatibant at a dose of 30 mg every 8 h for 4 days (n = 10) or standard of care (n = 10). Outcome and clinical improvement were similar and treatment well tolerated, but pulmonary involvement on discharge was reduce in the icatibant group. Subsequently, two larger studies were designed and are still recruiting patient (Malchair et al., 2022; Mansour et al., 2021a). Interestingly, one of the trials also incorporates a study arm investigating C1-INH as treatment for COVID-19 based on the same principle, i.e. inhibition of bradykinin.

6. The interaction of C1-INH with plasmatic cascades and the endothelium

C1-INH, a member of the serpin superfamily of serine-protease inhibitors, is a plasma glycoprotein that has manifold targets and biological functions. It is primarily secreted by hepatocytes, but many other cells are also capable of C1-INH synthesis such as monocytes, macrophages and endothelial cells (Prada et al., 1998). Its mean plasma concentration is approximately 0.24 g/L (corresponding to 1 U/ml). C1-INH is an acute phase protein, whose secretion is stimulated in various cell types by inflammatory cytokines such as interleukin-6 or interferon-gamma (Prada et al., 1998) and acts as a negative feedback loop to regulate an overactive CS, KKS and CAS in order to limit or avoid collateral damage to host cells. During sepsis, a 50–100% increase in antigenic levels and activity has been observed (Caliezi et al., 2002; Hirose et al., 2018). We have documented a similar increase in hospitalized COVID-19 patients of various severity (median 0.47 g/L, interquartile range 0.40–0.54 g/L) (Charitos et al., 2021). Proteases being inactivated by C1-INH include C1r and C1s (classical complement pathway), MASP-1 and MASP-2 (lectin pathway of complement), factor XIIa and plasma kallikrein (CAS and KKS), factor XIa and thrombin (coagulation system), and plasmin and tissue plasminogen activator (fibrinolytic system) (Beinrohr et al., 2008; Davis et al., 2010). Binding of C1-INH to any of its target proteases is followed by suicide inhibition, i.e., formation of tight complexes which are subsequently eliminated from the circulation (Wouters et al., 2008). C1-INH is the only known natural inhibitor of activated C1r and C1s of the classical complement pathway. However, some data indicate that the lectin pathway of complement is actually the primary target of C1-INH. Indeed, C1-INH inhibited MASP-2, the central activating protease of the lectin pathway, 50-fold faster compared to C1s (or other target proteases) (Kerr et al., 2008), and overall activation of the lectin pathway more effectively compared to the classical pathway and even more so compared to the alternative pathway (Nielsen et al., 2007).

C1-INH regulates the KKS and CAS by inactivating plasma kallikrein and FXIIa being responsible for 93% of the inhibition of the latter in plasma (de Agostini et al., 1984). In particular, C1-INH controls the zymogen to enzyme conversion of FXII and plasma kallikrein and hence the early activation steps of these plasmatic cascades. Decreased plasmatic antigenic levels of C1-INH result in uncontrolled production of vasoactive peptides (bradykinin), which leads to the characteristic episodes of local soft tissue swelling observed in hereditary angioedema (HAE) (Carugati et al., 2001; Drouet et al., 2022). The same may apply to a relative deficiency (e.g. consumption of C1-INH or profound activation of the KKS/CAS) leading to disinhibition and zymogen to enzyme conversion of target proteases followed by an increased release of bradykinin. Interestingly, MASP-1 has also been implicated in the pathophysiology of HAE, as C1-INH deficiency may cause uncontrolled activation of MASP-1, which may aggravate HAE (Hansen et al., 2015). Lastly, C1-INH modulates the intrinsic coagulation pathway and the fibrinolytic system, which may become important at very high, supra-physiological plasma concentrations. Indeed, very high doses of C1-INH were associated with thromboembolic events (Committee, 2000), which may be mediated by a reduced plasmin and increased thrombin generation at C1-INH concentrations > 3 U/ml (Tarandovskiy et al., 2019). Interestingly, the inhibitory activity of C1-INH is influenced by heparins, whereby heparin amplifies the neutralization of factor XIa and MASP-2 but dampens the inhibitory activity on factor XIIa (Conway, 2019).

