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REVIEW

The Role of Alpha-1 Antitrypsin in the Pathophysiology and Treatment of Inflammatory Lung Diseases

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Abstract: Alpha-1 antitrypsin (AAT) is a serine protease inhibitor that plays a critical role in maintaining pulmonary homeostasis through regulation of the protease–antiprotease balance and modulation of inflammatory responses. AAT primarily protects lung tissue by inhibiting neutrophil elastase, thereby preventing excessive extracellular matrix degradation and alveolar destruction. Disruption of this balance, particularly in alpha-1 antitrypsin deficiency (AATD), results in unchecked proteolytic activity and progressive lung injury, most notably contributing to chronic obstructive pulmonary disease (COPD). Beyond its antiprotease function, AAT exerts broader anti-inflammatory, immunomodulatory and anti-apoptotic effects, influencing cytokine release, neutrophil recruitment and oxidative stress pathways. These properties highlight its translational relevance, positioning AAT as a potential therapeutic agent across a spectrum of inflammatory airway diseases, including bronchiectasis, cystic fibrosis and interstitial lung diseases. Clinical evidence supports AAT augmentation therapy in AATD-associated COPD, while emerging research explores its efficacy in non-deficiency states characterised by excessive inflammation and protease burden. Overall, AAT represents both a key pathogenic factor when deficient and a promising biologic therapy in inflammatory lung disease. This literature review explores its mechanisms and potential for expanded clinical application.

Keywords: alpha-1 antitrypsin, inflammatory lung disease, protease inhibitor, chronic obstructive pulmonary disease, neutrophil elastase, augmentation therapy

Introduction

Inflammatory lung diseases represent a major cause of morbidity and mortality worldwide, posing a substantial and growing burden on global health systems. Conditions such as chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis (CF), bronchiectasis and interstitial lung diseases (ILDs) are characterised by persistent airway and/or parenchymal inflammation, a major contributor of disease pathophysiology.[1,2] According to the World Health Organization, COPD alone is among the leading causes of death globally, while asthma affects hundreds of millions of individuals and remains a significant contributor to disability-adjusted life years.[3,4] The prevalence of bronchiectasis is rising, owing to improved detection, and is associated with chronic infection, persistent inflammation and frequent hospital admissions.[5] Although less common, CF imposes a high individual disease burden and is associated with progressive respiratory decline despite advances in disease-modifying therapies.[6] ILDs encompass a heterogeneous group of disorders, including fibrotic conditions with poor prognosis, progressive lung function decline and limited treatment options. These diseases impose not only clinical and economic costs but also profound impacts on quality of life. Despite differences in aetiology and clinical presentation, many inflammatory lung diseases share common pathological mechanisms, including dysregulated immune responses, excessive neutrophilic inflammation and an imbalance between tissue-damaging proteases and their endogenous inhibitors.[7]

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A central feature of inflammatory lung disease pathogenesis is chronic inflammation within the airways and alveolar spaces, often driven by persistent exposure to environmental insults such as cigarette smoke, air pollution, allergens or recurrent infection.[8,9] Neutrophils play a prominent role in several inflammatory lung conditions, releasing a range of proteolytic enzymes and reactive oxygen species (ROS) intended to clear pathogens and insults.[10] However, excessive or uncontrolled neutrophil activity can result in collateral damage to host tissue, including degradation of extracellular matrix components, epithelial injury and disruption of mucociliary clearance.[11] This tissue damage perpetuates inflammation and susceptibility to infection, contributing to disease progression and irreversible loss of lung function. The balance between proteases and antiproteases is therefore critical in maintaining pulmonary homeostasis and disruption of this balance is recognised as a key driver of chronic lung disease.[12]

Alpha-1 antitrypsin (AAT) is a key component of the antiprotease defence system within the lung. AAT is a serine protease inhibitor (serpin), encoded by the *SERPINA1* gene, and is produced predominantly by hepatocytes in the liver before being secreted into the circulation.[13] From the plasma, AAT diffuses into tissues, including the lung, where it exerts its protective functions. While hepatocytes are the primary source of circulating AAT, additional local production by immune cells such as neutrophils, monocytes and alveolar macrophages has been described, particularly at sites of inflammation.[14] As an acute-phase protein, AAT levels increase in response to systemic inflammation, infection or tissue injury.

The clinical significance of AAT is most clearly illustrated by alpha-1 antitrypsin deficiency (AATD), a genetic condition causing reduced circulating levels or dysfunctional variants of AAT.[13] Individuals with severe AATD are at high risk of developing early-onset emphysema, particularly in the presence of additional environmental risk factors such as smoking. AATD has traditionally been viewed as a monogenic cause of COPD; however, emerging evidence suggests that alterations in AAT expression, function or activity may also contribute to the pathophysiology of a broader spectrum of inflammatory lung diseases, even in individuals without genetic deficiency. Reduced local AAT activity, overwhelming protease burden or functional inactivation of AAT by oxidative stress may all result in a relative antiprotease deficiency at sites of chronic inflammation and a subsequent protease: antiprotease imbalance (Figure 1).

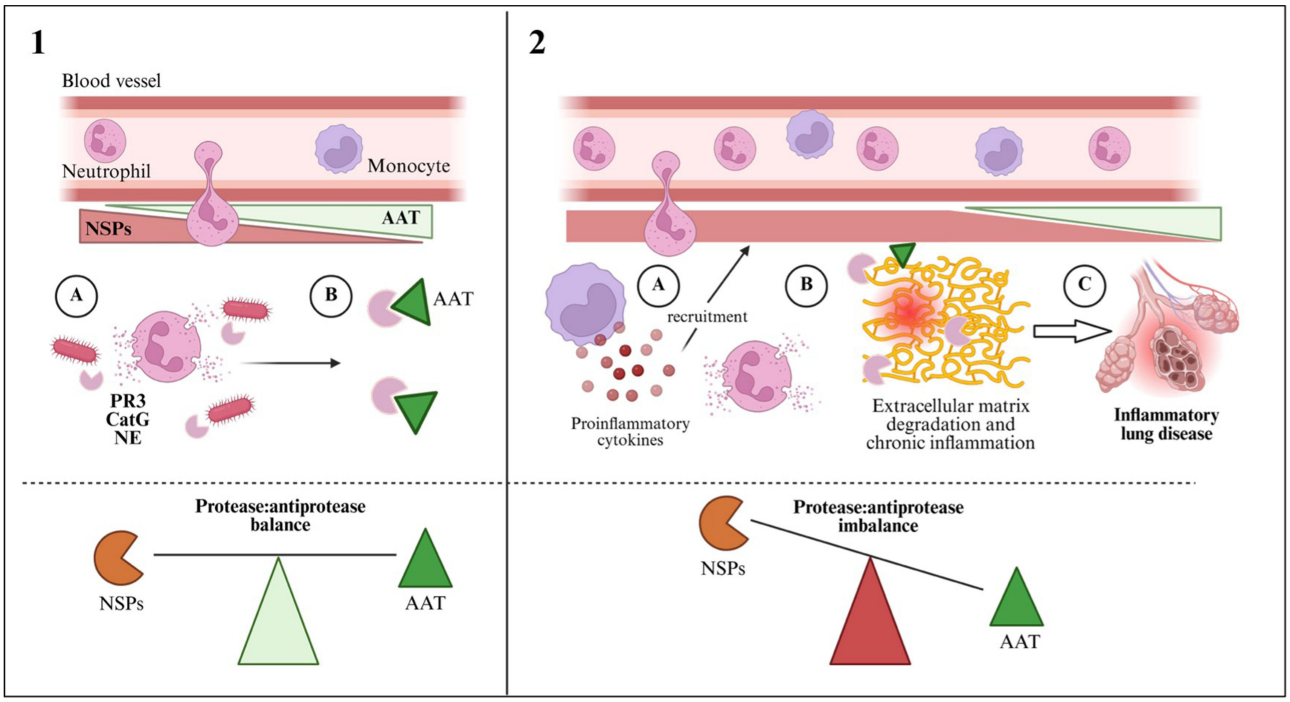

Figure 1 Protease–antiprotease imbalance in inflammatory lung disease. (**1**) (**A**) Under normal physiological conditions, monocytes and neutrophils respond to airway insults, such as bacterial infection. Neutrophils release several neutrophil serine proteases (NSPs), including proteinase 3 (PR3), cathepsin G (CatG) and neutrophil elastase (NE), to eliminate the insult. (**B**) Following clearance, protease activity is inhibited by alpha-1 antitrypsin (AAT), preventing unnecessary NSP release and activity. (**2**) In chronic inflammatory lung disease, (**A**) persistent inflammation results in continuous recruitment of neutrophils and monocytes. Elevated NSP levels, together with (in some cases) AAT deficiency, lead to a protease–antiprotease imbalance. (**B**) Uninhibited NSPs degrade elastin and other components of the extracellular matrix (ECM), driving further inflammation. (**C**) Collectively, ongoing tissue damage and chronic inflammation contribute to the development and progression of inflammatory lung disease.

