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LETTER TO EDITOR

C1 Esterase Inhibition: Targeting Multiple Systems in COVID-19

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To the Editor:

The COVID-19 pandemic is a worldwide health and socioeconomic burden requiring optimization of disease prevention, treatment, and management strategies. Here, this review of physiologic rationales, basic science and translational data, and preliminary clinical results suggests the involvement of C1 esterase inhibitor-related processes in COVID-19 pathology and specifies opportunities for further investigation.

C1 esterase inhibition regulates the complement, fibrinolytic, and contact systems (Fig. 1a). These cascades stimulate a range of immunologic and hematologic processes including inflammation, coagulation, and fibrinolysis, all of which are activated in COVID-19 [1–3]. In the complement system, C1 esterase inhibitor (C1-INH) protein binds to and inactivates C1r and C1s of the classical pathway, C3b of the alternative pathway, and mannose-binding lectin-associated serine proteases (MASPs) of the lectin pathway [4, 5]. This inhibition reduces complement-driven inflammation and coagulation. In the fibrinolytic and contact systems, C1-INH inhibits components of the coagulation cascade, plasmin, and kallikrein to affect both coagulation and fibrinolysis. Additionally, bradykinin, downstream of kallikrein, is an integral mediator of the contact system that increases vascular permeability.

Numerous medications involved in C1-INH pathways are clinically available for the treatment of hereditary angioedema (HAE), which is caused by deficient or dysfunctional C1-INH (Fig. 1b) [6, 7]. COVID-19 and HAE share clinical overlap with symptoms such as shortness of breath, diarrhea, abdominal pain, and facial swelling [8]. In HAE, increased vascular permeability results in angioedema that can manifest as facial and extremity swelling or mucosal edema of the respiratory and gastrointestinal tracts. It has been hypothesized that the dry cough, ground-glass lung opacities, and sensitivity to fluid overload in COVID-19 may be related to pulmonary angioedema [9–11]. Mechanistically, COVID-19 and HAE share innate immune activation that results in inflammation, endothelial dysfunction, and fibrinolysis. In the terminal complement cascade, dysregulation can result in thrombotic microangiopathy characterized by thrombosis and organ injury, a common finding in COVID-19 [1]. The terminal complement cascade can be initiated by the classical pathway via the C1 complex, the alternative pathway, and the lectin pathway.

Early use of C1 esterase inhibition for the treatment of COVID-19 has been promising. In Switzerland, administration of recombinant C1-INH reduced fever and inflammatory markers in patients with COVID-19, who had not improved despite hydroxychloroquine and antiviral therapies [12]. In the Netherlands, inhibition of the contact system via icatibant, a bradykinin receptor antagonist, was associated with decreased oxygen requirements in patients with COVID-19 [13]. Applicability of these results is limited by their observational nature and the small number and male predominance of enrolled patients. Expanded trials with recombinant C1-INH, icatibant, and lanadelumab—a kallikrein inhibitor—are currently under investigation and will assess clinical outcomes in larger, randomized studies [14–16]. Although preliminary results are promising, C1 esterase inhibition may not be sufficient to significantly modulate all potential downstream effectors within the complement cascade, which can have multiple means of activation. Clinical trials of these downstream targets such as C3, C5, and C5a are currently under investigation [17]. Randomized controlled clinical trials are needed.

In vitro and bioinformatic studies suggest that SARS-CoV can interact with C1-INH and dysregulate its anti-inflammatory cellular processes. High-throughput yeast two-hybrid screening demonstrates interactions between human