Apart from its interference with plasmatic proteases, C1-INH has also been implicated in other biological activities such as interaction with leukocytes, endothelial cells and microorganisms. Indeed, C1-INH has been shown to suppress tissue factor surface expression and subsequent activation of the coagulation system and cytokine release by monocytes in a bacterial sepsis model (Landsem et al., 2013). C1-INH inhibited selectin-mediated leukocyte adhesion on endothelial cells, which was independent of its protease activity (Cai et al., 2005). Complement activation (Divella et al., 2021) and thrombin activity on vascular endothelial cells (Caccia et al., 2011) was also modulated by C1-INH as was their overall activity after ischemia/reperfusion injury in experimental studies (Zhang et al., 2018).

Currently, therapeutic preparations of C1-INH are only licensed to prevent or treat acute attacks in the setting of HAE. Plasma derived and recombinant preparations share an identical protein structure. However, the recombinant human C1-INH (rhC1INH) has a different glycosylation pattern with abundant oligomannose residues as a consequence of its derivation from the breast milk of transgenic rabbits (B. Davis and Bernstein, 2011; van Veen et al., 2012). In comparison to plasma derived C1-INH, inhibition of most target proteases by rhC1INH is similar (van Veen et al., 2012). However, rhC1INH has a shorter half-life (3 vs. 30 h) and may target the lectin pathway of complement more effectively (Gesuete et al., 2009), at least during ischemia/reperfusion injuries. Despite the broad interference with several cascades and targets, major adverse events or unique toxicities have not been demonstrated in previous studies with the exception of a potential risk of allergic reactions in patients with rabbit dander allergy for rhC1INH (B. Davis and Bernstein, 2011).

6.1. Involvement of C1-INH in COVID-19

Due to the involvement of the CS, KKS and CAS in the immune response to SARS-CoV-2 infection and the unique role of C1-INH in regulating these plasmatic cascades C1-INH has been investigated in several COVID-19 studies. C1-INH was predicted to interact with SARS-CoV and SARS-CoV-2 in in vitro and bioinformatics studies (Pfefferle et al., 2011; Shen et al., 2020; Srinivasan et al., 2020). Markedly elevated C1-INH antigenic concentrations were consistently observed as we have reported already early in the pandemic (C1-INH concentration of 0.45–0.71 g/L) (Urwyler et al., 2020), and are most likely consistent with an acute-phase response in an attempt to limit inappropriate

activation of plasmatic cascades. Indeed, plasma concentrations of kallikrein-, factor XIa- and factor XIIa-C1-INH complexes were markedly elevated in COVID-19 patients compared to healthy controls but were not associated with COVID-19 outcome (Busch et al., 2020; Henderson et al., 2022; Lipcsey et al., 2021). C1-INH concentrations on admission correlated with inflammatory markers including their peak value but were also not associated with COVID-19 outcome (Charitos et al., 2021). C1-INH activity was also elevated in hospitalized COVID-19 cancer patients compared to healthy controls (Peerschke et al., 2021). In a proteomic analysis of sera, C1-INH expression was found to be significantly upregulated in severe vs. non-severe COVID-19 patients but also in COVID-19 compared to control individuals (Hausburg et al., 2021; Shen et al., 2020). Similarly, C1-INH concentration and activity was elevated in plasma but also in BALF of patients with life-threatening COVID-19 compared to healthy controls (Nossent et al., 2021). In contrast, serum C1-INH activity was found to be comparable in severe vs. non-severe COVID-19 patients vs. healthy controls and C1-INH concentrations even lower in SARS-CoV-2 infected vs. uninfected dialysis patients (Castanha et al., 2022; Medjeral-Thomas et al., 2021). Interestingly, severely affected COVID-19 patients demonstrated very high but also very low C1-INH activities in the former study. *SERPING1* gene expression in BALF was decreased in two small studies of COVID-19 patients vs. healthy or disease controls (Xiong et al., 2020; Z. Z. Zhou et al., 2020; F. Zhou et al., 2020). A combined analysis of the RNA sequencing datasets of these studies revealed an even more striking (80-fold) downregulation of C1-INH transcripts in BALF cells (Mast et al., 2021), which may point to a locally dysregulated CAS and CS, e.g. as a consequence of immune suppressive capabilities of SARS-CoV-2 (Thomson et al., 2020). However, this analysis was criticized for the use of inappropriate control samples and insufficient sequencing depths among others (FitzGerald and Jamieson, 2022) and hence it remains to be determined if C1-INH expression is truly reduced in BALF of COVID-19 patients. In contrast, a whole-genome RNA sequencing approach of nasopharyngeal swabs identified differentially upregulated C1-INH expression in SARS-CoV-2 infected vs. control individuals (Ramlall et al., 2020). In addition, single-nucleotide polymorphisms in the C1-INH gene SERPING1 were identified as associated with adverse clinical outcomes in a targeted genetic association study (Ramlall et al., 2020). In summary, COVID-19 is associated with an increase in systemic and local C1-INH concentrations.