Studying the role of AAT across other inflammatory lung conditions is therefore of importance. While the contribution of AAT deficiency to emphysema is well established, its involvement in diseases such as asthma, CF, bronchiectasis and ILDs is less defined and remains an active area of research. Understanding how AAT functions within different inflammatory contexts may reveal shared pathogenic mechanisms and identify opportunities for therapeutic intervention. Moreover, augmentation therapy with exogenous AAT is currently used in selected patients with AATD and there is growing interest in expanding AAT-based therapies to other inflammatory lung diseases, leveraging its anti-protease and anti-inflammatory properties.[15]

A comprehensive literature search was conducted to identify relevant studies examining the role of AAT in inflammatory lung diseases. Electronic databases including PubMed, Embase and Web of Science were searched from inception to December 2025 using combinations of keywords such as "alpha-1 antitrypsin", "AAT", "lung disease", "inflammation", "protease", "COPD", "bronchiectasis", "cystic fibrosis" and "interstitial lung disease". Studies were eligible for inclusion if they investigated the mechanistic, preclinical or clinical effects of AAT in respiratory disease. Both experimental and clinical studies were considered, while review articles were screened for additional relevant references.

Biology and Molecular Function of AAT

Alpha-1 antitrypsin (AAT) is a 52-kDa glycoprotein and a member of the serine protease inhibitor (serpin) superfamily, with an essential role in protecting tissues from excessive proteolytic damage.[13,16] AAT is an acute-phase protein, synthesised predominately in the liver, that rapidly increases up to 4-fold in response to inflammation or infection.[17]

It circulates in the plasma as an anti-protease but is particularly active in the lungs, where it inhibits neutrophil elastase (NE), cathepsin G, and other proteases released during inflammation. Its function extends beyond protease inhibition, encompassing significant anti-inflammatory, anti-apoptotic, and immunomodulatory effects. Like all serpins, AAT adopts a metastable conformation characterised by a central β-sheet A, several α-helices, and a critical reactive centre loop (RCL) that extends from the molecule's surface.[18] The RCL acts as a bait for target proteases, allowing AAT to form an irreversible complex that neutralises proteolytic activity. Exposure to cigarette smoke reduces the anti-NE activity of AAT by oxidising methionine residues on the active site of the molecule.[19]

Deficiency of AAT can occur due to a mutation in its encoding gene, *SERPINA1*. Alpha-1 antitrypsin deficiency (AATD) predisposes individuals to early-onset emphysema, liver disease and systemic inflammatory dysregulation.[13] Less common manifestations of AATD have been described, such as associations with spontaneous pneumothorax and Kartagener's syndrome.[20,21] Understanding the structure, genetics, and mechanism of action of AAT is central to appreciating its clinical significance. More than 200 allelic variants of *SERPINA1* have been identified, but the most recognised are the M, S, and Z alleles.[22] Rarer variants, including null and dysfunctional variants, are less characterised and are often described primarily through case reports. The M variant represents the wild-type form and is associated with normal circulating levels of AAT (approximately 105–164 mg/dl). The S (E264V substitution) and Z (E342K) alleles are pathogenic variants because they lead to reduced serum levels of the AAT protein. The S allele results in moderately reduced serum levels, around 60% of normal, due to impaired secretion efficiency, whereas the Z allele causes severe deficiency of <15% normal serum levels. The substitution from a negatively charged glutamate to a positively charged lysine disrupts normal protein folding and destabilises interactions that normally maintain the integrity of β-sheet. Consequently, the RCL of another AAT protein is aberrantly inserted, forming polymers of misfolded AAT and activating the unfolded protein response (UPR) in the endoplasmic reticulum.[23]

The liver is the main site of AAT production, responsible for over 80% of circulating levels. Hepatic expression is driven by cytokines and acute-phase signalling pathways.[24,25] AAT is an acute-phase reactant; during systemic inflammation, serum concentrations can increase three- to five-fold. This upregulation is mediated primarily by IL-6 signalling through the JAK–STAT3 pathway, activating the *SERPINA1* promoter.[26] Although hepatocytes produce the majority of AAT, several other cell types express SERPINA1, including alveolar macrophages, monocytes, airway epithelial cells and neutrophils (albeit to a much lower level).[13] Local synthesis is particularly important in the lung and other mucosal tissues, where AAT modulates inflammation directly at sites of injury. Macrophage-derived AAT can be released in response to pro-inflammatory stimuli such as lipopolysaccharide (LPS), TNF-α, and IL-1β.[14]

Cytokines exert potent regulatory effects on AAT expression. IL-6 induces acute-phase transcriptional upregulation in hepatocytes and monocytes.[27] TNF-α enhances regional AAT production by macrophages and epithelial cells, though its effect on hepatic production is more complex and may synergise with IL-6. These regulatory mechanisms ensure that AAT levels increase during inflammation when proteolytic burden is highest.

The primary physiological role of AAT is inhibition of serine proteases, particularly those released by activated neutrophils. The key target of AAT is neutrophil elastase (NE), of which it inhibits by presenting its RCL as a substrate mimic. When a circulating neutrophil detects a chemotactic gradient, it binds to the vascular endothelium and subsequently transmigrates through endothelial junctions into the tissue.[28] During this process, its granules polarise toward the leading edge, enabling the targeted release of elastase at sites of transmigration.

When NE cleaves the RCL, AAT undergoes a conformational change that traps the protease, forming a stable, irreversible complex that distorts the active site of the protease and renders it inactivated. In the airways, this prevents NE-mediated degradation of elastin, extracellular matrix proteins and structural components of the alveolar wall.

AAT also inhibits other serine proteases, such as protease-3 (PR3) and cathepsin G (CG), which are released alongside NE from azurophillic granules of activated neutrophils. Whilst NE is the dominant mediator of structural lung damage due to its potent elastolytic activity, PR3 and CG play more prominent roles in immune regulation and antimicrobial defence.

Total PR3 levels in neutrophils are relatively high but indirect enzymatic measurements indicate that its active concentration may be lower than that of NE.[29] Notably, PR3 exhibits a slower association rate with AAT, meaning it takes longer to be neutralised and can remain enzymatically active for a longer period before forming an inactive AAT-PR3 complex.[30] Consistent with these observations, analyses of airway secretions from both AAT-deficient and non-deficient individuals with COPD show that free, uninhibited PR3 is detected more frequently than unopposed NE, suggesting that PR3 may exert a more sustained contribution to the pathogenesis of COPD and emphysema.[31]

CG plays an important role in infection-driven inflammation and is critical for neutrophil response to chemotactic signalling.[32,33] It activates airway epithelial cells and stimulates secretion from airway submucosal glands.

The link between AATD and emphysema extends beyond protease inhibition. AAT has been shown to exert anti-apoptotic effects of alveolar epithelial and endothelial cells, reduce macrophage activation and suppress pro-inflammatory cytokine production.[34] Loss of these protective effects in AATD may accelerate alveolar destruction and impair tissue repair mechanisms.

AAT also possesses non-inhibitory functions. Beyond protease inhibition, AAT has numerous noncanonical biological roles including anti-inflammatory, anti-apoptotic and immunomodulatory effects (Figure 2). AAT reduces production of pro-inflammatory cytokines (eg, TNF-α, IL-1β) and limits neutrophil recruitment.[35] It can bind LPS and modulate Toll-like receptor signalling, decreasing excessive innate immune activation.[36] It also stabilises cell membranes and protects against oxidant-mediated injury.

