



Review Article

Immunological aspects of Alpha 1 Antitrypsin in COVID-19 infection among the Populace and Pregnant Women

Wassan Nori Mohammed Hassan^{1*}, Mazin A. A. Najm², Alaa Hussein Hasan³, Khulood H. Oudah²

1. College of Medicine, Department of Obstetrics and Gynecology, Mustansiriyah University, Baghdad, Iraq
2. Pharmaceutical Chemistry Department, College of Pharmacy, Al-Ayen University, Thi-Qar, Iraq
3. Alfarabi university college/Department of Medical laboratory techniques, Baghdad, Iraq

Corresponding author: Dr.wassan76@uomustansiriyah.edu.iq

ABSTRACT

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Since the COVID-19 pandemic alarm was made by the severe acute respiratory syndrome (SARS)-coronavirus (CoV) 2, several institutions and agencies have pursued to clarify the viral virulence and infectivity. The fast propagation of this virus leads to an unprecedented rise in the number of cases worldwide. COVID-19 virus is exceptionally contagious that spreads through droplets, respiratory secretions, and direct contact. The enveloped, single-stranded RNA virus has a specific envelop region called (S) region encoding (S protein) that specifically binds to the host cell receptor. Viral infection requires receptors' participation on the host cell membrane's surface, a key- step for the viral invasion of susceptible cells.

Recently, the Italian alpha 1 antitrypsin Registry results showed a close geographic distribution of positive cases like the one recorded for SARS -CoV-2 infection. AAT deficient patients presented with the highest infection rates. They were giving attention to alpha 1 antitrypsin AAT's role in COVID-19 infection. Alpha 1 antitrypsin deficiency (AATD) is undoubtedly the most common genetic condition in adults. AATD is characterized by decreased serum levels or impaired AAT action, raising the risk of developing many diseases, particularly pulmonary emphysema cirrhosis of the liver. This review will discuss the main immunological properties that AAT has as a protective agent against the infection and possible therapeutic application.

Introduction

Alpha1-Antitrypsin (AAT) is a serine protease inhibitor whose primary role is to suppress human neutrophil elastase's proteolytic action in the lung (1). Alpha 1 antitrypsin produced by the endoplasmic reticulum later on released by the Golgi apparatus and displayed in hepatic cells, neutrophils, placental cytotrophoblasts, the endothelial lining of blood vessels, and pulmonary alveolar cells (1,2). The mean-secreted liver concentration is roughly < 3.5 mg/ml pre-day(3). When a tissue injury occurs, or an acute inflammatory

response is triggered, the serum level of AAT in the blood is increased by 6-fold, coordinating local and systemic inflammation. As neutrophil recruiting continues, serum proteinases are poured, causing collateral tissue injury; AAT will set balance to prevent a repeated cycle of self-injury (3).

Alpha 1 antitrypsin deficiency (AATD) is genetic, acquired metabolic alignment with reduced serum levels or diminished AAT activity (2,4). AAT deficiency is a disease of protease-antiprotease deficiency in the lungs of inflammatory bases. Neutrophils mainly

drive this inflammation. Alpha-1 antitrypsin has many related pathways intensifying neutrophil reaction (5,6,7).

The basis for AAT augmentation therapy (purified human protein) in AATD is to restore antiprotease equilibrium in the lungs (2). The United States Food and Drug Administration (FDA licensed AAT replacement therapy) in 1987 however, its potential benefits are systemic, suggesting the use of alpha-1 antitrypsin in many inflammatory conditions (8,9,10).

We have revised therapeutic strategies for AAT therapy over the last decade and appear to reach beyond lung tissue defense from neutrophilia-induced elastase injury, intending to promote a healthy, anti-inflammatory, immunomodulatory role (11). Interestingly, augmentation treatment applied to persons with normal AAT genetically non-deficient. It resolves steroid-refractory graft-versus-host complications (11,12). Preclinical trials describe the gain in multiple sclerosis, rheumatoid arthritis, type 2 diabetes, acute myocardial infarction, and stroke. Being a hereditary disease, AATD has a geographic variation, with the greatest incidence rate in northern Italy, Spain, and Iran (13,14).

