Will Complement Inhibition be the New Target in Treating COVID-19 Related Systemic Thrombosis?

Running Title: Campbell & Kahwash; Complement Inhibition for COVID-19

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SARS-CoV-2 is a novel coronavirus responsible for the current pandemic resulting in an escalating number of cases and fatalities worldwide. Despite a high infection rate of COVID-19, only an estimated 15% of patients require hospitalization with 5% requiring intensive care. Nearly half (49%) of patients requiring intensive care died. How and why patients succumb to SARS-CoV-2 infection is not well understood. A poignant *New York Times* article described the sudden decompensation and death of a young physician after she had documented viral clearance and was preparing to go home.

Several early publications from Wuhan region focused on describing clinical characteristics of hospitalized COVID-19 patients with severe illness. These initial observational studies demonstrate in severe cases evidence of coagulation dysfunction through elevated d-dimer, elevated lactate dehydrogenase, elevated total bilirubin, and decreased platelets with slight or no changes in partial thromboplastin time or activated partial thromboplastin time. In patients with severe or fatal COVID-19, there is also evidence of end organ damage with acute kidney injury and primarily mildly elevated troponin. In Shi et al, a significantly higher percentage of patients with cardiac injury (average troponin I 0.19 ug/L) died compared to those patients without cardiac injury (51.2% vs 4.5%, respectively).¹

The mechanism of cardiac injury for COVID-19 is uncertain. No series of cardiac imaging data such as echocardiography or cardiac MRI has been published for patients with COVID-19. Theories include direct viral damage via ACE2 receptor, myocarditis, systemic inflammatory response with cytokine storm, destabilized coronary plaques, and aggravated hypoxia. In case reports of COVID-19-related myocarditis, patients had minimal pulmonary involvement, significant cardiac involvement, and recovered from COVID-19. Cardiac biomarkers in the myocarditis cases were much higher than the average values of cardiac injury
in COVID-19 patients reported in the observation studies. Whether myocarditis as a COVID-19 mechanism applies broadly is uncertain. Excessive cytokine release has also been observed in COVID-19 patients. High cytokines were also found in patients with SARS-CoV and MERS-CoV, but subsequent studies demonstrated that corticosteroids did not improve mortality and delayed viral clearance. Tocilizumab, an IL-6 inhibitor, is being studied as potential treatment option. However, elevated cytokines in this context may be a biomarker of critical illness with COVID-19 rather than the pathogenic mediator.

In a joint webinar between Chinese Cardiology Association and the American College of Cardiology on March 28, 2020, the Chinese cardiologists described diffuse microvascular thrombi in multiple organs on autopsy review of COVID-19 non-survivors. Given this diffuse thrombosis, Chinese physicians recommended treatment COVID-19 patients with systemic anticoagulation, but no trials or publications have evaluated this approach. Similar findings of diffuse multiorgan microvascular thrombosis without viral infiltrates were seen in an autopsy case report for a patient that died of SARS. Thrombotic microangiopathy (TMA) can occur in many different clinical scenarios including pathogenic complement activation.

The complement system is a mediator of the innate immune response that promotes inflammation, defends against bacterial infections, and often neutralizes infectious viruses. In brief, the complement cascade can be activated via the classical pathway triggered by antibody-antigen complexes, the alternative pathway stimulated by specific surface antigens, and lectin pathway initiated by binding mannose residues on the pathogen surface. These pathways converge on the common pathway. The common pathway includes production of C3a and C5a inflammatory mediators, C3b-initiated pathogen opsonization, and ends in formation of the C5b-9 membrane attack complex (MAC) that lyses target cells resulting in cell death (Figure 1A).
Two murine studies directly investigated complement activation in coronavirus infections and asked whether activation of the system would be protective or pathogenic. In a murine model lacking C3 and thus unable to activate the common complement pathway, SARS-CoV infection severity was decreased with less respiratory dysfunction and lower cytokine levels despite equal viral loads (Figure 1C). The author suggest that a significant portion SARS-mediated disease is likely immune-mediated. In a murine model of MERS-CoV infection, increased concentrations of C5a and C5b-9 were found in sera and lung tissues. Blocking C5a with a murine antibody alleviated lung and spleen damage with decreased cytokine response and viral replication (Figure 1D).