AAT inhibits caspase-3 activity and modulates pathways such as NF-κB and JNK, providing cytoprotective effects in epithelial and endothelial cells.[37] This contributes to tissue preservation during inflammation. Although less studied, AAT has been shown to influence adaptive immunity, likely as a result of changes in the cytokine milieu and the induction and maturation of dendritic cells (DCs).[38] In models of autoimmunity or allotransplantation, AAT has been shown to expand and enhance regulatory T cell (Treg) function.[39,40] Cumulatively, these effects help maintain immune homeostasis and limit chronic inflammation (Figure 3).

Even in individuals with normal AAT levels, oxidative stress, particularly from cigarette smoke or chronic inflammation, can inactivate AAT by oxidizing key methionine residues (Met358 and Met351) in the RCL.[41] Oxidized AAT loses its ability to inhibit NE, effectively reducing functional activity and exacerbating protease burden. This mechanism explains why smokers with AAT deficiency experience dramatically accelerated lung damage, and why chronic inflammatory conditions worsen tissue injury.

AAT in Pathophysiology of Inflammatory Lung Diseases

Inflammatory lung diseases represent a heterogeneous group of disorders characterised by dysregulated immune responses, persistent inflammation, and progressive structural damage to the airways or lung parenchyma. Despite differences in

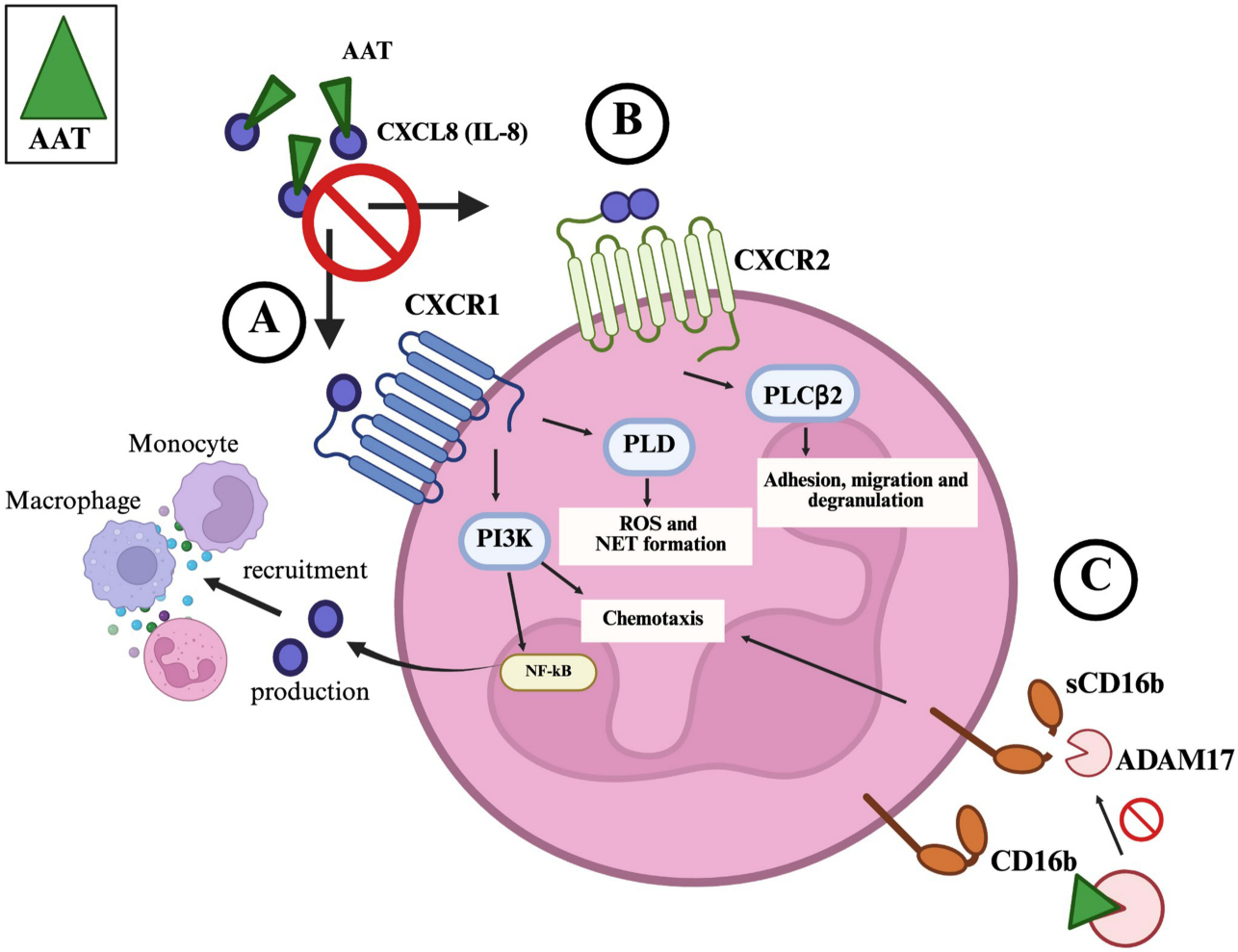

Figure 2 Alpha-1 antitrypsin (AAT) reduces neutrophil-driven inflammation. (**A**) AAT binds the chemokine CXCL8, preventing its interaction with CXCR1 on the surface of neutrophils. In the absence of AAT, CXCL8–CXCR1 signalling activates phosphoinositide 3-kinase (PI3K) and downstream NF-κB–mediated transcription of pro-inflammatory cytokines, including IL-8, promoting recruitment and activation of monocytes, macrophages and neutrophils. CXCR1 signalling also engages phospholipase D (PLD) pathways, leading to reactive oxygen species (ROS) generation and neutrophil extracellular trap (NET) formation. (**B**) CXCL8 binding to CXCR2 triggers phospholipase Cβ2 (PLCβ2)–dependent signalling, resulting in neutrophil adhesion, migration and degranulation. These processes are attenuated by AAT through sequestration of CXCL8. (**C**) AAT binds and inhibits the metalloproteinase ADAM17, preventing cleavage of the neutrophil surface receptor CD16b. Preservation of CD16b limits excessive neutrophil chemotaxis and contributes to the resolution of inflammation.
Abbreviations: AAT, alpha-1 antitrypsin; CXCL8, chemokine ligand 8; IL-8, interleukin-8; CXCR1, 2, chemokine receptor type 1, 2; PI3K, phosphoinositide-3-kinase; PLD, phospholipase D; PLCβ2, phospholipase Cβ2; ADAM17, A Disintegrin and Metalloproteinase 17.

aetiology and clinical presentation, many of these conditions share common pathogenic mechanisms, including excessive neutrophil recruitment, protease–antiprotease imbalance, oxidative stress and impaired resolution of inflammation.

Inherited deficiency of AAT (AATD) is a well-recognised genetic risk factor for COPD and emphysema, providing an example for understanding how protease-antiprotease imbalance drives lung disease.[42] Increasingly, AAT is also being implicated as a disease modifier in other inflammatory lung conditions, including bronchiectasis, cystic fibrosis (CF), interstitial lung diseases (ILDs) and acute inflammatory states, such as viral pneumonia.

Chronic Obstructive Pulmonary Disease and Emphysema

COPD is characterised by persistent airflow limitation and chronic airway inflammation, with neutrophils playing a central pathogenic role.[43] Elevated NE activity has been detected in sputum, bronchoalveolar lavage fluid and lung tissue from patients with COPD, particularly during acute exacerbations, and relates with disease severity and progression.[44,45] NE contributes directly to alveolar wall destruction by degrading elastin, leading to emphysema, and indirectly by stimulating mucous hypersecretion, impairing ciliary function, and activating pro-inflammatory signalling pathways.