Pathophysiology and protection method

Alpha-1-antitrypsin (AAT) is considered a significant inhibitor of serum protease (15), which acutely blocks the proteolytic enzymes-facilitated entry of COVID-19, found in serum and bronchoalveolar tissues, showing that effects are biologically crucial as part of a standard defense strategy against COVID-19 infection and severe lung injury (15,16). Low serum AAT levels correlated with the severity of COVID-19 infection and IL-6; a cytokine identified in the disease course as a biomarker for severity (17). The unique anti-inflammatory, immunomodulatory, and anti-coagulation role of AAT has essential effects on the disease's pathophysiology and its possible therapeutic role (17,18).

Alpha 1 antitrypsin is a transmembrane serine protease 2 inhibitor

Cell invasion of COVID-19 viruses relies on the coupling of viral spike (S) proteins to cell receptors. SARS-CoV-2 uses the ACE2 receptor for entrance (19). Before it can bind to this receptor, the virus needs to prime them. Trans-membrane serine protease 2 (TMPRSS2) is the major protease required for protein S' priming, a crucial step in cell invasion (20). Host proteases are speculated to cause discrepancies in the severity of infection, virulence, and dissemination.

There have been claims that disparity in protease-antiprotease could have a crucial role in the pathogenesis and infectivity of SARS-CoV-2. Therapeutic trials incorporating TMPRSS2 inhibitors have shown promising effects since they blocked viral entry (20,21). Alpha 1 antitrypsin is a novel inhibitor of TMPRSS2 anchored to an extracellular domain of TMPRSS2 in a configuration proper for catalytic activities. AAT's inhibitory action is suggested in the viral loading process of SARS-CoV-2 (20), where low serum levels associate infection severity. A high prevalence of AATD in North Italy was the leading cause of coronavirus infections' disastrous effects (12). AAT prevents H3N2 influenza A and B virus infections in the murine model, but these viruses do not need TMPRSS2 priming, which reinforced the idea that AAT can mediate anti-viral effects via multiple immunity mechanisms against COVID-19 (22,23).

Alpha 1 antitrypsin And Neutrophils:

Alpha 1 Antitrypsin inhibits neutrophil elastase and proteinase. Neutrophil elastase is an enzyme that catalyzes many structural proteins in the lungs and handles many innate immune mediators. Recently it was implicated in the SARS-CoV-2-substrate pathogenicity (24). It cleaves the S1-S2 junction of the viral S protein, where the coronavirus spike protein (S) facilitates early steps of viral infection, with the S1 domain responsible for receptor binding and the S2 domain mediates membrane fusion. In seriously ill COVID-19 patients, they saw higher neutrophil counts than those with mild infection and healthy control (25).

What supports the AAT role is the distinguished neutrophil inflammation seen in pneumonia patients lacking AAT (the genetic AATD) in line with autopsy results in patients with COVID-19 pneumonia, implying a shared pathological mechanism (26,27). Neutrophil extracellular traps (NETs) are components of the innate immune response to neutralize invading pathogens; it is called a double-bladed sword since NETs' toxicity exposes the host endothelial cells and parenchymal tissue to extensive damage (28,29,30). Unbalanced NET formation and neutrophil triggering can contribute to many ailments, including sepsis, thrombosis, acute lung injury, kidney diseases, and hypertension (30). AAT controls neutrophilia, and a neutrophil extracellular trap, making an essential step in reducing the COVID-19 course and comorbidities (31).