In humans, excessive complement activation occurs in a number of pathologic settings, leading to diffuse thrombotic microangiopathy (TMA) and end organ dysfunction (Figure 1B). Atypical hemolytic uremic syndrome (aHUS) is a rare disorder of uncontrolled complement activation characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. TMA in aHUS results in renal dysfunction and in rare cases, cardiac dysfunction. Patients often have an underlying genetic predisposition with variants in the complement cascade. Alternatively, infection, pregnancy, certain medications and auto-immune disorders can trigger complement-activating auto-antibodies. Importantly, aHUS is treatable with C5 complement inhibitor, eculizumab. If given early, eculizumab therapy can reverse both renal and cardiac dysfunction. Prior to the introduction of eculizumab, the prognosis of aHUS was poor with 67% of adults dying within 5 years. Transplant associated-TMA (TA-TMA) is also thought to be initiated by excessive complement activation trigged by endothelial injury from chemotherapy, radiation, or viral infection. A recent study showed that 78% patients with TA-TMA had a pathogenic or likely pathogenic variant in TMA and complement associated genes.
Importantly, endothelial injury is a hallmark of COVID-19. Like SARS-CoV, COVID-19 acts primarily through the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed widely in vascular tissues, including alveolar epithelium and cardiac pericytes.

Complement inhibition may be a promising treatment for severe COVID-19 by reducing the innate immune-mediated consequences of severe coronavirus infection, and would pair well with direct anti-viral therapy. The published clinical observations of severe COVID19 are consistent with excessive complement activation: elevated LDH, d-dimer, and bilirubin; decreased platelets; mild anemia; renal and cardiac injury; and reportedly diffuse TMA. Patients with severe and fatal cases of COVID-19 may have increased susceptibility to TMA through a genetic predisposition to pathogenic complement activation. Complement inhibition was associated with favorable outcomes in SARS-CoV and MERS-CoV murine models and reversed cardiac dysfunction in aHUS-TMA, which mimics the pathological findings seen in COVID-19. Complement inhibition may be a new target in treating COVID-19 related systemic thrombosis. This approach is worthy of further investigation with a randomized controlled clinical trial to investigate whether complement inhibition could improve the clinical course for COVID-19 patients with severe disease.

**Disclosures**

None
References


Figure Legend

**Figure. Coronavirus and Complement** A) Simplified diagram of the common complement pathway. Eculizumab inhibits C5 preventing breakdown into C5a and C5b, which is an integral component of the membrane attack complex (MAC). B) In humans, overactivation of the complement pathway can lead to thrombotic microangiopathy resulting in renal and cardiac dysfunction. In atypical hemolytic uremic syndrome, early treatment with Eculizumab reverses organ dysfunction. C) Based on Gralinski et al\(^2\) mouse model of SARS-CoV infection, lack of the C3 protein results in improved lung function, less cytokine release, and no change in viral load compared to mice with an intact complement system. D) Based on Jiang et al\(^3\) mouse model of MERS-CoV infection, antibody blockade of C5 results in improved lung function, less cytokine release and less viral load compared to untreated mice.
A. **Common Complement Pathway**

- C5
- C5a
- C5b-9

- Eculizumab

B. **Complement Overactivation in aHUS**

- Thrombotic Microangiopathy

- Organ Dysfunction

- Eculizumab Treatment

C. **SARS-CoV**

- C6, C7, C8, C9

- C5

- C5a

- C5b-9

D. **MERS-CoV**

- C6, C7, C8, C9

- C5a

- C5b-9

- Antibody

- Viral Load

- Cytokines