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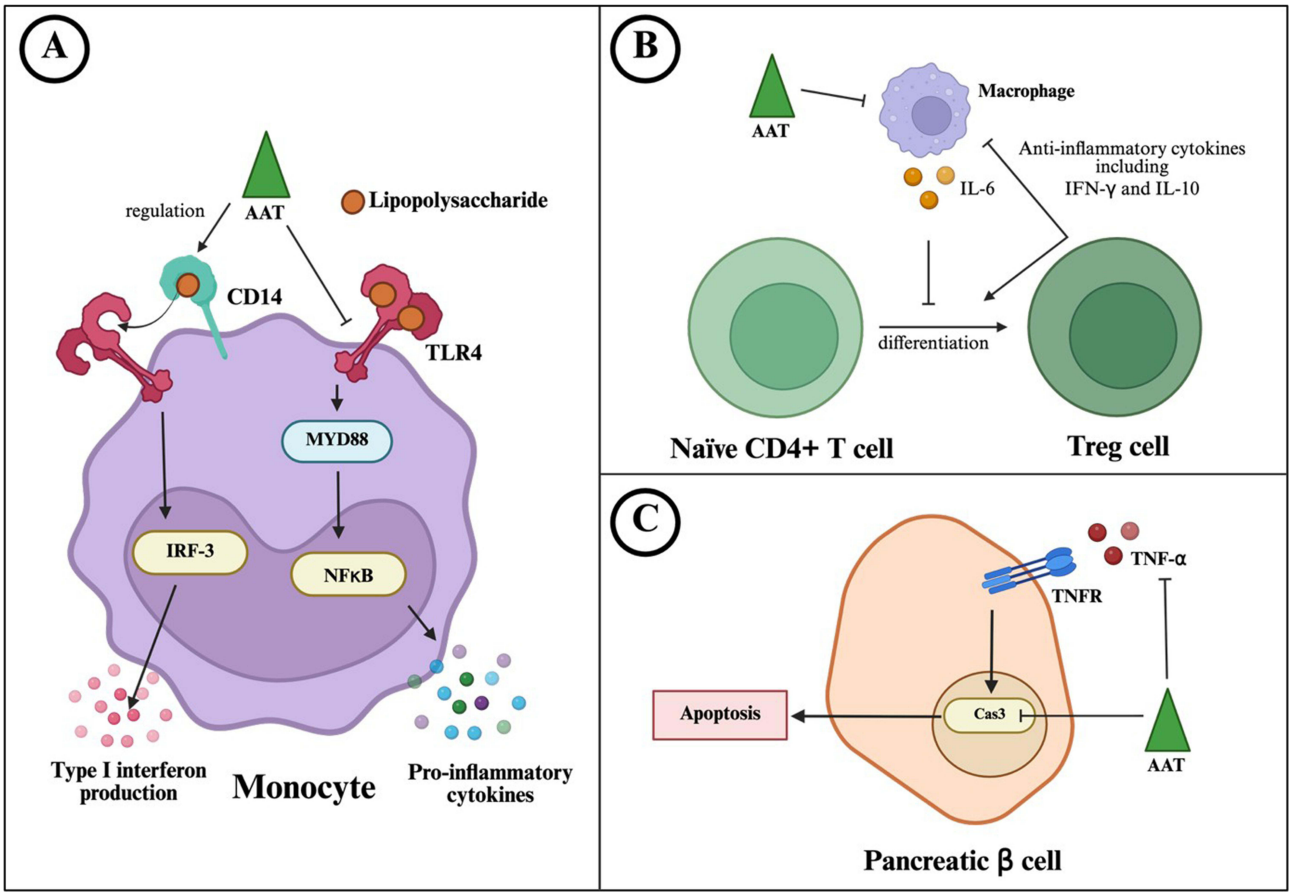

Figure 3 The anti-inflammatory and immunomodulatory roles of alpha-1 antitrypsin (AAT). (**A**) Lipopolysaccharide (LPS), an immunostimulatory component of Gram-negative bacteria, binds to Toll-like receptor 4 (TLR4) on the surface of macrophages. Binding of TLR4 (via CD14-independent pathway) activates the Myd88-dependent pathway, leading to the NFκB-mediated transcription of pro-inflammatory cytokines. Binding of LPS to CD14, and subsequent transfer to TLR4 (the CD14-dependent pathway) leads to the IRF-3-mediated transcription of type I interferons. AAT regulates expression of CD14 and thereby regulating type I interferon production. Similarly, AAT inhibits TLR4-mediated signalling and production of pro-inflammatory cytokines. (**B**) AAT inhibits macrophage activation, leading to reduced secretion of interleukin-6 (IL-6), a cytokine known to antagonise regulatory T-cell (Treg) differentiation. Uninhibited differentiation of CD4 T cells results in a larger number of Treg cells, which produce anti-inflammatory cytokines that further inhibit macrophage activation. This contributes to immune homeostasis. (**C**) Tumour necrosis factor-α (TNF-α) binds to TNF receptors on airway epithelial cells, initiating pro-apoptotic signalling that culminates in activation of caspase-3 and subsequent cell apoptosis. AAT attenuates TNF-α–mediated signalling and reduces caspase-3 activity, thereby limiting cell death and promoting cell survival.

Abbreviations: AAT, alpha-1 antitrypsin; TLR4, Toll-like receptor-4; Myd88, myeloid differentiation primary response 88; IRF3, interferon regulatory factor 3; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-6, IL-10, interleukin-6, 10; IFN-γ, interferon-gamma; TNF-α, tumour necrosis factor alpha; TNFR, tumour necrosis factor receptor; Cas3, caspase-3.

As the dominant inhibitor of NE in the lung, an inherited deficiency of AAT confers a strong genetic risk factor for the development of COPD. Individuals with AATD typically develop panacinar emphysema at a younger age than non-deficient COPD, which is accelerated by cigarette smoke exposure. Cigarette smoke increases neutrophil recruitment and hence, protease release, whilst also generating oxidative stress that can inactivate AAT through oxidation of methionine residues within its RCL. Inflammatory cells further perpetuate this through release of oxidants. The oxidisation of methionine residues (Met^{358} and Met^{351}) to methionine sulfoxide impairs its inhibitory activity towards NE.[46] The potential of oxidised AAT as a biomarker of COPD onset and severity was investigated in a study of 65 patients with COPD (including both smokers and non-smokers) and found.[47]

Smoke exposure promotes the polymerisation of AAT and polymers have been detected in the lungs of non-deficient COPD. A study by Bazzan et al showed the presence of AAT polymers within alveolar macrophages (AMs) from smokers without AATD, but not in non-smokers.[48] Further, the proportion of AMs containing polymers was associated with pack-years smoked and clinical outcomes, such as FEV1/FVC ratio and small airways disease, suggesting a relationship between polymer formation and pathophysiological changes in the airways.

While severe AATD accounts for a minority of COPD cases, non-deficient COPD also exhibit functional AAT insufficiency due to oxidative inactivation or excessive protease burden. Raised levels of AAT are observed in COPD and are associated with increased hospitalisations related to exacerbations.[49] This observation can partly be attributed to exposure to smoke, with levels remaining elevated after smoking cessation.[50] A study performed in the general population found a dose-dependent relationship between smoke exposure (both active and passive) and serum AAT levels, where levels were highest in those smoking ≥15 cigarettes a day.[51]

Bronchiectasis

Bronchiectasis is a chronic inflammatory airway disease characterised by irreversible bronchial dilatation, impaired mucociliary clearance and recurrent respiratory infections.[52] The disease is increasingly recognised as a heterogeneous condition with multiple underlying aetiologies, including post-infectious damage, immune deficiencies, autoimmune disease and genetic disorders such as cystic fibrosis and AATD. Regardless of initiating cause, bronchiectasis is sustained by a self-perpetuating cycle of infection and inflammation that leads to progressive airway remodelling and lung function decline.

Central to bronchiectasis pathophysiology is chronic neutrophil-dominated inflammation. Persistent bacterial colonisation, commonly involving organisms such as *Pseudomonas aeruginosa* and *Haemophilus influenzae*, drives continuous recruitment and activation of neutrophils into the airway lumen.[53] Release of neutrophil proteases and ROS damage airway epithelium, impair mucociliary clearance and further predispose to infection, in a process referred to as the vicious cycle hypothesis.[54,55]

Sputum biomarkers, particularly NE activity, have emerged as strong predictors of disease severity, exacerbation risk and mortality.[56] This highlights the central role of protease-mediated injury in bronchiectasis and provides a mechanistic framework in which AAT may exert protective effects.