Alpha 1 antitrypsin and Alveolar Macrophages:

To understand the effect of AAT in alveolar macrophages, we should know what apoptosis; a form of programmed cell death where distinctive biochemical and cellular changes occur ultimately ends in death. Apoptosis creates cell fragments named "apoptotic bodies" the phagocytic cells could engulf and end before the membrane integrity is broken (32). Removing those apoptotic cells by phagocytic cells is called efferocytosis, 'burying of dead cells.' It prevents tissue exposure to toxic enzymes, oxidants, and other intracellular components such as proteases (33,34). AAT improves alveolar macrophages (AM) engulfment power (phagocytosis) and efferocytosis, thus decreases α -TNF (tumor necrotizing factor) release along with other pro-inflammatory markers; it reduces levels of pro-inflammatory cytokine secreted in the sputum (1,35). AAT separated from the bronchial secretion proved to be capable of neutralizing COVID-19. Speculation of its ability to pass to the lungs into the site of invasion and replication of SAR-CoV-2 (36).

Alpha 1 antitrypsin and Complement System:

Viruses engage with complements receptors and components to avoid host-defense mechanisms. Complement is a crucial player in defense against infections, but excessive or defective activation can lead to collateral tissue damage (40). Most critically ill COVID-19 patients will develop lung function impairment because of an immunity response derangement rather than elevated virus load (41). The release of pro-inflammatory cytokines and the extravasation of blood neutrophils and monocytes contribute to disrupted air-blood barriers by inducing collateral tissue injury, particularly to bronchial epithelial and endothelial vascular cells. Besides, it has accredited damage to endothelial vascular cells for thrombotic microangiopathy (42). As we know that C3 plays a central role in the complement's activation system, C3a is an anaphylatoxin and the precursor of some cytokines (41-42). C3b serves as an opsonizing agent. Reports have shown widespread complement stimulation, detected by C3a generation and C3-fragment deposition in lung biopsy samples from

patients with severe COVID-19. Besides a significant increase in C5a serum concentrations (43).

Another defense mechanism of AAT is complemented protein; C3 b has increased opsonized pathogenic bacteria's phagocytosis through the complementary receptor pathway. Cleavage of the C3 part of the complement system is crucial in its activation (44). If protease activity exists in neutrophilic-derived infection, C3 will be degraded by the proteolytic effect and make complement in-active (44). The result is impaired immunological response of the body to the offending pathogen. AAT is a neutrophilic-protease inhibitor that can balance and protect the complement C3 component from degradation by dysregulated protease action. AAT set a new role during acute inflammation in the pulmonary tract in both deficient and non-deficient patients (45).

Alpha 1 antitrypsin and Serum Fibrinogen:

Fibrinogen is a recognized obstructive pulmonary disease biomarker used to assess the severity, exacerbation, and mortality in chronic obstructive airway disease (46). Blood fibrinogen degradation product increases in AATD patients in severe airflow obstruction and decreases in AAT augmentation therapy. Similarly, results showed a useful disease activity marker in patients with severe COVID-19 infection (47).

Advantages of AAT Augmentation Therapy:

The possible therapeutic anti-viral activities of AAT in SARS-CoV-2 infection were a topic of research. Introducing AAT during COVID-19 infection has decreased the viral load and replication in the target cells and tissues, such as salivary glands, which have significant pathological effects for viral dissemination. Thus, safe to say that AAT limits disease severity in affected persons and limits the virus's epidemiological spread to others (48).

Therapeutic AAT activity was equivalent to camostat action, a drug recently used in COVID-19 that prevents SARS-CoV-2 cell entry by modifying cell permeability; AAT inhibits extracellular proteases. It exhibits his activities in the cell's exterior (49).

Azouz NP et al. (50) proved that extracellular protease action is rate-limiting within the SARS-CoV-2 cell entry phase, impeding SARS-CoV-2 entry and modifying the host cell's exterior. The frustrating reports of Hydroxychloroquine, which interacts with the function of intracellular cathepsins in drug testing and in vitro analysis, are further compatible with the crucial role of extracellular proteases (51,52).

Camostat as an anti-viral drug may rapidly lose potency due to the high number of mutations occurring in the viral genome, not to mention the intracellular effect of camostat, leading to unintended inhibition of intracellular protease. Another advance of AAT is targeting the extracellular host proteases (TMPRSS2) (53).

