



# Targeting complement cascade: an alternative strategy for COVID-19

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## Abstract

The complement system is a stakeholder of the innate and adaptive immune system and has evolved as a crucial player of defense with multifaceted biological effects. Activation of three complement pathways leads to consecutive enzyme reactions resulting in complement components (C3 and C5), activation of mast cells and neutrophils by anaphylatoxins (C3a and C5a), the formation of membrane attack complex (MAC) and end up with opsonization. However, the dysregulation of complement cascade leads to unsolicited cytokine storm, inflammation, deterioration of alveolar lining cells, culminating in acquired respiratory destructive syndrome (ARDS). Similar pathogenesis is observed with the middle east respiratory syndrome (MERS), severe acquired respiratory syndrome (SARS), and SARS-CoV-2. Activation of the lectin pathway via mannose-binding lectin associated serine protease 2 (MASP2) is witnessed under discrete viral infections including COVID-19. Consequently, the spontaneous activation and deposits of complement components were traced in animal models and autopsy of COVID-19 patients. Pre-clinical and clinical studies evidence that the inhibition of complement components results in reduced complement deposits on target and non-target tissues, and aid in recovery from the pathological conditions of ARDS. Complement inhibitors (monoclonal antibody, protein, peptide, small molecules, etc.) exhibit great promise in blocking the activity of complement components and its downstream effects under various pathological conditions including SARS-CoV. Therefore, we hypothesize that targeting the potential complement inhibitors and complement cascade to counteract lung inflammation would be a better strategy to treat COVID-19.

**Keywords** SARS-CoV-2 · ARDS · Inflammation · MASP2 · Complement cascade · Complement inhibitors

## Introduction

Innate immunity plays a critical role against various invading pathogens, in that, antigen-presenting cells, physical barriers, complement components, coagulation cascade, and immunoglobulins synergistically regulate opsonization, inflammation, and phagocytosis (Maloney et al. 2020). Innate immunity is massive and erstwhile it is puzzling to decide where the system ends, and the rest of the coordination begins (Beutler 2004). A gridded network is maintained by these immune components to preserve homeostasis and

to evade unsought immune response (Maloney et al. 2020). Although the innate immune system may not identify every antigen entering the host, it can recognize diverse microorganisms mainly based on pathogen-associated molecular patterns (PAMPs) present on the cell surface. The notable examples of PAMPs are bacterial lipopolysaccharides, peptidoglycan, lipoteichoic acids, mannans, bacterial DNA, double-stranded RNA, glucans (Medzhitov and Janeway Jr 2000), and viral surface protein (Wang and Liu 2016).

Duly, the complement system is a wing of an innate immune response having multifaceted biological effects against a wide range of bacterial, fungal, and viral infections. The complement cascade consists of soluble factors and cell surface receptors that can sensitize and counteract against both invading- (Stoermer and Morrison 2011) and self-antigens (Conigliaro et al. 2019). The complement system bridges the innate and adaptive immune response through humoral immunity, and by modulating T- and B-cell functions (Carroll 2004). The potential complement components

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and their role in innate immunity are listed in Table 1. Neutrophils and mast cells are activated by the complement cascade and eventually act as key mediators of inflammation in several diseases and disorders (Mollnes et al. 2002). Complement pathways, which, when activated, lead to consecutive enzyme reactions, breakdown of complement components C3 and C5, and, result in by-products formation (C3a and C5a). These anaphylatoxins elicit a plethora of physiochemical responses that in turn activate phagocytic cells, release cytokines, chemokines, reactive oxygen species (ROS), adhesion molecules, and inflammation at the site of infection (Sarma et al. 2006). Immunoglobulins and cytokines are critical components of antiviral immunity (Smith and Nemerow 2019). Antibodies neutralize viruses by preventing cell membrane binding, inhibiting membrane fusion, and penetration with the disassembly of viral capsid proteins. Besides, antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis culminate in reducing viral infections through classical complement cascade (Smith and Nemerow 2019) that results in opsonization and phagocytosis. However, inappropriate activation of the

complement system exacerbates many acute lung injury disorders (Sarma et al. 2006). Moreover, many pathogens have acquired resistance to complement, which leads to exploiting the complement molecules and facilitates inflammation (Agrawal et al. 2017).