NE is a key effector of airway damage in bronchiectasis, capable of degrading elastin, collagens, and other extracellular matrix components, as well as disrupting epithelial tight junctions.[57] Elevated NE activity is associated with more frequent exacerbations, accelerated lung function decline, and poorer clinical outcomes of bronchiectasis.[56] Inadequate AAT activity, whether due to genetic deficiency, functional impairment, or overwhelming protease burden, can exacerbate airway injury. Severe AAT deficiency is an established but relatively uncommon cause of bronchiectasis, where it can occur independent of COPD.[58] However, bronchiectasis is increasingly recognised as a frequent manifestation among individuals with AATD, even in the absence of severe emphysema.[59,60] Observational studies suggest that bronchiectasis may be underdiagnosed in AATD populations and that protease-mediated airway injury contributes independently to disease burden. Importantly, even in individuals without AATD, local depletion or inactivation of AAT within the inflamed airway may create a functional protease–antiprotease imbalance, similar to that seen in genetic deficiency.[12]

Beyond its antiprotease activity, AAT may influence airway inflammation and mucous properties in bronchiectasis.[61] NE contributes to mucous hypersecretion and increased viscosity by stimulating goblet cell hyperplasia and degrading structural components of mucous. By inhibiting NE, AAT may indirectly improve mucous rheology and enhance mucociliary clearance. These findings support the concept that AAT serves as an important regulator of the inflammatory milieu in the bronchiectatic airway.

Clinical data on AAT augmentation therapy in bronchiectasis are limited and instead trials have focussed on reducing the protease burden. Inhibition of the neutrophil serine protease dipeptidyl peptidase 1 (DPP-1), also known as cathepsin C, was assessed in the WILLOW trial.[62] Bronchiectasis patients receiving the drug experienced less exacerbations of disease and a lower FEV1 decline than those receiving placebo. Smaller studies and post-hoc analyses suggest that exogenous AAT can reduce airway NE activity and inflammatory biomarkers.[63] In patients with coexistent AATD and bronchiectasis, augmentation therapy has been associated with stabilisation of lung function and reduced exacerbation frequency.[63]

Collectively, outside severe AATD, available evidence supports a role for AAT as a disease modifier in bronchiectasis, influencing the severity and progression of airway inflammation rather than acting as a primary aetiological factor. This suggests that targeted modulation of protease–antiprotease balance may represent a therapeutic strategy in selected patients with neutrophil-driven disease.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by mutations in the *CFTR* gene, resulting in defective chloride transport, dehydrated airway surface liquid and impaired mucociliary clearance.[64] Chronic bacterial infection and excessive neutrophilic inflammation are hallmarks of CF lung disease and are the principal drivers of morbidity and mortality.

The CF airway is characterised by persistent neutrophilic inflammation. Neutrophils are recruited in large numbers in response to chronic infection and their activation results in the release of high concentrations of NE into the airway lumen. NE levels in CF sputum often exceed those observed in other inflammatory lung diseases by several orders of magnitude, overwhelming endogenous antiprotease defences.[65,66] NE contributes to lung damage in CF through multiple mechanisms, including degradation of extracellular matrix components, disruption of epithelial barriers and impairment of innate immune defence.[67] NE degrades antimicrobial peptides, immunoglobulins, and complement proteins, thereby reducing bacterial clearance and perpetuating infection. This protease-dominated environment establishes a sustained inflammatory state that accelerates structural lung damage.

Although CF is not associated with a deficiency of AAT, the protease–antiprotease balance in the CF airway is disrupted.[68] Endogenous AAT is present but insufficient to neutralise the overwhelming NE burden. Furthermore, oxidative stress within the inflamed airway inactivates AAT, further reducing its functional capacity. This imbalance has prompted interest in therapeutic strategies aimed at augmenting antiprotease activity, rather than solely targeting infection.

Preclinical studies and early-phase clinical trials have investigated aerosolised AAT therapy in CF, aiming to deliver high concentrations of functional AAT directly to the airway (Table 1).[69] These studies have demonstrated reductions in NE activity and inflammatory biomarkers in sputum following treatment. Some trials have reported modest improvements in lung function or quality-of-life/symptom scores, although results have been variable.

While aerosolised AAT has not yet demonstrated clear clinical efficacy, these studies provide proof-of-concept that augmenting antiprotease defences can modify the inflammatory environment of the CF lung. Ongoing advances in CFTR

Table 1 Ongoing Clinical Trials Investigating the Therapeutic Potential of Alpha-1 Antitrypsin.

Disease	Proposed Mechanism(s) of Action	Clinical Trial Number	Trial Phase	Intervention Type	Primary Outcome
COPD (non-AATD)	Anti-inflammatory, inhibition of NE, reduction of oxidative stress	NCT07125664	Phase II	IV AAT	Change in level of circulating (plasma) IL-6
Bronchiectasis (non-AATD)	Anti-protease, modulation of neutrophil-driven inflammation	NCT05582798	Phase IV	IV AAT	Change in sputum NE activity from baseline
		NCT03383939	Phase II	Inhaled AAT	Change in AAT levels in BAL from baseline
Cystic fibrosis	Anit-inflammatory, inhibition of NE, reduction of airway epithelial apoptosis	NCT00486837	Phase II	Inhaled AAT	Change in free elastase in induced sputum from baseline
		NCT01684410	Phase II	Inhaled AAT	Safety and tolerability (adverse event frequency)
COVID-associated lung injury	Anti-inflammatory, inhibition of protease-mediated viral entry, cytoprotective	NCT04385836	Early phase I	Inhaled AAT	Clinical improvement, as measured Ordinal Scale for Clinical Improvement
		NCT04799873	Observational	Inhaled AAT, combined inhaled/IV	Disease course including deterioration, death, ICU admission or ventilation

(*Continued*)

Table 1 (Continued).

Disease	Proposed Mechanism(s) of Action	Clinical Trial Number	Trial Phase	Intervention Type	Primary Outcome
Type 1 diabetes mellitus	Anti-apoptotic, immunomodulatory, preservation of pancreatic β-cells	NCT01319331	Phase I	IV AAT	Safety and feasibility
		NCT01661192	Phase II	IV AAT	Safety and tolerability
		NCT01304537	Phase I/II	IV AAT	Safety and tolerability
Graft-versus-host-disease	Anti-inflammatory, immune regulation, protection against tissue injury	NCT03459040	Phase II	IV AAT	Frequency of high- risk patients who develop steroid refractory GVHD
		NCT02523821	Phase I/II	IV AAT	Safety (toxicity); stability or improvement of GVHD
		NCT01700036	Phase II	IV AAT	Percentage of patients who achieve complete or partial resolution of GVHD
Acute myocardial infarction	Anti-inflammatory, tissue-protective	NCT01936896	Phase I/II	IV AAT	C-reactive protein (area under the curve)
Alcohol-associated hepatitis	Anti-inflammatory	NCT06582329	Phase II	IV AAT	Change in serum IL-6 within 1 week from baseline
Eosinophillic oesophagitis	Anti-protease, anti-inflammatory	NCT05485155	Phase II	IV AAT	Change in oesophageal AAT concentration from baseline

Abbreviations: NE, Neutrophil Elastase; IV, Intravenous; IL-, Interleukin; GVHD, Graft-versus-Host Disease.

modulator therapy may further shift interest toward adjunctive anti-inflammatory strategies, including AAT-based approaches, to address residual inflammatory burden.

Interstitial Lung Disease and Idiopathic Pulmonary Fibrosis

Interstitial lung diseases (ILDs) comprise a heterogeneous group of disorders characterised by inflammation and fibrosis of the lung interstitium. Idiopathic pulmonary fibrosis (IPF) is the most common and severe form, marked by progressive fibrosis, declining lung function and poor prognosis.[1] While the inflammatory component of IPF is less prominent than in airway diseases, immune dysregulation and epithelial injury play critical roles in disease initiation and progression. Current models of IPF pathogenesis display repetitive alveolar epithelial injury, aberrant wound healing and excessive fibroblast activation, leading to extracellular matrix deposition.[70]

Neutrophils and other inflammatory cells are present in the IPF lung and increased levels of proteases and inflammatory mediators have been detected in BAL fluid.[71,72] Early studies detected NE-AAT complexes in the bronchoalveolar lavage (BAL) of patients with pulmonary fibrosis.[73] Although inflammation is not the primary driver of fibrosis, it is increasingly recognised as an important contributor to early disease processes.