However, based on a SARS-CoV-2 protein-protein interaction network analysis Thomson et al. (2020) speculated that the interaction of C1-INH with SARS-CoV-2 proteins may limit its regulatory activity causing a relative C1-INH deficiency. Interaction with SARS-CoV-2 may result in cleaved C1-INH proteins with impaired function and consequently increased inflammatory activity of the respective regulated plasmatic cascades. In line, modified (cleaved) C1-INH was previously identified in severe sepsis patients which rendered C1-INH inactive again promoting a relative C1-INH deficiency (Nuijens et al., 1989). Consistent with this hypothesis, C1-INH activity correlated negatively with D-dimer levels in COVID-19 patients (Peerschke et al., 2021). Given the formation of 1:1 complexes between C1-INH and respective proteases, C1-INH concentrations are insufficient to inhibit all target proteases in any of the plasmatic cascades even at a resting state (Peoples and Strang, 2021). Given the profound activation of the CAS, CS and KKS during COVID-19, depletion of C1-INH and a relative deficiency despite its acute-phase related increase is very likely and may impact on thromboinflammation and its associated complications.

Patients with HAE provide a unique opportunity to study the impact of absolute C1-INH deficiency on the severity and outcome of COVID-19. Based on the depletion of ACE2 and the activation of the CS, KKS and CAS during SARS-CoV-2 infection, it was hypothesized that HAE patients may be at increased risk to develop severe COVID-19 and that SARS-CoV-2 infection may trigger HAE attacks (Xu et al., 2020). However, no individual developed severe disease in 13 and 16 HAE patients infected with SARS-CoV-2 (Grumach et al., 2021; Milota et al., 2022), and COVID-19 outcome was described as similar compared with the general population in another study of 56 HAE patients and in a survey of more than 800 HAE patients (Olivares et al., 2022; Veronez et al., 2021). Interestingly, HAE patients on subcutaneous prophylactic (but not intravenous) C1-INH reported a reduced SARS-CoV-2 infection rate compared to household controls and HAE patients not on any HAE medication (Veronez et al., 2021). Of note, most patients with HAE included in these studies were rather young (less than 70 years of age) and the presence of a healthy adherer bias (i.e. that patients who receive one preventive therapy will also participate in other healthy behaviors) (Shrank et al., 2011) or a bias because of a more intensive doctor-patient relationship in HAE patients cannot be ruled out.

7. Rationale for the use of C1-INH to prevent disease progression in COVID-19 and potential pitfalls

C1-INH has been identified as a promising treatment candidate early in the pandemic based on the involvement of C1-INH regulated plasmatic cascades and pathways in COVID-19, supporting translational data and promising preliminary results (Adesanya et al., 2021; Thomson et al., 2020; Urwyler et al., 2020). We have outlined the activation of three C1-INH-regulated plasmatic cascades and its consequences in COVID-19, which may be associated with a relative C1-INH deficiency despite an acute phase response and may facilitate ongoing activity of these cascades. In addition, the interaction of C1-INH with activated endothelial cells may influence the disease course after SARS-CoV-2 infection. Given its broad inhibitory activity on various cascades, C1-INH acts as a major anti-inflammatory protein and may reduce collateral damage caused by hyperinflammation during sepsis and similar systemic inflammatory response syndromes such as COVID-19. Indeed, C1-INH consistently improved outcomes in animal models of sepsis (Liu et al., 2007; Singer and Jones, 2011). Results from a human pilot study suggested that C1-INH treatment may dampen the inflammatory response after challenge with *Escherichia coli* lipopolysaccharide (Dorresteijn et al., 2010). However, endothelial activation was not influenced. Studies in human sepsis have demonstrated that C1-INH treatment may improve organ function and outcome (Caliezi et al., 2002; Hack et al., 1993; Igonin et al., 2012). In particular, it decreased complement and neutrophil activation (Zeerleder et al., 2003). Also, reduced occurrence of capillary leakage after allogeneic stem cell transplantation has been observed in line with a decrease in the complement C5 activation product C5a (Nurnberger et al., 1997, 1994). Lastly, C1-INH was able to block MASP-2 mediated overactivation of the complement system and lung injury induced by infection with adenovirus expressing the N protein of several CoVs (Gao et al., 2020). The same was achieved using an anti-MASP-2 antibody implicating that the N protein may induce complement activation trough the MASP-2 mediated lectin pathway of complement.