In this sense, the regulation and dysregulation of complement systems and their sought-after roles in various pathological conditions have been studied (Carroll 2004; Guo and Ward 2005; Rus et al. 2005; Conigliaro et al. 2019). In fact, there are three main phases of complement activation such as (1) recognition of foreign molecules, (2) formation of convertase enzymes that can cleave C3 and C5, and (3) fabrication of MAC for cell lysis (Rus et al. 2005). The classical, alternative, and mannose-binding lectin (MBL) pathways are activation cascades of various host–pathogen interaction conditions, converging at the juncture C3, from where the central complement cascade proceeds (Stoermer and Morrison 2011). Among the three pathways of complement activation, the MBL pathway is primary in viral infections (Matsushita and Fujita 1992; Kjaer et al. 2013) to induce a proinflammatory response

**Table 1** Represents the complement components and their role in innate immunity

S. no.	Complement components	Role in innate immune system	References
1.	C1	Circulate in plasma in huge amount; link adaptive and humoral immunity to complement system	Mak et al. (2014)
2.	C2	It is necessary for the formation of C3 convertase; a key enzyme for complement activation	Krishnan et al. (2009)
3.	C3	Act as point of convergence of activation pathways; enhance direct effector functions; coordinate downstream immune response	Ricklin et al. (2016)
4.	C3a	Act as anaphylatoxin; trigger granulation of mast cells and basophils; can cause smooth muscle contraction, increase in capillary permeability, vasodilation	Mak and Saunders (2006) and Yang (2013)
5.	C3b	Initiating MAC assembly; enabling the pathogens to bind on phagocytes expressing CR1; solubilizing immune complexes; enhance antigen presentation to T cells; directly provide defense against virus	Mak et al. (2014)
6.	C5	Helps to form membrane attack complex	
7.	C5a	Stimulate neutrophil degranulation and the respiratory burst; macrophage and monocytes enhance their expression of adhesion molecules in response to C5a; can cause smooth muscle contraction, increase in capillary permeability, vasodilation	Mak and Saunders (2006) and Yang (2013)
8.	C5b	First complement component to initiate MAC formation and responsible for cytolytic function of complement	Chow (2005)
9.	C6, 7, 8, 9	Forming membrane attack complex	Ábel and Agnello (2004)
10.	Factor B	Component of the alternative pathway and form a zymogen complex; cleaved by factor D; functionally similar to component C2	Pangburn (1986) and Schwaeble et al. (2020)
11.	Factor D	Highly specific serine protease cleaves factor B; necessary for the formation of C3 convertase	Forneris and Gros (2013)
12.	Factor H	Essential for regulating alternative pathway; regulates the formation of C3 and C5 convertases; controls complement-mediated damage	Ferreira et al. (2010) and Cree (2014)
13.	Factor I	Cleaves C4b and C3b	Du Clos and Mold (2013)
14.	MASP-1	Supporting the activation of MBL pathway with MASP-2	Dobó et al. (2009)
15.	MASP-2	Directly activate MBL pathway	Dobó et al. (2009)

(Ling et al. 2012). For instance, human pathogenic viruses including HIV, SARS-CoV, Ebola virus, Dengue virus (DENV), and West Nile virus (WNV) have been found to directly interact with MBL (Stoermer and Morrison 2011). The dysregulation of the complement system plays key roles in the pathogenesis of respiratory disorders like acute lung injury (ALI). The highly pathogenic viruses such as influenza A, H1N1, H5N1, H7N9, SARS-CoV, and MERS-CoV cause ALI. Therefore, treatment with C3aR antagonist or anti-C5a antibody was applied to reduce the severity of lung inflammation in H5N1-infected mice (Sun et al. 2013; Wang et al. 2015; Huang et al. 2020).

MBL gene polymorphism is also a susceptible factor for viral invasion (Zhang et al. 2005). Functional polymorphisms of G-2518A at the chemokine (CeC motif) ligand 2 gene (CCL2) and MBL codon of 54 variants (A/B) are susceptible against SARS, and believed to enhance the risk of SARS-CoV infection (Tu et al. 2015). The activation of MBL pathway by altering the MASP-2 binding motif leads to the generation of C3 convertase, MAC formation, and lung injury (Shen et al. 2020). MASP-2 either cleaves the complement component C4 and C2 to generate C3 convertase (Farrar et al. 2006) or directly cleave C3 (Schwaible et al. 2011). The interaction between MBL and SARS-S is based on a single N-linked glycosylation site in SARS-S (N330) (Zhou et al. 2010).