Emerging evidence suggests that AAT may influence fibrotic pathways through mechanisms distinct from its role in neutrophil-driven airway diseases. AAT has been shown to modulate transforming growth factor-beta (TGF-β) signalling, a central pathway in fibrosis, and to inhibit epithelial cell apoptosis.[74] Inhibition of apoptosis, by AAT, is mediated through multiple pathways. For instance, AAT has been shown to directly or indirectly inhibit key executioner caspases (particularly caspase-3), thereby limiting the downstream cascade that leads to programmed cell death.[75] In addition, AAT helps stabilise mitochondrial membranes, reducing cytochrome C release which prevents activation of intrinsic apoptotic pathways, as well as dampening pro-inflammatory- and ROS-induced cellular injury.[76]

In vitro studies indicate that AAT can promote fibroblast proliferation and reduce collagen production, suggesting potential tissue repair properties.[77]

AAT as a therapeutic agent in ILD is of interest, owing to its combined anti-inflammatory, anti-apoptotic and potential anti-fibrotic effects. While no large clinical trials of AAT therapy in IPF have been completed, preclinical data suggest that AAT could modulate key pathogenic pathways. It may be of particular interest to investigate in patients with combined pulmonary fibrosis and emphysema (CPFE) where two potentially AAT related pathologies are seen simultaneously.

Acute Inflammatory Lung Disease: Viral Infections and COVID-19

Acute inflammatory lung diseases, particularly those caused by viral respiratory infections, are characterised by rapid activation of innate immune responses, extensive cytokine release and recruitment of neutrophils to the lung.[78] While inflammation is essential for viral clearance, excessive or dysregulated immune responses can lead to severe lung injury, acute respiratory distress syndrome (ARDS) and systemic complications. The COVID-19 pandemic highlighted the critical role of host inflammatory responses, rather than viral burden alone, in determining disease severity and outcomes.[79]

Respiratory viruses such as influenza viruses, respiratory syncytial virus (RSV) and coronaviruses initiate infection by invading airway and alveolar epithelial cells, triggering pattern recognition receptors and downstream inflammatory signalling pathways.[80] This results in rapid recruitment of innate immune cells, particularly neutrophils, to the lung. Activated neutrophils release proteases and ROS, which collectively contribute to epithelial damage and vascular permeability.[81]

In severe viral pneumonia and ARDS, excessive neutrophil activation leads to widespread tissue injury that may persist even after viral clearance. Elevated levels of NE have been detected in BAL fluid and plasma of patients with severe viral infections, associating with markers of lung injury and poor clinical outcomes.[82] This protease-rich inflammatory environment closely resembles that observed in chronic neutrophilic lung diseases, suggesting that similar regulatory mechanisms, including antiprotease activity, may influence disease severity. In vitro studies have shown that AAT is able to mediate virus reduction in bronchial epithelial cells exposed to cigarette smoke and observational studies suggested that individuals with lower circulating AAT levels or impaired AAT function are more susceptible to severe outcomes during acute inflammatory lung disease.[83,84]

Under physiological conditions, AAT limits protease-mediated tissue injury during acute inflammation. However, during severe viral infections, the rapid influx of activated neutrophils can overwhelm endogenous antiprotease defences. In addition, oxidative stress generated during acute inflammation may inactivate AAT, reducing its capacity to neutralise NE. This creates a transient, but profound, protease–antiprotease imbalance that contributes to acute lung injury.[85]

Beyond its role as a protease inhibitor, AAT has been proposed to exert direct antiviral and immunomodulatory effects. One mechanism is the inhibition of transmembrane protease serine 2 (TMPRSS2), a host protease required for viral entry by several respiratory viruses, including SARS-CoV-2.[86] In vitro studies have demonstrated that AAT can inhibit TMPRSS2 activity, thereby reducing viral entry into host cells. One study screened a library of peptides from BAL fluid, where it identified AAT as an endogenous antiviral factor, potently inhibiting the entry of SARS-CoV-2 into primary airway epithelial cells in an air-liquid-interface culture.[87] However, effects were primarily demonstrated at the level of viral entry and the antiviral property of AAT is not understood during established or prolonged infection.

In addition to potential antiviral effects, AAT has been shown to modulate immune responses by reducing pro-inflammatory cytokine release, inhibiting neutrophil activation and limiting endothelial and epithelial injury. Combined, these properties of AAT potentiate its use as a therapy for attenuating the hyperinflammatory responses associated with severe viral pneumonia, including the "cytokine storm" observed in COVID-19.

During the COVID-19 pandemic, multiple observational studies identified associations between dysregulated protease–antiprotease balance and disease severity.[84,88] Elevated NE activity and markers of neutrophil activation were consistently linked to worse outcomes, including respiratory failure and mortality. Conversely, higher circulating AAT levels were associated with improved outcomes in some cohorts, suggesting a protective role. The ratio of interleukin-6 (IL-6) to AAT has been proposed as a biomarker of disease severity, reflecting the balance between pro-inflammatory signalling and endogenous anti-inflammatory capacity. Patients with severe COVID-19 often exhibited disproportionately high IL-6 levels relative to AAT, indicating an inadequate inhibitory response.

The experience of COVID-19 has renewed interest in host-directed therapies that modulate inflammatory responses, rather than targeting pathogens directly. While its role in acute viral infections is not yet fully defined, accumulating

evidence suggests that AAT may influence disease severity by mediating the balance between effective host defence and collateral tissue damage. Further studies are needed to identify patient subgroups most likely to benefit from AAT-based interventions and to clarify the timing and route of administration that may optimise therapeutic effects.

Therapeutic Potential and Targeting Strategies for AAT

AAT replacement has emerged as a promising therapeutic strategy for a range of inflammatory lung diseases, extending beyond classical AATD to conditions such as bronchiectasis, cystic fibrosis and COVID-19, where protease-driven lung injury contributes to disease progression. Current treatment strategies are largely focussed on symptom control, reducing exacerbations and slowing disease progression, rather than directly reversing underlying tissue damage. Standard therapy for COPD includes bronchodilators (β2-agonists and antimuscarinics), inhaled corticosteroids for selected patients and, in those with frequent exacerbations, prophylactic antibiotics. Therapeutic approaches are diverse and continue to evolve, such as the introduction of CFTR modulators in CF, cathepsin inhibition in bronchiectasis and anti-fibrotics for ILD, namely nintedanib and pirfenidone.[89] AAT-based approaches may complement standard therapies, by targeting a fundamental pathogenic mechanism, whilst also exerting broader anti-inflammatory and immunomodulatory effects.

Evidence for AAT-based therapies varies, with established clinical use in augmentation for AATD-associated COPD, alongside early-phase clinical trials and preclinical studies investigating their potential in non-deficiency lung disease. Plasma-derived AAT augmentation therapy remains the most conventional intervention in subjects with a deficiency, delivering exogenous protein to restore circulating and pulmonary levels. Advances in biotechnology have enabled the development of recombinant AAT, offering a scalable alternative to plasma-derived products, while inhaled formulations aim to achieve high local concentrations in the airway with potentially reduced systemic exposure. More recently, gene and cell-based therapies are under investigation to provide sustained, endogenous production of functional AAT, with the ultimate goal of addressing both systemic and pulmonary protease-antiprotease imbalances.

AAT Augmentation for the Treatment of AATD

Plasma-Derived AAT Augmentation

AATD is characterised by reduced circulating levels of functional alpha-1 antitrypsin (AAT), resulting in an imbalance between neutrophil-derived serine proteases, particularly NE and their endogenous inhibitors. In the lung, uninhibited NE activity leads to progressive destruction of alveolar walls, culminating in panacinar emphysema.[90] Augmentation therapy restores this protease–antiprotease balance by supplementing circulating AAT levels, thereby reducing airway tissue injury.

Since the 1980s, intravenous (IV) augmentation therapy using plasma-derived AAT has been the standard of care for individuals with severe AATD and emphysema across the US and several European countries, excluding the UK.[91] Augmentation therapy is not recommended for individuals with the MZ genotype, given the lack of evidence for clinical benefit, nor for the treatment of AATD-associated liver disease, as IV AAT does not address intracellular polymer accumulation in hepatocytes. Treatment is also discouraged in individuals who continue to smoke, as ongoing tobacco exposure drives neutrophilic inflammation and NE release, contradicting any protective effect of supplementation.

