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Review

Alpha-1 Antitrypsin Substitution for Extrapulmonary Conditions in Alpha-1 Antitrypsin Deficient Patients

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Abstract

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder which most commonly manifests as pulmonary emphysema. Accordingly, alpha-1 antitrypsin (AAT) augmentation therapy aims to reduce the progression of emphysema, as achieved by life-long weekly slow-drip infusions of plasma-derived affinity-purified human AAT. However, not all AATD patients will receive this therapy, due to either lack of medical coverage or low patient compliance. To circumvent these limitations, attempts are being made to develop lung-directed therapies, including inhaled AAT and locally-delivered AAT gene therapy. Lung transplantation is also an ultimate therapy option. Although less common, AATD patients also present with disease manifestations that extend beyond the lung, including vasculitis, diabetes and panniculitis, and appear to experience longer and more frequent hospitalization times and more frequent pneumonia bouts. In the past decade, new mechanism-based clinical indications for AAT therapy have surfaced, depicting a safe, anti-inflammatory, immunomodulatory and tissue-protective agent. Introduced to non-AATD individuals, AAT appears to provide relief from steroid-refractory graft-versus-host disease, from bacterial infections in cystic fibrosis and from autoimmune diabetes; preclinical studies show benefit also in multiple sclerosis, ulcerative colitis, rheumatoid arthritis, acute myocardial infarction and stroke, as well as ischemia-reperfusion injury and aberrant wound healing processes. While the current augmentation therapy is targeted towards treatment of emphysema, it is suggested that AATD patients may benefit from AAT augmentation therapy geared towards extrapulmonary pathologies as well. Thus, development of mechanism-based, context-specific AAT augmentation therapy protocols is encouraged. In the current review, we will discuss extrapulmonary manifestations of AATD and the potential of AAT augmentation therapy for these conditions.

Abbreviations: alpha-1 antitrypsin deficiency, **AATD**; alpha-1 antitrypsin, **AAT**; chronic obstructive pulmonary disease, **COPD**; graft-versus-host-disease, **GVHD**; cystic fibrosis, **CF**; myocardial infarction, **MI**

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Introduction

Genetic Alpha-1 Antitrypsin Deficiency is More Than a Lung Condition

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder caused mainly by homozygosity for the Z allele of the SERPINA1 gene. This severe form of AATD is associated with an accumulation of alpha-1 antitrypsin (AAT) in hepatocytes that fails to reach desired levels in the circulation, eventually leading to a variety of clinical symptoms of which pulmonary emphysema is most noted. AATD individuals tend to develop chronic obstructive pulmonary disease (COPD) at a young age, perhaps explaining the overall high lung graft survival rates within this group (6.2 years for AATD and 5.3 years for non-AATD–related COPD).[1] Since uncontrolled neutrophil elastase activity is considered a pivotal factor in the development of emphysema in AATD patients, inhibiting neutrophil elastase activity and delaying the progression of emphysema has been the primary endpoint of AAT augmentation therapy for patients with AATD in the past several decades.[2-4]

The state-of-the-art approach for treating lung disease in genetic AATD is comprised of weekly slow-drip infusions of plasma-derived human AAT at 60mg/kg. This treatment protocol maintains serum AAT levels of at least 11μM, a concentration that is presumably protective to the lung in the event of neutrophil elastase-related damage. Intravenous AAT augmentation therapy for AATD was approved by the U.S. Food and Drug Administration in the United States in 1988, and soon after by regulatory agencies around the world. Table 1 summarizes the current international guidelines for the indication of AAT augmentation therapy.

Table 1. Current International Guidelines and Criteria for Alpha-1 Antitrypsin Augmentation Therapy

Organization	Criteria	Reference
The Spanish Society of Pulmonology and Thoracic Surgery	• Age ≥ 18 years. • AATD levels ≤ 35% of the normal values. • PiZZ phenotype or rare deficient variants. • Abstinence from smoking for at least six months. • Pulmonary emphysema confirmed by clinical profile accompanied by FEV_1/FVC < 0.70 and FEV_1 < 80%. • Confirmation of accelerated loss of pulmonary function in non-index cases. • Exclusion of associated IgA deficiency. • Patient's commitment to the treatment.	5
The Medical and Scientific Advisory Committee of the Alpha-1 Foundation	• Individuals with an FEV_1 less than or equal to 65% predicted. • For those with lung disease related to AATD and an FEV_1 > 65%, we recommend discussion with each individual regarding the potential benefits of reducing lung function decline with consideration of the cost of therapy and lack of evidence for such benefit. • Individuals with necrotizing panniculitis. *Intravenous augmentation therapy is not recommended for:* • Individuals with the MZ genotype of AATD. • Individuals with lung disease due to AATD who continue to smoke. • Individuals with AATD and emphysema or bronchiectasis who do not have air flow obstruction. • The treatment of liver disease due to AATD. • Individuals who have undergone liver transplantation.	6