Upregulation of complement genes MASPI and ficolin-1 were observed with the primary infection of SARS-CoV-1 with the ferret model (Cameron et al. 2012), which is in agreement with a recent preprint report (Blanco-Melo et al. 2020). ALI followed by the excessive activation of complement cascade was observed with MERS-CoV-murine model. In addition, alleviated lung damage was observed through the C5a-C5aR axis (Jiang et al. 2018). The role of the complement components (C3a and C5a) was obvious in lung inflammations of MERS (Jiang et al. 2019). Anaphylatoxin C5a is highly suggested as an inflammatory molecule, which can provoke pro-inflammatory cytokines (Guo and Ward 2005). As a result, the elevated levels of anaphylatoxins was considered as a clinical marker of ARDS (Hammerschmidt et al. 1980). Carvelli et al. (2020) revealed the direct correlation between the severity of SARS-CoV-2 and the level of soluble C5a. The C5a-C5aR1 (CD88) axis influences the regulation of inflammatory responses through the activation of neutrophils and monocytes in conditions like ALI and ARDS. The use of anti-C5aR1 therapeutic monoclonal antibodies prevented the recruitment and activation of human myeloid cells, and reduced ALI in human C5aR1 knock-in mice (Carvelli et al. 2020). In this review, we highlight the involvement of the complement system in aggravating the SARS-CoV-2 infection and suggest the

therapeutic strategies through inhibiting the complement components.

## Complement cascade and SARS-CoV-2

Though complement is a stakeholder of a healthy immune system, uncontrolled activation of complement leads to inflammation (Conigliaro et al. 2019). It was revealed that the viruses interact with complement components and its receptors to escape from the host-defense mechanisms (Lindahl et al. 2000). It is noteworthy that the unsolicited complement activation during coronavirus infection contributes to the SARS. The pathophysiology is driven by immune cells, which were observed in severe cases of SARS-CoV infection (Huang et al. 2020). Patients with SARS-CoV-2 are highly susceptible to develop ARDS. The impairment of respiratory function has been accredited with inflammation and infiltration of immune cells (Risitano et al. 2020). The overlapping features of ARDS such as diffuse alveolar damage (DAD) with edema, hyaline membrane formation, and inflammation were observed in COVID-19 patients (Magro et al. 2020). In a case study, immuno-histochemistry revealed the complement-mediated microvascular injury in five SARS-CoV-2 individuals. Extensive deposits of complement components C5b-9, C4d, and MASP2 were found in the lungs of two individuals infected with SARS-CoV-2. Further, thrombotic microvascular injury with the signs of viral cytopathic or fibroproliferative changes was observed by Magro et al. (2020).

The correlation among ARDS, complement cascade, and SARS-CoV pathogenesis was studied in complement deficient ( $C3^{-/-}$ ) mouse model. Even though the viral load was unchanged, the pathogenesis of respiratory infections was reportedly decreased in  $C3^{-/-}$  mice. The deposition of complement molecules in the lungs of SARS-CoV-infected mice culminated in immune-mediated damages in the lungs (Gralinski et al. 2018). Jiang et al. (2018) reported the influence of complement molecules on lung damage in MERS-CoV human DPP4 transgenic (hDPP4-Tg) mouse model. They further revealed excessive complement activation during viral infection, which altogether promotes acute lung injury and increases C5a and C5b-9 levels in sera and lung tissues, respectively. In contrast, the reduced inflammatory response was witnessed by inhibiting C5a and its receptor. It was substantiated that the deregulated host immune response paves the way for the excessive complement activation, and promotes tissue damage through the C5a-C5aR axis. The autopsy provided evidence of severe interstitial pneumonia with excessive infiltration of lymphocytes, macrophages, and neutrophils in diffused and thickened alveolar septa (Jiang et al. 2018). The immune surveillance by complement molecules swiftly responds to viral infections and triggers

inflammation. For instance, elevated levels of downstream components of C3 were observed in patients affected with dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (Nascimento et al. 2009). C3 is a vital pro-inflammatory peptide that facilitates robust pro-inflammatory and immune-modulatory signals in various viral infections (Prodeus et al. 1997). As a consequence, reduced peritoneal mast cell degranulation, TNF- $\alpha$ , and neutrophil infiltration were observed with C3<sup>-/-</sup> mice. Interestingly, treatment with purified C3 protein enhances the activation of mast cells, TNF- $\alpha$ , and neutrophil infiltration (Prodeus et al. 1997). Very recently, the pivotal role of IgG on complement driven lung inflammation and pulmonary arterial hypertension (PAH) has been augmented (Frid et al. 2020).