Slamming the door in front of the virus instead of killing it along with infected cells is a safer strategy. Treatment with purified human AAT significantly increases efferocytosis, phagocytosis, and total alveolar macrophages scavenging action (34) Compromised scavenging activity result in pathogen persistence, bacterial colonization of the lower airways attributing to inflammation, tissue destruction, and frequent exacerbations (54).

Dead cells in the lung alveoli will induce local tissue damage set for acute respiratory distress syndrome (28). Clearing those Infected dead cells by pyroptosis will trigger a cytokine release. In severe cases, cytokine storm and intravascular thrombosis auscultate the disease severity (29). All are ominous prognostic factors for patients' survival (55). Infusion of purified human AAT to deficient

individuals at physiological dose can decrease inflammatory cytokine release and decrease lung damage after bacterial infections (56). Infusion in non-genetic AAT patients decreased post-translational changes to the AAT native molecule, resulting in an "acquired" functional AAT-deficient case. A condition noticed following environmental exposure to cigarettes and pathogens (57). Supplement with the native AAT suggests regaining normal functional AAT levels in severe airway disease (58). Convalescence serum shows substantial suppression of SARS-CoV-2 entry (59). In convalescent plasma therapies, the abundance of AAT in donated plasma can play an added defensive role as non-immunoglobulin components (6). Convalescent plasma treatment is effective for its users. However, the major benefits were accredited to neutralizing antibodies. Only minor benefits from the transition of the intravenous immunoglobulin (IVIG) standard show that the IgG antibody is not the only serum ingredient that can play a significant role in reducing the stress of COVID-19 in patients (59).

Alpha 1 antitrypsin and pregnancy:

The physiological changes that women suffer from during pregnancy and alteration in cellular immunity make them more vulnerable to viral infection as COVID-19 infection (60). The earlier SARS pandemic in 2013 has shown increased maternal morbidity and mortality rates than the general population. Recently, arguments have revised our policy, implying that we must relay the latest epidemic's expertise rather than the experience of past outbreaks (61).

Low global mortality rates of COVID-19 among children and pregnant women are reported in the literature. Three Confirmed SARS-CoV-2 cases of pregnant women were admitted to intensive care admission (3%) with no documented fatalities. Breslin et al. described that a significant part of mothers, including those with ICU admissions, had been discharged well (61). An important issue raised here: Why did the morbidity and mortality ratio for pregnant women not increase?

An interesting paper addressing the immunological aspects of COVID-19 infection among children and pregnant women (59) gave several suggestions for the causes why these two groups did not suffer from increased risk.

One hypothesis accredited convulsant serum, rich in immunoglobulins and other immunological markers (62,63). AAT is one of the serum markers and shows a physiological increase of 4-6 times in pregnant compared to non-pregnant.

Alteration in serum levels of AAT linked to many harmful consequences for pregnancies (8) as abortion, preterm labor, and preeclampsia could be the cause of protecting pregnant women against severe infection? Keeping in mind that most reported cases in this group were mild-moderate?

Further work is warranted to unveil this extraordinary cytokine's hidden aspects and its application.

Conclusion

Alpha 1 antitrypsin can act as a natural inhibitor of SARS-CoV-2 infection, especially among severe cases as concentrations of AAT rise. Its unusual protective action in animal and cellular immunity is the foundation for its application as a therapeutic agent. AAT will limit disease severity in affected persons and limit the virus's epidemiological spread to others via respiratory secretion, which forms a potential assay for vaccine production. Introducing AAT in the drugs panel against COVID-19 shows an appealing suggestion, as it can reduce case severity and reduce the transmission rate with a

good safety profile. It will investigate whether the levels of AAT in the lungs or serum of COVID-19 patients are adversely associated with virus load or disease progression. There are still unresolved chapters in the life cycle of the virus that needs monumental work to grasp the course and consequences of the outbreak properly, and AAT is a promising choice in this sense.

Conflict of Interest

No conflict of interest.

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