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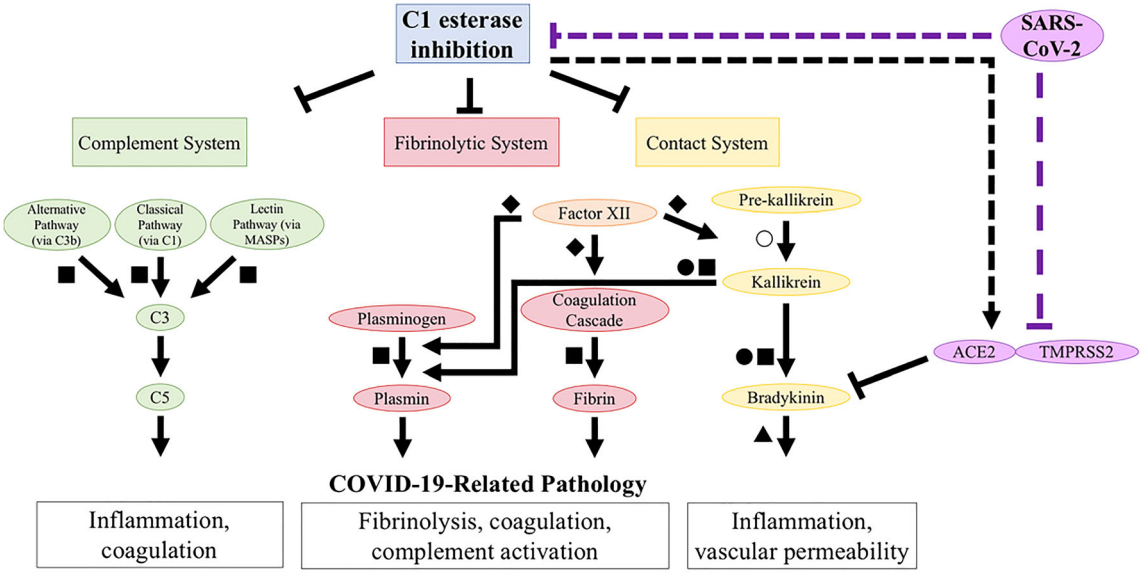
a



b

Key	Class	Name	Route	HAE Use	Significant Side Effects or Study Phase
■	Plasma-derived C1 esterase inhibitor	Berinert	IV	Acute treatment	Antibody development, anaphylaxis (rare), thromboembolism (rare)
		Cinryze	IV	Prophylaxis	
		HAEGARDA	SC	Prophylaxis	
■	Recombinant human C1 esterase inhibitor	Ruconest	IV	Acute treatment	Antibody development, anaphylaxis (rare)
		AAVrh-10hC1EI	IV	Prophylaxis	Preclinical studies ongoing
▲	Bradykinin receptor antagonist	Icatibant (Firazyr)	SC	Acute treatment	Antibody development, injection-site reactions
		PHA-022121	PO	Acute treatment	Phase 1 study ongoing
●	Kallikrein inhibitor	Ecallantide (Kalbitor)	SC	Acute treatment	Antibody development, anaphylaxis
		Lanadelumab (Takhzyro)	SC	Acute treatment	Upper respiratory infections, injection-site reactions, anaphylaxis (rare)
		KVD 900	PO	Acute treatment	Phase 2a study ongoing
		BCX 7353	PO	Acute treatment, Prophylaxis	Phase 3 study ongoing
		ATN-249	PO	Prophylaxis	Phase 1 study completed
○	Pre-kallikrein inhibitor	IONIS-PKK$_{RX}$	SC	Prophylaxis	Phase 1 study completed
◆	Factor XII inhibitor	CSL 312	SC	Prophylaxis	Phase 2 study ongoing
		ALN-F12	SC	Prophylaxis	Preclinical studies ongoing
		ARC-F12	SC	Prophylaxis	Preclinical studies ongoing

Fig. 1 C1 esterase inhibitor-related cellular processes and therapeutic targets. **a** C1 esterase inhibition physiologically regulates the complement, fibrinolytic, and contact systems, all of which may be involved in COVID-19 pathology. SARS-CoV-2 could dysregulate these systems by direct interaction with C1 esterase inhibitor or ACE2 and TMPRSS2. **b** Multiple medications target C1 esterase inhibitor-related pathways for management of hereditary angioedema, which is caused by C1 esterase inhibitor deficiency or dysfunction. Dash: hypothesized mechanism; HAE, hereditary angioedema; IV, intravenous; SC, subcutaneous; PO, oral