## Complement components and inflammation

Both complement molecules and neutrophils are key sentinels of innate immunity, and mediators of acute inflammation together lead to the modulation of thrombogenic pathways. During this process, a cross-talk is mediated by neutrophils between C5a receptor and tissue factors (Ritis et al. 2006). Neutrophilia in SARS-CoV infected patients is associated with poor outcome and extension of complement activation (Yen et al. 2006; Gralinski et al. 2018). Neutrophils driven by complement cascade are the first effector cells, which rapidly infiltrate into the site of infection. In response to potent chemotactic factor C5a from complement activation, neutrophils migrate to remote tissues with their C5a receptors. C5 plays a dual role, in that, it attracts neutrophils through chemotaxis, and stimulates expression of tissue factor. Stimulation of neutrophils, monocytes, and other cells by C5a headed towards the extrinsic coagulation pathway and promote thrombosis in remote sites (Ritis et al. 2006).

The anaphylatoxin C5a is a potent mediator of acute lung injury in MERS and SARS infection (Wang et al. 2015). Complement factor C5a is the strongest inflammatory peptide that triggers pro-inflammatory cytokines (Guo and Ward 2005). Increased levels of C5a in circulation was believed as a clinical marker of ARDS associated with severe sepsis, cytokine storm, and multiorgan failure (MOF) (Hammerschmidt et al. 1980). Upregulation of C3 and C5, and exuberant synthesis of pro-inflammatory cytokines was found in SARS-CoV-2 infection (Conti et al. 2020; Risitano et al. 2020). Consequently, the inflammatory milieu of lungs was accomplished by the release of anaphylatoxins C3a and C5a (Lindahl et al. 2000; Conti et al. 2020). The deposits of complement macromolecules C5b-9, C4d, and MASP 2 on the microvasculature of different organs have been reported (Magro et al. 2020). It was found that treatment with eculizumab (an anti-C5 monoclonal antibody)

leads to hyperactivation of the complement system in 64% of hospitalized COVID-19 patients through which, it improved the health status (de Latour et al. 2020).

Anaphylatoxin C5a with its receptor (C5aR1) influences the activation of inflammatory responses by mobilizing neutrophil and monocytes. The role of C5a-C5aR1 axis on SARS-CoV-2 pathogenesis is documented by Carvelli et al. (2020). Enhanced local complement activity is observed in COVID-19 patients' blood samples through transcriptomics analysis. In addition, the presence of C5b9 is witnessed in immuno-stained lung sections. Elevated expression of C5aR1 receptors on circulating neutrophils and monocytes were also observed in COVID-19 patients. Further, C5a is encountered in broncho-alveolar lavage fluid (BALF) of ARDS patients with COVID-19. The increased level of C5a in COVID-19 is perhaps contributed by the activation of lectin and classical complement pathway. Taken together, the blockade of C5a-C5aR1 is focused as a potential therapeutic approach. It was further evidenced by avdoralimab, a human monoclonal antibody and an antagonist of C5aR1 that prevents the binding of C5a (Carvelli et al. 2020).

ARDS is caused by fluid accumulation in the lungs. C5a, besides being an activator of neutrophils via C5a-receptor, is also a potent chemoattractant of neutrophils (Kew 2014). Recent reports suggest endothelial dysfunction results in the production of leukocyte adhesion molecules in COVID-19 patients (Teuwen et al. 2020). Leukocyte adhesion molecules along with cytokine storm and increased C5a levels may eventually increase the vascular permeability (Teuwen et al. 2020). Increased vascular permeability, in turn, allows the fluid to pass through the inter-endothelial gaps, and facilitates fluid accumulation in the lungs (Teuwen et al. 2020). The BALF contains proteins, lipids and a variety of cells including endothelial and immune cells from the adjacent tissues (Zhou et al. 2020). This mechanism also results in the adhesion and extravasation of monocytes and neutrophils into the tissue and alveoli, together with results in tissue damage. Targeting C5a is, therefore, one of the possible strategies to reduce the effects of hyper-immune activation in COVID-19.