Plasma-derived AAT products, such as Prolastin® and Zemaira® are purified from pooled human donor plasma and administered at a standard dose of 60 mg/kg weekly. This raises serum AAT concentrations above the historically proposed "protective threshold" of approximately 11 μM (80 mg/dL). A randomised, double-blind, placebo-controlled Phase II study in individuals with severe AATD showed that 12 weeks of once-daily inhaled AAT (80 or 160 mg) significantly increased AAT concentration, antiprotease activity, and AAT–neutrophil elastase complexes in the epithelial lining fluid, while reducing neutrophil proportions, indicating restoration of local protease homeostasis and anti-inflammatory effects in the lung.[92] Inhaled AAT was well tolerated, and plasma M-AAT levels increased in a dose-dependent manner, demonstrating both local airway and systemic effects. While the standard 60 mg/kg weekly regimen reliably restores serum AAT above the protective threshold, it is unclear whether higher doses confer additional clinical benefit. Trials comparing standard and high-dose regimens are ongoing, but increased dosing must be carefully balanced against substantially higher costs and treatment burden.

The 11 μM threshold, however, is derived from observational epidemiological data rather than direct experimental evidence defining a biological threshold for lung injury. Consequently, genotype and phenotype are considered more reliable predictors of emphysema risk and progression than absolute serum AAT levels alone.[93]

Early evidence supporting IV augmentation therapy emerged from observational cohort studies, which suggested slower decline in forced expiratory volume in one second (FEV_1) and reduced mortality among treated individuals compared with untreated controls. However, FEV_1 has significant limitations as a surrogate endpoint in AATD, given its insensitivity to early parenchymal loss and its variability in advanced disease. This recognition prompted a shift toward imaging-based endpoints, particularly quantitative computed tomography (CT) lung densitometry, which directly measures emphysema progression.

The RAPID trial represented a pivotal advance in the evidence base for augmentation therapy.[94] In this double-blind, placebo-controlled randomised trial, patients with severe AATD-associated emphysema were assigned to receive weekly IV AAT or placebo over a two-year period. The primary endpoint was annual change in lung density measured by CT at total lung capacity. Treatment with IV AAT resulted in a statistically significant reduction in the rate of lung density loss compared with placebo, providing robust evidence that augmentation therapy slows structural lung destruction. Importantly, the RAPID trial demonstrated that CT densitometry is a more sensitive and clinically meaningful outcome measure than spirometry in this context. The lack of a significant difference in FEV_1 decline between treatment groups underscored the inadequacy of spirometric endpoints alone to capture disease modification in AATD. The open-label extension study, RAPID-OLE, further strengthened the case for early initiation of therapy.[95] Patients originally assigned to placebo who crossed over to active treatment experienced a reduction in the rate of lung density decline once therapy commenced. However, lung tissue lost during the placebo phase was not recovered, highlighting the irreversible nature of emphysematous destruction and reinforcing the importance of early intervention to preserve lung structure.

In parallel with randomised trials, large registry-based studies have investigated the long-term effects of augmentation therapy.[96] Multinational observational analyses have demonstrated a significant reduction in all-cause mortality among patients with severe AATD receiving IV AAT, even after adjusting for baseline FEV_1 and its rate of decline.[97] Notably, this survival benefit appeared to be independent of spirometric preservation, suggesting that augmentation therapy may exert additional effects beyond structural lung protection.

Recombinant AAT Augmentation

Limitations associated with plasma-derived products, including supply constraints and the need for lifelong weekly infusions, have driven the development of recombinant and engineered AAT molecules. Advances in protein engineering have enabled the creation of fusion proteins designed to extend circulating half-life and reduce dosing frequency while preserving antiprotease activity. One such strategy involves linking AAT to the Fc region of immunoglobulins, thereby exploiting neonatal Fc receptor recycling pathways to prolong serum persistence.[98] Early clinical studies have demonstrated favourable pharmacokinetics and tolerability, with ongoing trials assessing whether these constructs can achieve sustained restoration of functional AAT levels and comparable protection against lung tissue loss. The imnmunogenicity, long-term safety and comparative efficacy relative to plasma-derived therapies are unclear.

Inhaled AAT Augmentation

Inhaled AAT therapy is an alternative or adjunct to IV augmentation, aiming to deliver AAT directly to the lung and airway surface where protease activity is highest. Nebulised delivery improves local bioavailability of AAT and early phase studies have demonstrated that inhaled AAT can increase epithelial lining fluid concentrations and reduce biomarkers of airway inflammation.[99] However, achieving consistent and therapeutically significant deposition throughout the diseased lung has proven challenging, particularly in individuals with advanced airflow obstruction or heterogeneous emphysema distribution. Furthermore, maintaining sustained antiprotease activity may require frequent dosing. Despite these challenges, ongoing Phase 3 trials using optimised inhalation devices and formulations are evaluating whether inhaled AAT can slow emphysema progression or reduce exacerbation frequency (NCT04204252).

Beyond AATD, inhaled AAT is of particular interest in diseases characterised by prominent neutrophilic airway inflammation, such as bronchiectasis and cystic fibrosis.[63,100] In these conditions, excessive protease activity contributes

to airway damage and infection susceptibility. Delivery of antiprotease augmentation directly to the airways may offer therapeutic benefit over systemic augmentation, although robust clinical evidence is still lacking.

While augmentation therapy effectively restores circulating AAT levels, it does not address the underlying genetic defect or the hepatic accumulation of mutant protein in AATD. Genetic therapies therefore represent an attractive strategy with the potential to modify disease, offering the possibility of durable or even curative interventions that could simultaneously target both lung and liver manifestations of AATD.

Genetic-Based Therapies to Restore Functional AAT

RNA-based approaches aim to modify SERPINA1 expression at the transcript level without permanently altering genomic DNA.[101] RNA interference (RNAi) therapies are designed to reduce the production of mutant Z-AAT by selectively degrading SERPINA1 mRNA in hepatocytes.[102] By lowering intracellular levels of misfolded protein, RNAi approaches reduce hepatocellular stress, inflammation, and fibrosis. However, because these therapies also reduce the synthesis of any residual wild-type AAT, they may exacerbate systemic deficiency and therefore require concomitant augmentation therapy to protect the lung. In contrast, RNA editing approaches seek to directly correct the pathogenic PiZZ mutation at the mRNA level, converting mutant transcripts into wild-type sequences capable of producing functional AAT. This strategy offers the theoretical advantage of simultaneously reducing polymer accumulation in the liver while restoring circulating AAT levels. Early clinical studies have demonstrated proof-of-concept, with a substantial proportion of circulating AAT following treatment consisting of the wild-type M form (NCT06405633). These findings suggest that RNA editing can partially reprogram hepatocytes to produce functional protein without altering the underlying genome. Despite these promising early results, RNA-based therapies face several challenges. The effects are transient, necessitating repeated dosing to maintain therapeutic benefit. Efficient and selective delivery to hepatocytes remains critical, with lipid nanoparticle and ligand-based targeting strategies currently under evaluation.[103] Long-term safety and durability of response need to be investigated through extended clinical follow-up.

DNA-level editing represents a more definitive approach, aiming to correct the underlying *SERPINA1* mutation permanently. Advances in CRISPR-based technologies have enabled the development of base editors that can perform single-nucleotide conversions without inducing double-strand DNA breaks. This is particularly relevant for AATD, as the PiZ mutation results from a single base substitution, making it an ideal candidate for base editing strategies.

Preclinical studies have demonstrated successful correction of the PiZ mutation in hepatocytes, resulting in restored secretion of functional AAT and reduced intracellular polymer accumulation.[104] Early-phase clinical trials are assessing the safety and feasibility of in vivo base editing in humans (NCT06389877). For a successful response, DNA-editing therapies should achieve uniform editing across a sufficient proportion of hepatocytes, whilst avoiding off-target genomic effects. Although early, these findings potentiate DNA base editing as a curative therapy that prevents both lung and liver disease.

Most genetic therapies for AATD have focused on the liver, reflecting its central role as the primary source of circulating AAT and the site of polymer-induced toxicity. However, this strategy assumes efficient secretion and adequate delivery of corrected AAT to the lung, which may not fully address local protease–antiprotease imbalance in all individuals. Lung-targeted genetic therapies, including viral vector-mediated delivery of functional SERPINA1 to airway epithelial cells, have therefore been proposed as an alternative or complementary approach. By enabling local AAT production within the respiratory tract, such strategies could theoretically provide higher regional concentrations of AAT at sites of active inflammation. While early-phase studies of inhaled or vector-based lung gene delivery have demonstrated feasibility, challenges related to transduction efficiency, immune responses, and durability of expression remain significant. Further, ethical and regulatory factors must be considered for permanent genome editing therapies. While the somatic nature of these interventions avoids the heritable risks associated with germline editing, careful evaluation of risk–benefit balance will be critical, particularly given the variable severity and late onset of AATD manifestations.

