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JPRR JOURNAL OF PULMONOLOGY AND RESPIRATORY RESEARCH
ISSN 2639-9954

Mini Review

Current Practices for Severe Alpha-1 Antitrypsin Deficiency Associated COPD and Emphysema

MJ Nicholson[1]* and M Seigo[2]

[1]Department of Thoracic Medicine and Surgery, Temple University Hospital, Philadelphia, PA, USA
[2]Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA

Abstract

Alpha-1 antitrypsin deficiency is a genetic disorder that can lead to chronic obstructive pulmonary disease and emphysema. Although it is the most well-studied genetic risk factor for emphysema, data is still scarce. Traditionally, medical therapy is similar to standard chronic obstructive pulmonary disease patients. Over the past several decades, enzyme augmentation therapy has emerged as a highly utilized alpha-1 antitrypsin-specific therapy. It has become the standard of care for severe alpha-1 antitrypsin deficiency despite unclear effects on a multitude of clinical outcomes. Significant data supports interventional therapies, including lung volume reduction surgery and bronchoscopic lung volume reduction, for chronic obstructive pulmonary disease patients without alpha-1 antitrypsin deficiency. These interventions have less robust data in the treatment of alpha-1 antitrypsin-induced chronic obstructive pulmonary disease. This review will explore the data regarding various treatment options for severe alpha-1 antitrypsin deficiency associated with chronic obstructive pulmonary disease and emphysema.

More Information

***Address for correspondence:** MJ Nicholson, DO, Pulmonary and Critical Care Fellow, PGY6, Department of Thoracic Medicine and Surgery, Temple University Hospital, 3401 N Broad St, Philadelphia, PA, 19140, USA, Email: Michael.Nicholson@tuhs.temple.edu

Submitted: July 19, 2024
Approved: July 25, 2024
Published: July 26, 2024

How to cite this article: Nicholson MJ, Seigo M. Current Practices for Severe Alpha-1 Antitrypsin Deficiency Associated COPD and Emphysema. J Pulmonol Respir Res. 2024; 8(2): 044-047. Available from: https://dx.doi.org/10.29328/journal.jprr.1001058

Introduction

Alpha-1 Antitrypsin Deficiency (AATD) is caused by a mutation in the SERPINA1 gene on chromosome 14, which encodes the serine protease α-1 antitrypsin (AAT) [1]. A deficiency in AAT leads to excessive proteolytic damage to the lung parenchyma and the development of early emphysema [2]. The severity of the disease varies based on the degree of mutation. Normal individuals carry two copies of the wild-type "M" allele. Mutations can be heterozygous, affecting one allele, or homozygous, affecting both alleles. The most clinically relevant mutation is the homozygous "ZZ" mutation, which involves loss-of-function mutations in both alleles. This results in significantly low circulating AAT levels and an increased risk for pulmonary manifestations [3]. Approximately 95% of severe cases of AATD are due to the homozygous "ZZ" mutation [1]. Severe AATD is the most widely recognized genetic risk factor for Chronic Obstructive Pulmonary Disease (COPD), with approximately 1-2% of patients with emphysema having severe AATD [2,4]. Population-based screening studies have estimated a prevalence of approximately 70,000 patients in the United States with severe AATD [5].

The pulmonary manifestations of AATD-associated COPD are similar to those of COPD caused by common etiologies such as tobacco smoke and biomass fuel. Previously, many cases went undiagnosed due to these similarities [6-8]. Delays in diagnosis lead to delays in initiation of therapy and, consequentially, worse clinical outcomes [9]. However, several characteristic features more common in AATD can raise suspicion for the diagnosis. AATD-associated emphysema tends to occur more prominently in the lower lobes, manifests as panacinar emphysema, and presents earlier in life with severity of emphysema disproportionate to the quantity of tobacco exposure [1,10]. The National Heart, Lung, and Blood Institute registry identifies the average age at diagnosis as 46 years old [8]. However, limiting clinical suspicion to these factors can lead to underdiagnosis. One study found that 37% of AATD patients had predominantly upper-lobe disease, contradicting the assumptions regarding affected lobes [11]. Currently, it is recommended to check serum α-1 antitrypsin levels in all patients diagnosed with COPD to avoid missed diagnoses [12,13].