## Complement inhibitors as potential therapeutic agents

The merit of targeting complement components has gained attention in unusual clinical disorders such as paroxysmal nocturnal hemoglobinuria, and atypical hemolytic uraemic syndrome. The necessity of finding a new generation of complement inhibitors has been supported by clinical, pre-clinical, and human genome-wide analyses (Mastellos et al. 2019). Targeting complement molecules has been reported in vivo (Kumar et al. 2020) and with coronavirus-infected

patients (Plosker 2012; Diurno et al. 2020). Presently, molecules impede the function of C3, C5, and convertases are considered as potential targets of COVID-19 (Diurno et al. 2020; Mastaglio et al. 2020). The complement molecules C3, and C5, convertases of C3 and C5, anaphylatoxins such as C3a, and C5a are considered as potential downstream components in the complement cascade (Mastellos

et al. 2019). The above-said complement components are chiefly involved in the pathological conditions of a variety of inflammatory disorders, therefore, most inhibitors are designed to target these molecules. The complement inhibitors designed based on monoclonal antibody, protein, peptide, oligonucleotide, small molecule, and plant metabolite are represented in Table 2. Hitherto, eculizumab, an inhibitor

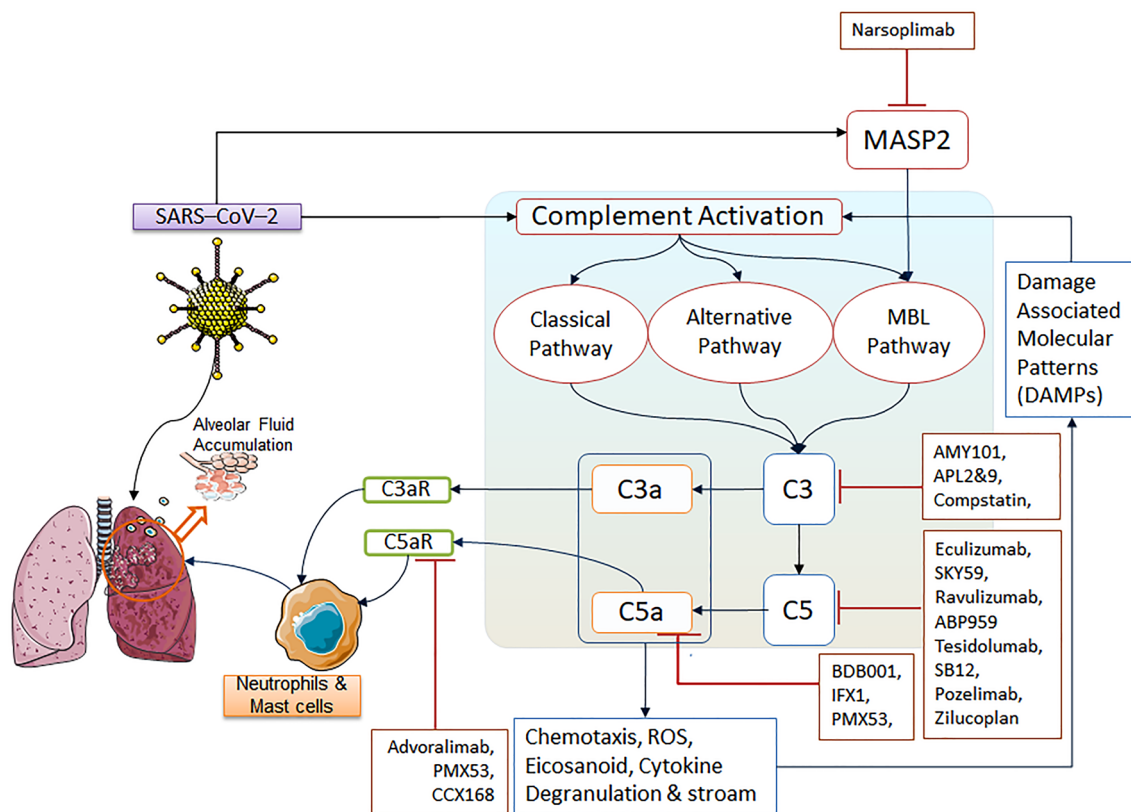
**Table 2** Represents the list of complement inhibitors and their targets