	Additional recommendations regarding dosing of intravenous augmentation therapy: • Weekly doses higher than the current FDA-approved dose are not recommended. • Monitoring of trough AAT blood levels to evaluate the adequacy of AAT augmentation dosing is not recommended.	
The American Thoracic Society and the European Respiratory Society	• The use of intravenous augmentation therapy for individuals with established airflow obstruction from AATD.	48
National Institute for Health and Care Excellence	• Patients identified as having AATD should be offered the opportunity to be referred to a specialist center to discuss the clinical management of this condition. • AAT replacement therapy is not recommended for patients with AATD.	8
Canadian Thoracic Society	• AAT augmentation therapy may be considered in non-smoking or ex-smoking patients with COPD (FEV_1 25% to 80% predicted) attributable to emphysema and documented AATD (level ≤11 μM), who are receiving optimal pharmacological and nonpharmacological therapies (including comprehensive case management and pulmonary rehabilitation) because of benefits in CT scan lung density and mortality.	9

AATD=alpha-1 antitrypsin deficiency; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; AAT=alpha-1 antitrypsin; COPD=chronic obstructive pulmonary disease

Present-day protocol carries inherent limitations: the financial burden associated with life-long plasma-derived AAT infusions often prevents authorities from granting financial drug coverage to this rare condition, thus limiting drug availability.[10] In addition, patient compliance is suboptimal considering the lifelong requirement for weekly visitations at an infusion center. Considering that AATD is a relatively under-diagnosed condition and the recent appreciation of some several-fold more individuals who carry one of many forms of AAT insufficiency, including heterozygote AATD and patients with mutated alleles of AAT,[11] it would be an understatement to conclude that, presently, not all AATD patients receive AAT augmentation therapy.

Apart from emphysema, AATD is also associated with extrapulmonary manifestations.[12,13] These include liver diseases, such as cirrhosis and chronic hepatitis, as well as various forms of vasculitis, diabetes and panniculitis.[13] Several issues can be raised if one considers the extrapulmonary manifestation of AATD. Can non-COPD patients with diagnosed AATD benefit from AAT augmentation therapy? If so, would the current treatment protocol be suitable for such conditions, considering the collection of unique end-points unrelated to emphysema? This article will review the clinical indications for AAT augmentation therapy that address extrapulmonary conditions secondary to AATD, which are presently not covered by existing practice guidelines or systematic reviews.

Discussion

The Therapeutic Potential of Alpha-1 Antitrypsin Beyond Inhibition of Neutrophil Elastase

The therapeutic repertoire of AAT has been revisited in the past decade and its attributes appear to extend beyond the protection of lung tissue from neutrophil elastase-related damage.[14-16] In gut-associated graft-versus-host-disease (GVHD), AAT therapy has provided phenomenal positive outcomes in both preclinical and clinical trials.[17-23] A positive trend is also observed with AAT administration to patients with acute myocardial infarction[24] following impressive preclinical data.[25-27] The failure of *endogenous* AAT levels to display an appropriate rise has been linked to poor cardiac prognosis[28] and to pregnancy complications.[29-32] Organ and cell transplantation studies in animals exhibit positive outcomes when supplemented with AAT therapy,[33] and are presently under evaluation in multiple clinical trials. Other immune-related conditions that respond well to AAT in preclinical studies include rheumatoid arthritis,[34] systemic lupus erythematosus,[35] multiple sclerosis,[36] type 1 autoimmune diabetes[37] and ulcerative colitis,[38]

the latter suggested to be a common comorbidity of AATD.[39] With regards to diabetes, 3 clinical trials have recently depicted a positive trend in protection of pancreatic cell death, precluded mostly by sample size and large patient diversity.[40-42] In addition, conditions of ischemia-reperfusion injury, such as renal acute-tubular necrosis and brain stroke, respond well to AAT therapy in respective animal studies.[43-47]

Alpha-1 Antitrypsin Therapy for Improving Transplantation Outcomes

AAT therapy has been extensively investigated in preclinical pancreatic islet transplantation studies. For example, AAT monotherapy (60mg/kg) was reported to prolong allogeneic islet graft survival, as well as induce antigen-specific regulatory T cell expansion and promote strain specific tolerance.[48,49] These studies lay the platform for subsequent studies relating to organ transplants. Indeed, AAT is being explored in clinical trials for islet transplantation and lung transplantation (NIH clinical trial registries NCT02614872 and NCT02520076).[50]