This review will focus on the current treatment guidelines for AATD-associated COPD. It will highlight the most recent data regarding augmentation and interventional therapies. The goal is to provide clinicians with a novel synthesis of societal guidelines, landmark trials, and the implications of smaller, recent studies. We will identify the limitations of current data and future study directions.

Discussion

AATD-associated COPD is treated with the same standard of care therapies as AAT-replete COPD. Recommendations for chronic therapies, such as inhaled bronchodilators, inhaled corticosteroids, supplemental oxygen therapy, and pulmonary rehabilitation mimic those for AAT-replete individuals [13]. Smoking cessation is crucial in the prevention and control of obstructive lung disease in AATD patients. The rate of FEV1 decline decreases significantly in AATD patients who quit successfully [14]. The European Respiratory Society (ERS) recommendations emphasize optimizing these maintenance therapies in conjunction with augmentation and interventional therapies to achieve the best outcomes [15].

Lung transplantation is an option for AATD with COPD patients who meet the criteria for referral. Previous data indicated approximately 12% of all lung transplants performed for COPD are in patients with AATD [16]. Post-transplant survival data is mixed. Some studies suggest post-transplant survival is similar to AATD-replete COPD patients [17,18]. One study of AATD patients matched for FEV1, age, sex, and smoking history demonstrated a median survival of 11 years for those who underwent a lung transplant, compared to 5 years for those who did not [19]. However, a similar study found no increase in survival post-transplant, although it did note a significant improvement in quality of life [20]. The guidelines for lung transplant referral and listing mirror those for AAT-replete COPD patients. Special consideration should be given to hepatic workup throughout the evaluation process for AATD patients [21].

Acute exacerbations of COPD in AATD patients should be treated with the same standard of care as AAT-replete patients. This includes therapies such as corticosteroids and non-invasive ventilation when needed. An additional consideration is the increased elastolytic activity in the lungs during acute infection. Due to the significant baseline elastase activity driving AATD emphysema, early antibiotics are recommended for all AATD acute COPD exacerbations with any signs of purulence [13]. Appropriate prevention methods are crucial as the frequency and duration of acute exacerbations are higher in AATD compared to AAT-replete patients [22].

Augmentation therapy is the only FDA-approved, disease-specific treatment for AATD. This therapy involves intravenous supplementation of plasma-purified AAT to raise serum AAT levels. The goal is to increase AAT levels above the "protective threshold" and prevent accelerated destruction of lung parenchyma by elastases [23]. The efficacy of augmentation therapy has been extensively studied through systematic reviews, meta-analyses, and randomized control trials. The RAPID-RCT was a landmark, placebo-controlled trial powered to detect treatment effects on the rate of lung density decline. The trial showed a reduced rate of lung density decline in the augmentation group compared to placebo. Lung density was measured by Computed Tomography (CT) [24]. Following this, the 2-year open-label extension trial, RAPID-OLE, was conducted. Patients who initially received a placebo and then received augmentation therapy demonstrated a decrease in their rate of lung density decline. They did not, however, regain lung density previously lost during the initial trial [25]. Based on this data, the authors emphasized the importance of initiating augmentation therapy promptly to avoid irreparable parenchymal damage. Other clinical indicators, such as the rate of FEV1 decline, rate of exacerbations, and symptomatology were unchanged with augmentation therapy in both trials [24,25]. CT lung density is correlated with other clinical outcomes, such as mortality and symptomatology, making it an important marker for analysis [26]. Current U.S. guidelines recommend augmentation therapy for patients with severe AATD and FEV1 < 65% predicted [27].