S. no.	Molecule	Target	Company	Stage	Clinical trial code/references
<b>Monoclonal antibody-based inhibitors</b>					
1	Eculizumab	C5	Alexion	IV	NCT02574403
2	Ravulizumab	C5	Alexion	III	NCT03131219 NCT02949128
3	Narsoplimab/OMS721	MASP-2	Omeros	II	NCT02682407 NCT03205995
4	AMY101	C3	Amyndas	I	NCT03316521
5	BDB-001	C5a	Staidson Biopharmaceuticals	II	NCT04449588
6	Sutimlimab	C1s	Sanofi/Bioerativ	III	NCT03347422, NCT03347396
7	Lampalizumab	Factor D	Genentech/Roche	III	NCT02247531, NCT02247479
8	Advoralimab/IPH5401	C5aR1	Innate Pharma	I	NCT03665129
9	Tesidolumab/LFG-316	C5	Novartis	I	NCT02878616
10	Pozelimab/REGN3918	C5	Regeneron	I	NCT03115996
11	SKY59/RO7112689	C5	Hoffmann-La Roche	I/II	NCT03157635
12	ABP959	C5	Amgen	III	NCT03818607
13	SB12	C5	Samsung Bioepis	I	NCT03722329
<b>Peptide/protein-based inhibitors</b>					
14	Conestat alfa	C1esterase	Pharming Group	II	NCT04414631
15	CINRYZE	C1 esterase	Shire Pharmaceuticals Ltd	Approved	NCT02052141
16	APL-2	C3	Apellis	II	NCT03453619
17	APL-9	C3	Apellis	II	NCT04402060
18	Coversin/rVA576	C5	Akari Therapeutics	III	NCT03829449
19	Zilucoplan	C5	Ra Pharma	III	NCT04115293
20	IFX-1	C5a	InflaRx	II	NCT03712345
21	PMX-53	C5a/C5aR			Kumar et al. (2020)
22	C1-INH/Berinerit	C1r/C1s	Cedars-Sinai Medical Center	I	NCT02134314
23	Mirococept	C3 and C5 convertases			Xiao et al. (2016)
24	TP10/ CDX1135	C3/C5 convertases	Avant Immunotherapeutics	II	NCT00082121
<b>Oligonucleotide-based inhibitors</b>					
25	Cemdisiran or ALN-CC5	C5	Alnylam Pharmaceuticals	II	NCT03841448
<b>Small molecule-based inhibitors</b>					
26	CCX168	C5aR1	ChemoCentryx	II	NCT02384317
27	ACH0144471	Factor D	Achillion	II	NCT03459443 NCT03124368
28	ACH145951	Factor D			Yu et al. (2020)
29	LPN023	Factor B	Novartis	II	NCT03373461
30	1-(3,4-Dimethoxyphenyl)-3-(1-phenylethyl) urea	C5-convertase			Zhang et al. (2012)
<b>Plant metabolite-based inhibitors</b>					
31	Rosmarinic acid	C3 convertase			Englberger et al. (1988)
32	Boswellic acid	C3 convertase			Kapil and Moza (1992) and Knaus and Wagner (1996)

of the complement system is the only FDA-approved drug (Soliris; Alexion Pharmaceuticals Inc., Cheshire, CT, USA). It is a humanized monoclonal antibody, which possesses a terminal complement inhibitor that binds to human C5 complement protein with high affinity, and blocks the generation of complement pro-inflammatory molecules C5a and C5b-9 (Rother et al. 2007). Eculizumab is used to treat various autoimmune diseases. Besides, patients with a confirmed diagnosis of SARS-CoV-2 infection, severe pneumonia, and ARDS were treated with eculizumab and showed better recovery. Anti-complement C5 therapy with eculizumab is a potent strategy to treat SARS-CoV-2 infection (Diurno et al. 2020). The schematic representation complement cascade with a special focus on the role of complement inhibitors during SARS-CoV-2 infection is depicted in Fig. 1.

Ravulizumab has been studied in patients with paroxysmal nocturnal hemoglobinuria (PNH), which was funded by

Alexion Pharmaceuticals. A rapid and sustained reduction in the complement-mediated hemolysis was observed while the patients were treated with ravulizumab (Kulasekararaj et al. 2019b). Six COVID-19 patients diagnosed with ARDS have been medicated with narsoplimab, a human immunoglobulin gamma 4 (IgG4)-based monoclonal antibody, which targets MASP2 in the MBL pathway. Narsoplimab is considered an effective medication for COVID-19 treatment, because it reduces endothelial cell damage, inflammation, and thrombotic risk (Rambaldi et al. 2020). Compstatin-based complement C3 inhibitor AMY-101 is administered for a patient infected with SARS-CoV-2 with the symptoms of ARDS. Intercepting C3 molecules block all downstream pro-inflammatory mediators of ARDS associated with SARS-CoV-2. The role of AMY-101 is well-studied as an anti-inflammatory agent under COVID-19 infection (Mastaglio et al. 2020). A very recent study reported an open label-2 cohort