Lung transplantation is an established procedure for AATD patients in cases of end-stage pulmonary disease. According to a 2014 report of the International Society for Heart and Lung Transplantation, 6% of adult lung-grafted patients between 1995-2012 were individuals diagnosed with AATD, as opposed to 33% who were AAT-replete graft recipients.[51] In a U.S. study, post-transplantation lung function, prevalence and severity of acute cellular graft rejection, as well as survival rates, were compared between AATD lung graft recipients and AAT-replete COPD lung graft recipients.[52] While the study did not find differences in post-transplantation forced expiratory volume in the single-lung–grafted patients, AATD patients who received a double-lung transplant displayed significantly faster decline rates in spirometric lung functions after transplantation. Of note, 13.3% of AATD patients received augmentation therapy after lung transplantation. It is common practice to abandon AAT augmentation therapy after lung transplantation in AATD patients, as recommended by the American Thoracic Society/European Respiratory Society guidelines.[7] However, while these individuals might have intact *lung*-derived AAT, their liver-derived systemic AAT levels remain below normal. Thus, for AATD patients who receive lung transplants, AAT therapy should be considered during related systemic AATD manifestations.

Alpha-1 Antitrypsin Therapy for Bacterial Infections

AAT has been shown to reduce *P. aeruginosa* bacterial burden in the lungs and circulation of infected mice,[53] a finding that was reproduced in multi-strain bacterial peritonitis and sepsis models.[54] Accordingly, AAT-treated AATD patients were found to experience lower rates of bacterial pneumonia[55] and inhalation of AAT was shown to reduce bacterial burden in the lungs of cystic fibrosis (CF) patients.[56] These studies show that native AAT does not inhibit bacterial growth in culture, but rather modulates the host immune system. In addition, AAT turns antibacterial upon direct exposure to high levels of local nitric oxide, which is abundant in infected tissues.[54]

While COPD is a well-documented manifestation of AATD, AATD patients seem to suffer from a higher frequency of exacerbations compared to Global Initiative for Obstructive Lung Disease-staging controlled non-AATD COPD patients[13,57]; AATD-patients experience about 2 moderate-to-severe annual exacerbations[58,59] compared to one annual exacerbation in non-AATD COPD patients.[60] These COPD exacerbations were associated with pneumonia and suggested to be in line with greater mortality rates[61] and longer hospitalization periods[13] than non-AATD COPD cases. AATD patients are commonly instructed to use face-masks in public places, regardless of whether or not they are treated with AAT. Indeed, several studies have found that AATD patients were more likely to suffer from higher pulmonary bacterial loads,[62] bronchiectasis,[63-65] chronic polypoid sinusitis[66] and mycobacterial abscesses[67] compared to non-AATD individuals. Moreover, patients who suffer from both AATD and CF were more likely to develop chronic bacterial colonization with *P. aeruginosa* earlier in life, compared to non-AATD CF patients.[68] Further research is required to establish the effect of AAT on bacterial infections in AATD individuals, yet short-term AAT augmentation should be considered in cases of bacterial infections or as preconditioning prior to immunosuppression in cases such as transplantation.

Alpha-1 Antitrypsin Therapy for Expediting Wound Healing

Dermatological manifestations that are associated with AAT deficiency include panniculitis, vasculitis, psoriasis, urticaria and angioedema.[7] A common denominator with respect to all these conditions can be described as the inability of skin tissue to resolve inflammation and achieve tissue repair.

Panniculitis is one of the most studied, skin-related AATD clinical phenotypes. Similar to emphysema, it has been suggested that the underlying cause of panniculitis is a dysregulated inflammatory process in the skin.[69-71] A case study of a 31-year-old with PiZZ AATD–related panniculitis demonstrated the presence of Z-type AAT in the skin[72]; the same study reports that high dose, long-term augmentation therapy reduced both frequency and severity of the skin-related disease.

Resolution of inflammation is an essential step in the wound healing process.[73] Considering the anti-inflammatory properties of AAT and its physiological rise during acute phase responses and late stages of pregnancy, it is reasonable to predict that AATD patients will be more susceptible to episodes of unresolved inflammation. Should this unresolved inflammation occur in blood vessel walls, vasculitis may develop and in turn lead to skin ulceration and delayed wound healing.[74]

This notion is exemplified by a recent case study in which a severe postoperative wound healing disturbance was depicted in a 50-year-old *untreated* AATD patient; the stagnant wound was resolved once AAT augmentation therapy was initiated.[75] The authors of that study suggest weighing AAT augmentation therapy in all AATD patients as part of perioperative treatment protocols.