Another aspect to be considered for the rationale of using C1-INH as COVID-19 treatment is the presence of hypoxia as a critical component of severe COVID-19 and as a consequence of acute lung injury and a decrease in oxygen exchange (Gibson et al., 2020). In addition, microthrombi present in the vasculature of several organs may exaggerate hypoxia and tissue ischemia (Menter et al., 2020). Ischemic damage involves the activation of endothelial cells and plasmatic innate immune cascades. In particular, the lectin pathway of complement has been found to be involved in aggravating tissue injury after ischemia in animal models and human studies (Asgari et al., 2014; Busche et al., 2009; Osthoff et al., 2011; Trendelenburg et al., 2010; Walsh et al., 2005). Conversely, C1-INH as a strong lectin pathway inhibitor has been found to ameliorate ischemic injury in several organ disease models including the heart, brain and kidneys (Castellano et al., 2010; Gesuete et al., 2009; Panagiotou et al., 2018) and is investigated in clinical trials of ischemia after renal transplantation and coronary angiography (Jordan et al., 2018; Panagiotou et al., 2020).

In summary, the rationale for the use of C1-INH in the context of

SARS-CoV-2 infection includes that C1-INH treatment may 1) dampen uncontrolled complement activation and collateral lung damage by inhibiting MASP-1 and MASP-2 in addition to classical pathway activation, 2) reduce capillary leakage and subsequent pulmonary edema by direct inhibition of factor XIIa and kallikrein and subsequent bradykinin release, inhibition of MASP-1 mediated upregulation of B2 receptors on endothelial cells and reduced upregulation of B1 receptors on endothelial cells (Dobo et al., 2011) as a consequence of a reduced complement mediated inflammatory response, 3) reduce the generation of microthrombi by inhibiting MASP-1 induced clot formation and factor XIIa amplified thromboinflammation, and 4) preserve the regulatory role of endothelial cells. As a repurposed drug C1-INH offered the opportunity to exploit these potential benefits knowing its pharmacological profile and being aware of potential adverse events (Fig. 4).

While C1-INH has been suggested as suitable drug candidate to ameliorate the hyperinflammatory response to SARS-CoV-2 infection, several pitfalls should also be discussed, some of which have only been elucidated during the pandemic. For example, the lectin pathway of complement has been initially implicated as the major driver of complement activation, and binding of MBL or MASP-2 to SARS-CoV-2 demonstrated with subsequent complement activation (Gao et al., 2020; Magro et al., 2020a; Stravalaci et al., 2022), (Ali et al., 2021; Malaquias et al., 2021). Subsequently, it became clear that the S protein of SARS-CoV-2 directly activates the alternative pathway (Yu et al., 2020) and that circulating immune complexes may activate the classical pathway (Castanha et al., 2022) in line with results from autopsy studies (Macor et al., 2021). In addition, activation of the classical and alternative pathway rather than the lectin pathway was associated with disease severity and outcome (Castanha et al., 2022; Charitos et al., 2021; Lipcsey et al., 2021; Sinkovits et al., 2021). Unfortunately, C1-INH is a much weaker inhibitor of classical and in particular alternative compared to lectin pathway activation (Kerr et al., 2008), (Nielsen et al., 2007). Another aspect involves the cross-activation of the complement system downstream of the lectin and classical pathway proteases that are inhibited by C1-INH. For example, factor XIa inhibited the regulatory complement factor H of the alternative pathway enhancing alternative pathway activity (Puy et al., 2021). Activated platelets may trigger alternative pathway activation (Del Conde et al., 2005; Peerschke et al., 2010), and the proteases of the coagulation and fibrinolysis cascades (both activated during COVID-19 but not or only poorly influenced by C1-INH) are capable of cross-activating the complement system at the level of C3 or C5 (Amara et al., 2010; Kanse et al., 2012). Lastly, COVID-19 is characterized by a local activation of plasmatic cascades that progresses to a systemic activation early in the disease (Busch et al., 2020). As such, even two-fold elevated C1-INH concentrations may not be sufficient to significantly inhibit all potential downstream effects of the CS, KKS and CAS (Peoples and Strang, 2021; Ravindran et al., 2004) given excessive cross-activation and limited inhibition of e.g. the alternative pathway activation. Interestingly, high concentrations of C1-INH were necessary to inhibit kallikrein in the presence of (activated) endothelial cells suggesting that physiological C1-INH concentrations are sufficient to control low-level kallikrein concentration but are probably insufficient in the setting of significant kallikrein activation, e.g. during COVID-19 (Ravindran et al., 2004). Along these line, C1-INH treatment failed in reducing tissue damage in a porcine model of systemic and profound ischemia/reperfusion injury (Nielsen et al., 2022) in contrast to previous studies investigating local and limited organ ischemia that may involve local activation and inhibition over a small organ area during a short period of time (Castellano et al., 2010; Gesuete et al., 2009). Consequently, the exact dose of C1-INH required to significantly interfere with these plasmatic cascades in COVID-19 is unknown but may include very high doses, which may or may not be associated with an increased thrombotic potential given conflicting previous evidence (Schreiber et al., 2006; Tarandovskiy et al., 2019). Reassuringly, animal models using doses of up to 500 U/kg (i.e. 10x the registered dose of C1-INH for HAE) have not shown an increased risk for thromboembolic events (Castellano et al., 2010). Even more important, the time point to administer C1-INH may be crucial, as the consequences of cascade activation may already be evident and too profound when C1-INH treatment is initiated late (after the "point of no return"). Later stages of inflammation may be less amenable to C1-INH treatment. In contrast to C5 inhibitory strategies C1-INH treatment has not been associated with an increased risk for bacterial or viral infections or any effect on viral replication (Bork et al., 2013). Lastly, successful interruption of escalating thromboinflammation by C1-INH will most likely require a sustained increase in its plasma concentration and hence administration over an extended period of time. Given the short half-life of both the recombinant and plasma-derived human