Utilising the Broader Anti-Inflammatory Properties of AAT for the Treatment of Non-Deficiency Inflammatory Lung Diseases

Beyond its primary role as a serine protease inhibitor, AAT exerts a wide range of immunomodulatory, anti-inflammatory and tissue-protective effects.[105] These pleiotropic effects potentiate the application of AAT as a therapeutic agent in

inflammatory and fibrotic diseases outside the context of AATD. Clinical studies are comparatively sparse to those in AATD, often consisting of small, early-phase trials with limited sample sizes and short follow-up periods, restricting the ability to draw definitive conclusions regarding efficacy.

Both endogenous and exogenously administered AAT have been shown to influence key inflammatory signalling pathways, regulate cytokine expression, modulate oxidative stress, and attenuate apoptotic and fibrotic responses.[106] Importantly, many of these effects appear to be independent of direct elastase inhibition, suggesting that AAT may function as a broader homeostatic regulator of immune responses. One of the most consistently described anti-inflammatory actions of AAT is its ability to suppress activation of the nuclear factor kappa B (NF-κB) signalling pathway, a central regulator of innate immune responses.[107] NF-κB activation drives the transcription of numerous pro-inflammatory genes, including cytokines, chemokines, adhesion molecules, and enzymes involved in oxidative stress. Experimental studies have demonstrated that AAT inhibits NF-κB nuclear translocation in macrophages, neutrophils and epithelial cells exposed to inflammatory stimuli such as lipopolysaccharide or cigarette smoke extract.[108,109] This suppression is associated with reduced expression of downstream mediators including interleukin-8 (IL-8), tumour necrosis factor-alpha (TNF-α), and interleukin-1β. The precise mechanisms underlying this effect remain incompletely defined but may involve stabilisation of inhibitor κB (IκB), interference with upstream kinases, or direct interactions between AAT and cell surface receptors.[110,111] In the context of chronic lung disease, NF-κB inhibition by AAT may be particularly relevant, as persistent pathway activation contributes to sustained neutrophilic inflammation, protease release, and progressive tissue injury.[112]

Modulation of these cytokines has impact on neutrophil recruitment and activation. IL-8, a potent neutrophil chemoattractant, is consistently reduced in experimental models following AAT treatment. This reduction may reflect both NF-κB–dependent transcriptional suppression and direct binding of AAT to IL-8, thereby limiting its bioavailability and chemotactic activity.[113] Similarly, AAT has been reported to downregulate TNF-α production by monocytes and macrophages, dampening downstream inflammatory cascades.[114] In parallel, AAT may promote the release of anti-inflammatory mediators such as interleukin-10, contributing to a shift toward resolution of inflammation. These cytokine-modulatory effects suggest that AAT can influence immune cell phenotype and function, favouring anti-inflammatory or pro-resolving states. Importantly, these actions are not restricted to AAT-deficient settings. In vitro and in vivo studies have demonstrated similar immunomodulatory effects of AAT in models of acute lung injury, sepsis and autoimmune inflammation, supporting the concept of AAT as a general anti-inflammatory agent. Ongoing clinical trials are seeking the efficicacy of AAT as a therapy for type 1 diabetes, with the hypothesis that AAT may protect β-cells (Table 1).[115] These findings provide a mechanistic basis for observations that augmentation therapy may exert anti-inflammatory benefits beyond simple restoration of antiprotease capacity.

Oxidative stress plays a central role in the pathogenesis of many chronic lung diseases, contributing to epithelial injury, impaired repair mechanisms, and activation of pro-fibrotic pathways. AAT has been shown to exert antioxidant effects through both direct and indirect mechanisms. These include scavenging of reactive oxygen species, preservation of endogenous antioxidant defences, and inhibition of oxidant-producing enzymes released by activated neutrophils. In parallel, AAT has been implicated in the regulation of apoptosis, particularly in epithelial and endothelial cells. Experimental models suggest that AAT can inhibit caspase activation and reduce apoptosis induced by inflammatory or oxidative insults.[116] By preserving cell viability and barrier integrity, AAT may limit secondary inflammatory amplification and tissue remodelling. These cytoprotective effects are of particular relevance in acute inflammatory states such as acute respiratory distress syndrome (ARDS), where widespread epithelial and endothelial apoptosis contributes to alveolar–capillary barrier disruption and respiratory failure. A randomised, placebo-controlled trial used IV AAT as a treatment for ARDS, secondary to COVID-19, and demonstrated a significant reduction in plasma IL-6 concentration in the control arm.[117]

The COVID-19 pandemic renewed interest in therapies capable of modulating dysregulated inflammation and preventing long-term fibrotic sequelae following viral pneumonia. AAT was proposed as a candidate therapeutic in this context, based on its combined anti-inflammatory, anti-protease, and cytoprotective properties.[118] Preliminary studies have suggested that AAT may attenuate inflammatory responses in severe viral infections and community-acquired pneumonia, although robust clinical trial data are still lacking.[119]

Beyond COVID-19, AAT may have broader applicability in ARDS of diverse aetiologies, as well as in chronic fibrotic lung diseases characterised by persistent inflammation and aberrant repair.[74] Importantly, these potential indications extend the relevance of AAT therapy beyond genetically defined populations, raising questions regarding dosing, delivery routes, and long-term safety in non-AATD patients.

Emerging evidence suggests that AAT may also exert anti-fibrotic effects, modulating pathways involved in fibroblast activation, extracellular matrix deposition, and tissue remodelling. In preclinical models, AAT has been shown to attenuate transforming growth factor-beta (TGF-β) signalling, a key driver of fibrosis in multiple organs. By limiting fibroblast proliferation and myofibroblast differentiation, AAT may reduce excessive collagen deposition and scar formation. These findings have prompted interest in the potential application of AAT in interstitial lung diseases (ILDs), including idiopathic pulmonary fibrosis, as well as in fibrotic complications following severe lung injury. Although clinical data remain limited, early experimental results provide a compelling rationale for further investigation.

Despite preclinical evidence, translation of AAT's anti-inflammatory and anti-fibrotic properties into clinical practice remains challenging. Optimal dosing regimens for immunomodulatory effects may differ from those required for protease inhibition, and the relative contributions of systemic versus local (inhaled) delivery remain to be defined. It remains unclear whether exogenous AAT can achieve sufficient concentrations at sites of inflammation to confer meaningful clinical benefit. The lack of large, well-powered randomised controlled trials limits definitive conclusions.

Furthermore, distinguishing disease-modifying effects from non-specific anti-inflammatory actions will be essential in designing future trials. Nevertheless, the expanding understanding of AAT as a multifunctional immunomodulator has altered perceptions of its therapeutic potential. These insights not only support continued optimisation of AAT therapy in deficiency states but also novel applications in a wide range of inflammatory and fibrotic lung diseases.

Conclusion

AAT is increasingly recognised as a central regulator of inflammatory homeostasis in the lung, with roles extending beyond its classical function as a neutrophil elastase inhibitor. Dysregulation of AAT, whether through genetic deficiency or functional insufficiency in the setting of chronic inflammation, contributes directly to protease-driven tissue injury, persistent neutrophilic inflammation and progressive lung damage. Therapeutic strategies have evolved from augmentation therapy in AATD to emerging gene- and RNA-based approaches aimed at restoring sustained endogenous production.

Growing evidence that AAT exerts pleiotropic anti-inflammatory, immunomodulatory and potentially anti-fibrotic effects has expanded its relevance to a range of inflammatory lung diseases beyond AATD and COPD. Preclinical studies consistently demonstrate protective effects of inflammation, protease activity and tissue integrity, supporting a mechanistic rationale for therapeutic application. However, translation into clinical benefit remains limited by a relative lack of large, well-powered randomised controlled trials, heterogeneity in study design and uncertainty regarding optimal patient selection, dosing and delivery strategies.

AAT represents a promising disease-modifying therapy that targets fundamental pathways of inflammation and tissue injury. Future research should prioritise clinical trials, to fully realise the therapeutic potential of AAT across inflammatory lung diseases.

Data Sharing Statement

Data sharing is not applicable to this article as no data was created or analysed in this study.

Author Contributions

DAS; conceptualization, writing – original draft, writing – review and editing. AMT; conceptualization, writing – review and editing, supervision. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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