Experiments with AAT therapy in preclinical studies suggest that AAT augmentation therapy can accelerate wound healing rates and reduce the penumbra effect following ischemic injury in both cardiac and cerebral tissues.[27,46] Accordingly, a recent clinical trial found that AAT augmentation therapy in non-AATD patients diagnosed with ST elevation myocardial infarction (MI) significantly reduced C-reactive protein levels, as well as displayed overall improved cardiac function, suggesting that the repair process of the injured cardiac tissue was somewhat superior under AAT augmentation,[24] agreeing with previous observations of improved prognosis in acute MI patients who had high circulating levels of AAT.[28]

Taken together, whether one regards a case of a non-healing skin wound or an internal injury, it is possible that untreated AATD patients will experience some compromised form of tissue self-repair, and that supplementing their treatment protocols around such an event with AAT infusions may address this difficulty. In addition, considering that the major outcome used to challenge augmentation therapy efficacy has been lung emphysema, one must contemplate whether the weekly bolus approach holds optimal biological function when it comes to the intricate process of wound healing.

Not All Alpha-1 Antitrypsin Deficiency Patients Receive Alpha-1 Antitrypsin Augmentation Therapy

Some countries do not provide AAT augmentation therapy. In others, low patient compliance may render the treatment immaterial. This phenomenon may be greater than presently conceived, considering the emergence of *relative* AAT insufficiency in the form of heterozygote deficiency and inactive variants of AAT. In addition, AAT levels are known to rise during inflammation; a subclinical episode of inflammation may increase serum AAT levels, thus masking true baseline AAT levels.[78] This is specifically important in the case of heterozygote deficiency, since some MZ individuals may in fact have low levels of AAT (<80mg/dl) and thus may be eligible for augmentation treatment. Indeed, heterozygote AATD individuals are also at risk for developing lung and skin-associated manifestations.[71,77-79]

With these hurdles in mind, it is proposed that AAT therapy may be justified if not for life, then for a medical circumstance: transplantation procedures, elective susceptibility to infections and events of tissue wounding are a few of a list of examples for clinical conditions that might warrant periodic AAT augmentation irrespective of compliance towards a life-long treatment plan.

When and How Much?

Augmentation therapy protocols are presently designed to satisfy a diminished risk for emphysema. However, based on the collective research from the past decade, therapy should be tailored for each clinical context in which a patient with AATD happens to be involved. If the presently afforded regimen satisfies lower emphysema rates down the

line, does it also necessarily address the benefits of AAT preconditioning for transplant surgery? Does the protocol support wound repair? Minimize diabetes? Protect nerve cells or cardiomyocytes from ischemia-reperfusion injury? The pharmacokinetics of weekly AAT infusions is one of a short spike in AAT followed by a prolonged low trough before the next infusion session takes place.[40,80] While this protocol may postpone the advent of emphysema, it does not represent the physiological steady-state production of AAT in non-deficient individuals or healthy pregnancies.[81,82] In addition, it does not represent *inducible* levels of AAT during inflammation or other conditions that are not related to neutrophil elastase imbalance. The work by Baranovski et al provided a high-resolution examination of AAT dosing and routes of administration for cell survival, a condition that represents a non-emphysema–associated endpoint.[83] More research should be undertaken in order to explore the possibility of condition-specific AAT augmentation protocols.

Why is Alpha-1 Antitrypsin Deficiency Not Associated with Every Condition That is Presently Emerging as Responsive to Exogenous Alpha-1 Antitrypsin Therapy?

There is a phenomenal redundancy in the functions of SERPINs; lacking one may be compensated by others, depending on the function at hand. It is highly probable that other SERPINs hold clinical benefits, yet these proteins are either not available yet, or otherwise may hold adverse outcomes (e.g., antithrombin III). The fact that raising the level of AAT in some medical conditions provides advantage to the struggling tissues, may represent a mere peek at the capacity of the organism to heal.

It is owing to the rare condition of genetic AATD that we are presently aware of this protein as a legitimate clinical tool, both diagnostic and therapeutic. AATD has provided us with decades of prolonged clinical use that has laid the safety concern to rest. We must now point AAT therapy towards a more mechanistic, context-specific and physiological-oriented clinical application.

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Declaration of Interest

All authors of this manuscript declare no conflict of interest.

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