**Fig. 1** Overview of the role of complement inhibitors targeting complement cascade during SARS-CoV-2 infection. Upon infection, SARS-CoV-2 primarily affects the respiratory tract and alveolar cells of the lung through ACE receptors. Subsequently, SARS-CoV-2 directly interacts with MASP2 through a single N-linked glycosylation site in SARS-S and activates the MBL pathway. The classical and alternative pathways are also activated as a part of the viral defense, and triggers complement component C3, which culminates in increased secretion of C3a and C5a. These anaphylatoxins trigger cytokines storm, mast cells degranulation, activation of leukocytes and its infiltration into alveoli. The unsolicited activation

of complement cascade starts here through DAMPs, and makes the lung vulnerable to complement deposits, excess neutrophil infiltration and pathogenesis of ARDS. Hence, inhibiting the downstream complement components such as C3 and C5, the convertases of C3 and C5, the anaphylatoxins C3a and C5a and its receptors will be a better approach to reduce the pathogenesis of ARDS. Inhibition of the above complement components would reduce the severity of the pathological conditions caused by the virus. Moreover, it will provide a window period for eliminating viral load with antiviral drugs for COVID-19 patients

trial of recombinant C5a monoclonal antibody BDB-001 in COVID-19 patients and showed improved clinical conditions within a few days of treatment (Gao et al. 2020).

The potential role of Sutimlimab on C1s inhibition was revealed from phase 3 cardinal study with Cold Agglutinin Disease (CAD) patients (Röth et al. 2019). FDA has granted a review of Sutimlimab for the treatment of hemolysis in adult patients with CAD. Since patients with COVID-19 are also displaying the symptoms of autoimmune hemolytic anemia (AIHA) (Lazarian et al. 2020), Sutimlimab can be used as a choice for the treatment of coronavirus. Similarly, the clinical use of lampalizumab and its pharmacokinetic, pharmacodynamic, and biodistribution studies on the inhibition of complement component factor D has been reported with Cynomolgus Monkey (Le et al. 2015). Further, the direct activation of alternative pathways by SARS-CoV-2 spike protein has been reported by Yu et al. (2020). They have used ACH145951, an antagonist of factor D to eliminate the expression of alternative pathways by inhibiting factor D, thus resulting in the prevention of C3c and C5b-9 accumulation. Though factor D targeting is proved as a potential approach to diminish undesirable complement expression, lampalizumab can also be experimented for COVID-19. Targeting complement component C5 is considered as the positive approach for treating pathological conditions of COVID-19 (Diurno et al. 2020). It can be aided using monoclonal antibodies such as Pozelimab (Latuszek et al. 2020), Tesidolumab (Jordan et al. 2020), Crovalimab/SKY59 (Röth et al. 2020), and ABP 959 (Chow et al. 2020), which are under various phase trials. Given the potential of these antibodies in inhibiting C5, we suggest it for COVID-19 treatment.

Conestat Alfa (Ruconest) is a human recombinant C1 esterase inhibitor obtained from genetically modified rabbits' milk. The drug was approved in the United States for the treatment of acute attacks and hereditary angioedema (Cruz 2015). University Hospital, Basel, Switzerland sponsored the phase 2 clinical trial of Conestat Alfa for non-critical SARS-CoV-2 pneumonia patients against the disease progression of ALI and ARDS. Cinryze, another successful inhibitor of C1 esterase has been used in hereditary angioedema (HAE) (Gupta et al. 2018). Cinryze can also be explored for treating pathological conditions of ALI and ARDS since it is similar to Conestat Alfa, which also targets C1 esterase. Autoimmune hemolytic anemia (AIHA) is a rare complement-dependent autoimmune disease. Systemic inhibition of C3 complement components with APL-2 has been demonstrated in phase-2 open-label study against AIHA (Grossi et al. 2018). APL-2 is in phase 3 trial for the patients with PNH, a complement-mediated disease. Based on these auxiliary reports, we suggest using Conestat Alfa for the treatment of pathological conditions of coronavirus. Coversin (Kuhn et al. 2016) and Zilucoplan (Howard Jr et al.