C1-INH and seven different SARS-CoV proteins [18, 19]. C1-INH is predicted to interact directly with ACE (61% similar to ACE2) and TMPRSS1 (50% similar to TMPRSS2) [20]. Interestingly, bradykinin, a downstream effector of the contact system, is a substrate of the angiotensin-converting enzyme 2 (ACE2) protein that is required along with

transmembrane protease, serine 2 (TMPRSS2) for SARS-CoV-2 cell entry [21]. In addition, C1-INH was identified amongst ten serum proteins that most accurately predict progression to respiratory distress in COVID-19 and amongst the six proteins predicted to interact with SARS-CoV-2 that are most broadly connected to expression of other genes [22, 23]. A genetic association study identified a *SERPING1* single-nucleotide polymorphism (SNP) as one of seven complement-related SNPs most associated with adverse clinical outcomes in COVID-19 infection [24].

C1-INH may be suppressed in SARS-CoV infection, leading to unchecked inflammation. Antiviral interferon cytokines can induce C1-INH expression, and preclinical studies have shown that C1 esterase inhibition reduces inflammation [25, 26]. However, in vitro SARS-CoV infection increases interferon-stimulated gene expression—with the notable exceptions of *ACE2* and *SERPING1*, the gene that encodes the serine protease inhibitor: C1-INH [27]. As a whole, the *SERPING1*-related gene networks are amongst the most up-regulated in SARS-CoV infection [28]. In two genomic analyses of patients with COVID-19 infection, *SERPING1* expression in bronchoalveolar lavage fluid (BALF) was decreased [29–31]. These BALF decreases are coupled with increases in *SERPING1* blood expression in COVID-19 [23, 30, 32]. Another study showed that *SERPING1* BALF expression was generally decreased in patients with non-SARS-CoV-2 community-acquired pneumonias, suggesting a broader role for C1-INH involvement in pneumonia [31]. Decreases in *SERPING1* BALF expression are likely cell-specific processes, secondary to secretion from or consumption in resident lung cells. Serologic increases in *SERPING1* expression likely represent a physiologic response rather than a pathologic propagation.

Administration of medications that target C1-INH pathways may supplement endogenous anti-inflammatory and antiviral efforts to improve COVID-19 disease courses. Medication repurposing utilizes the benefits of already-established pharmaceutical production protocols and awareness of medication pharmacokinetics and pharmacodynamics. It will be particularly important to carefully assess the risk-benefit profiles of such strategies in COVID-19. Lanadelumab, a kallikrein inhibitor, is associated with increased risk of upper respiratory tract infections in clinical trials [33]. There are conflicting preclinical reports about increased thrombogenesis with C1 esterase inhibitors [34].

Thrombosis also occurs in several complementopathies including paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) syndrome [35]. All of these diseases respond to complement inhibition. These clinical observations and the association of SNPs in complementopathy-related genes with adverse COVID-19 outcomes may reflect complement-driven hypercoagulability and endothelial dysfunction as shared processes in COVID-19 and complement disorders [24]. Trials of various complement inhibition strategies in COVID-19 are ongoing. Targeting these pathways at a proximal step via C1-INH may be a promising approach.

Involvement of C1-INH-related pathways in COVID-19 pathology collectively appears rooted in basic science rationale, supporting translational data, and promising preliminary clinical results. The results from the aforementioned trials should prompt collaborative research into C1-INH-related mechanisms of disease etiology and therapy. Specifically, investigations could explore the biochemical confirmation of host and host-viral protein interactions, analysis of host genetics and protein expression to determine predictors of morbidity, clinical review of patients diagnosed with both COVID-19 and complement disorders, and expansion of randomized controlled studies. While social distancing, personal protective equipment, disease screening, and vaccine development are cornerstones of COVID-19 prevention, studies of therapeutic intervention should be concomitantly advanced. Such efforts will be critical to efficiently and effectively reduce the health and socioeconomic burdens of the COVID-19 pandemic.

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Compliance with Ethical Standards

Conflict of Interests The authors declare that they have no conflict of interest.

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