Lung Volume Reduction Surgery (LVRS) involves resection of diseased, hyperinflated lobes via thoracic surgery. The use of LVRS for AATD is controversial. Initial small observational studies showed varied outcomes [28,29]. In 2003, the National Emphysema Treatment Trial (NETT) completed the most extensive evaluation of LVRS outcomes by investigating 1218 patients. Patients with upper lobe disease had significant improvement in their exercise capacity. A subgroup of upper lobe disease patients with low exercise capacity also experienced a survival benefit. Patients undergoing LVRS for non-upper lobe disease demonstrated increased mortality and less significant improvements in exercise capacity compared to medical therapy alone. The authors determined these patients were poor candidates for LVRS due to increased mortality and minimal functional gain [30]. With the majority of AATD patients experiencing non-upper lobe disease, these findings question the effectiveness of LVRS in AATD. Sixteen severe AATD patients participated in the NETT, with ten undergoing LVRS. Increased 2-year mortality was seen in the AATD LVRS group compared to the AATD medical therapy group. Analysis comparing AATD to AAT-replete patients undergoing LVRS demonstrated less significant improvements and shorter duration of FEV1 improvement, as well as smaller increases in exercise capacity for the AATD group [31]. In the years following these studies, LVRS outcomes have improved due to better patient selection, the utilization of video-assisted thoracoscopic surgery (VATS), unilateral intervention, and increased experience [32,33]. However, due to the initial poor results, recent data for LVRS in AATD is limited. No large-scale trials have examined LVRS in AATD since the NETT. Societal recommendations regarding LVRS for AATD are mixed. The Alpha-1 Foundation guidelines recommend against LVRS for AATD, while the ERS recommends individual assessment by a multidisciplinary team rather than completely avoiding the procedure [13,34]. Both societies recognize the role of this therapy is unclear.

Bronchoscopic Lung Volume Reduction (BLVR) is a modern,

non-surgical alternative to LVRS. It involves bronchoscopic placement of one-way endobronchial valves into diseased, hyperinflated lobes. One-way valves allow air to exit, but not enter, treated lobes. This leads to atelectasis of hyperinflated lobes allowing other regions of the lung to function more effectively. Large trials, including LIBERATE AND EMPROVE, have demonstrated the significant benefits of BLVR in AAT-replete COPD populations [35,36]. More recent studies have even suggested a survival benefit is possible with BLVR [37]. While small numbers of AATD patients were included in these trials, formal AATD-specific analyses are lacking. Several smaller studies have recently examined the role of BLVR in AATD with encouraging results. One study combined AATD patients from several large trials, totaling 53 patients, to assess pulmonary function testing (PFT), exercise capacity, and symptomatology at 6-month follow-up. Significant improvements were seen in all of the studied variables [38]. A more recent 20-patient prospective study supported these findings, demonstrating significant improvement in PFTs, exercise capacity, and symptomatology at 6-month follow-up. These improvements did not persist at the 12-month follow-up [39]. These studies contribute to a growing body of literature supporting the short-term effectiveness of BLVR in AATD, questioning its long-term sustainability.

Many questions remain regarding the future of AATD therapy. Augmentation therapy's impact on clinical factors outside of radiographic progression is unclear. Controversy surrounds the appropriate dosing, timing, and molecule used for augmentation. Further studies are needed to define the specific benefits, other than imaging changes, experienced by severe AATD patients undergoing augmentation. Multiple biomarkers to predict emphysema progression and clinical response to augmentation therapy are in development but are still far from having clinical implications. Lung volume reduction, both surgical and bronchoscopic, has mixed data, leading many clinicians to caution against its implementation for AATD patients. BLVR has shown significant promise but requires further research. Future studies should focus on the intermediate and long-term benefits of BLVR. Direct comparison of BLVR outcomes between AATD and AAT-replete populations would also be useful. The main limitation to gathering AATD data is the rarity of the disease. More robust screening programs that identify undiagnosed severe AATD patients may provide the medical community with significantly more data to uncover the most effective therapies for this population.

Conclusion

AATD-associated COPD is a complex disorder with several similarities, but also major differences from AAT-replete COPD. Standard COPD medical therapies are effective in both the maintenance and treatment of acute exacerbations. Lung transplantation is a viable option for patients with severe COPD secondary to AATD who meet the criteria for listing. Augmentation therapy has shown significant improvement in the rate of CT emphysema progression, though its impact on clinical factors such as FEV1, exercise capacity and survival remains unclear. LVRS had poor initial outcomes for both AAT-replete non-upper lobe disease and AATD-associated COPD in general. As a result, further studies of LVRS in AATD are limited, especially with the emergence of BLVR. AATD patients undergoing BLVR have experienced significant benefits, but the quantity of data is limited. Further research on BLVR and AATD is necessary to better characterize the extent of its clinical impact.

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