2020) are C5-specific complement inhibitors reported for their activity against anti-hemolytic and Severe Generalized Myasthenia Gravis (SGMS). Complement-mediated-hemolysis is also observed with SARS-CoV-2 patients by Yu et al. (2020). Hence, Coversin and Zilucoplan, antagonists of C5 can be exploited for treating COVID-19 pathological conditions. Anaphylatoxins C3a and C5a mobilize the inflammatory mediators to alveoli of the lungs. The molecules IFX-1 and PMX-53 have been reported as antagonists of C5a (Li et al. 2014; Lu et al. 2020) opt for the pathological conditions of ARDS. Mirococept (APT070) (Xiao et al. 2016) and TP10 (Li et al. 2006) are proved to inhibit the convertase family of enzymes in various animal studies. Inhibitors of C3 and C5 convertases have the ability to block downstream complement components involved in the pathogenesis of ARDS, and using these inhibitors to treat COVID-19 patients would be appropriate.

Avacopan (CCX168), Danicopan (ACH-0144471), LNP023, and 1-(3,4-dimethoxyphenyl)-3-(1-phenylethyl) urea are small molecules accounted for their inhibitor activity against complement components. Avacopan is proved as C5aR antagonist by phase 2 CLEAR trial in patients with anca associated vasculitis (AAV) (Bunch et al. 2018). Drugs targeting C5aR are under clinical trial for COVID-19 patients with severe pneumonia; thus, Avacopan also opts for the studies of SARS-CoV-2. Factor D is a serine protease allowing the formation of a C3 convertase in the complement pathway. Danicopan is proved as an inhibitor of factor D with Paroxysmal Nocturnal Hemoglobinuria (PNH) patients in phase 2 open-label study (Kulasekararaj et al. 2019a). LNP023 is an orally-administered inhibitor of factor B, which binds to its active site of factor B and results in blockade of C3 cleavage (Zipfel et al. 2019). Factors B and D are essential components of alternative pathways that can proteolytically activate C3 and C5 convertases. Though factor D targeting drugs are already under clinical trials of COVID-19, Danicopan and LNP023 can be explored against pathological conditions of SARS-CoV-2. A small-molecule based on 1-(3,4-dimethoxyphenyl)-3-(1-phenylethyl) urea with the effect of inhibiting C5-convertase was reported by Zhang et al. (2012). The small molecule inhibitors focus on the C5 component as a potential target, and its mechanism of action on C5 inhibition was demonstrated by Jendza et al. (2019).

Phytochemicals exhibit immunomodulatory effects and are considered as alternative medicine. Usage of phytochemicals to hamper the breakdown of C3 and C5 might be a promising strategy to prevent or reduce lung inflammation in COVID-19 patients. Interestingly, rosmarinic acid and boswellic acid extracted from *Rosmarinus officinalis* and *Boswellia serrata*, respectively, have been reported to inhibit complement C3 convertase. The effect of rosmarinic acid on C3 convertase was demonstrated with rat and guinea

pig models of acute lung injury and shock. It was found that rosmarinic acid was involved in the inhibition of C3 convertase, complement activation, and complement-dependent inflammation (Englberger et al. 1988). In addition, the role of boswellic acid on the inhibition of C3-convertase was demonstrated in vitro and in vivo (Kapil and Moza 1992; Knaus and Wagner 1996).

## Conclusion

Even though the complement system acts as a crucial player of the innate and adaptive immune system, its dysfunction escalates the inflammation in ALI, ARDS, etc. The anaphylatoxins such as C3a and C5a play a central role in mobilizing the inflammatory mediators to the alveoli. The deposit of complement components on alveoli of lungs has been witnessed by animal studies and autopsy results. The complement deficient-mice model authenticated the role of complement inhibitors under severe pathological conditions of MERS. Therefore, inhibition of complement components would perhaps be an appropriate strategy in downing the pathology of COVID-19. It is interesting to note that various inhibitors are available and show great promise against MERS, SARS, and ARDS. The complement inhibitors usually target various components of the cascade and address various effector pathways and its downstream effects. Therefore, a detailed understanding of complement inhibitors, their molecular target, mode of action, regulatory loops and networks, crosstalk with other immunological molecules, acute and chronic side-effects will grant the use of these inhibitors for the benefit of COVID-19 patients. Conclusively, an emerging list of novel complement inhibitors and the concurrent results in clinical trials show that complement inhibitors are very promising drugs for any inflammatory diseases.

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## Compliance with ethical standards

**Conflict of interest** The authors don't have any conflict of interest.

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