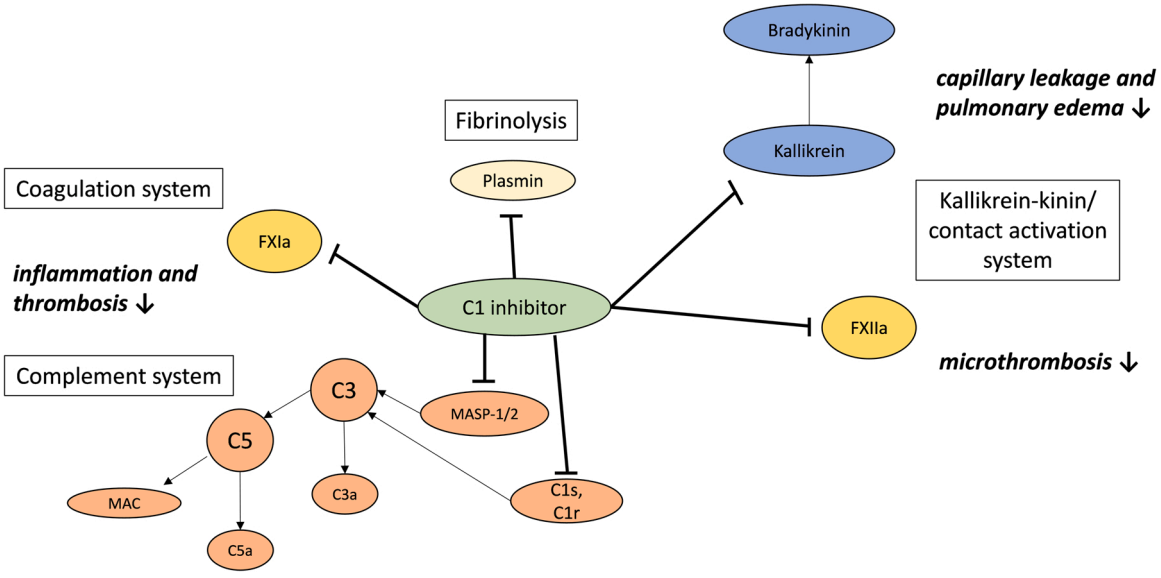

Fig. 4. C1-INH: A multiple-action, multiple-target inhibitor in COVID-19. C1-INH interferes with several plasmatic cascades participating in coagulation, fibrinolysis and thromboinflammation. In COVID-19, it may dampen inflammation, capillary leakage and pulmonary edema and may reduce thrombosis.
Adapted from Wouters D et al. C1 inhibitor: just a serine protease inhibitor? New and old considerations on therapeutic applications of C1 inhibitor. Expert Opinion on Biological Therapy. 2008. Abbreviations: MASP, mannose-binding lectin-associated serine protease; MAC, membrane attack complex.

C1-INH (3 and 30 h, respectively) this may be another pitfall (Plosker, 2012).

8. C1-INH treatment in COVID-19

Only two studies have reported results of C1-INH administration in COVID-19 patients. Although convalescence plasma studies may also be regarded as C1-INH treatment studies, the fact that usually only one or two units of plasma are administered and potential effects of C1-INH contained in the plasma cannot be discerned from the benefit of anti-SARS-Cov-2 antibodies contained in the plasma, makes any conclusions regarding C1-INH efficacy impossible.

We reported the first five COVID-19 patients with moderate to severe pulmonary involvement treated with rhC1INH (conestat alfa) over 48 h (8400 U initially followed by 4200 U every 12 h) (Urwyler et al., 2020). Fever and inflammatory markers improved in all but one patient. Outcome was favorable compared to a matched control population admitted during the same period of time [mechanical ventilation or death occurred in 53% of the control population vs. only 1 (20%) in the conestat alfa group]. This study is limited by its observational nature and small sample size. Subsequently, two randomized controlled open label trials were designed that test the hypothesis that conestat alfa may prevent mechanical ventilation and death in moderately affected COVID-19 patients using slightly different dosing schemes [8400 U initially followed by 4200 U every 8 h for 72 h in the first study (Urwyler et al., 2021) and 50 U/kg (maximum dose of 4200 U) every 12 h for 96 h in the second study (ClinicalTrials.gov Identifier: NCT04530136)]. In the investigator-initiated trial patients presenting to the hospital with evidence of pulmonary involvement and at least one risk factor for disease progression were enrolled at five sites in Switzerland, Brazil and Mexico. This study was terminated early for several reasons and full results will be reported in a timely manner. However, preliminary data indicate insufficient inhibition of CS and KKS activation (data not shown).

In the only published randomized clinical trial, 30 hospitalized COVID-19 patients with moderate severity and presenting to the hospital early after symptom onset were randomized to plasma-derived C1-INH, icatibant or standard of care (Mansour et al., 2021b). C1-INH was dosed as 20 U/kg body weight on day 1 and again on day 4. C1-INH did not influence any outcome including clinical improvement and length of stay with the exception of a reduced pulmonary involvement on CT scan and an increase eosinophil count at discharge. Inflammatory markers were also similar as were adverse events. An extension of the trial is currently underway with the aim of recruiting 174 patients, and results should be available soon (Mansour et al., 2021a).

9. Conclusion

The COVID-19 pandemic had detrimental consequences in many parts of the world. In particular, progression of disease with the requirement for mechanical ventilation has challenged health care systems worldwide during the first waves and led to the deaths of millions of patients. Stopping the progression of pulmonary disease is a crucial target of past, present and future research. The success of immunosuppressive drugs such as corticosteroids and anti-interleukin-6 antibodies have underscored the significance of an overactivated immune system. In this regard, the CS, KKS, CAS and activated endothelial cells have been shown to contribute to thromboinflammation in COVID-19. Similar to the broad anti-inflammatory properties of corticosteroids, the use of C1-INH appears as an attractive option in this setting, as it is the natural inhibitor of several human proteases and may be able to interfere with hyperinflammation, vasodilation and local edema, hypercoagulability and formation of microthrombi while at the same time maintaining an excellent safety profile and being licensed in various countries. However, several caveats remain including the selection of the appropriate dose and treatment duration required to interfere with thromboinflammation. Hence, results from the few randomized controlled trials of C1-INH in COVID-19 will hopefully shed light on its therapeutic potential in this systemic inflammatory disease. Irrespective of the results, compounds targeting the CS, KKS or CAS should be investigated in future infectious diseases models and human trials given their significant involvement.

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CRediT authorship contribution statement

Pascal Urwyler: Conceptualization, Methodology, Investigation, Visualization, Writing – original draft. **Stephan Moser:** Investigation, Visualization, Writing – review & editing. **Marten Trendelenburg:** Resources, Writing – review & editing. **Parham Sendi:** Resources, Writing – review & editing. **Michael Osthoff:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Project administration.

Conflict of interest

Dr. Trendelenburg reports receiving grants from the Swiss National Science Foundation, Roche, Novartis, and Idorsia outside of the submitted work. Dr. Osthoff reports receiving grants from the Swiss National Science Foundation and Pharming Technologies B.V. for the investigator-initiated trial of rhC1INH in COVID-19 (ClinicalTrials.gov Identifier: NCT04414631), and from the Botnar Research Centre for Child Health outside the submitted work, and consulting fees from Pharming Technologies B.V. No other disclosures or conflicting interests with regards to this work have been reported.

Data Availability

No data was used for the research described in the article.

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