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A REVIEW OF ALPHA -1 ANTITRYPSIN DEFICIENCY DISEASE

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ABSTRACT

AAT deficiency is a prevalent but under-recognized hereditary disorder that increases the risk of developing cirrhosis and hepatocellular carcinoma as well as chronic obstructive pulmonary disease (COPD) and liver disease. Emphysema and lung parenchyma destruction are caused by an imbalance between leukocyte elastase, the main natural antiprotease, and other inflammatory proteases. Clinical signs, such as pulmonary and extrapulmonary characteristics (e.g., liver disease, panniculitis, and vasculitis). Individuals with COPD brought on by AATD should receive the standard COPD therapy (e.g., smoking cessation, preventive vaccinations, bronchodilators, supplemental oxygen when indicated, rehabilitation, etc.). In addition to the standard COPD medication, AATD has a specific therapeutic option called intravenous augmentation therapy, which involves injecting purified pooled human plasma AAT.

KEYWORDS : Alpha-1 antitrypsin, Alpha-1 antitrypsin deficiency, chronic obstructive lung disease, pulmonary emphysema,Vasculitis, panniculitis,Augmentation Therapy etc

INTRODUCTION

Introduction An ordinary illness called AAT deficiency raises the risk of liver and chronic obstructive pulmonary disease (COPD). Alpha-1 proteinase inhibitor (Pi), also known as AAT, is the main protease inhibitor present in human serum and is a marker of the hereditary condition known as AATD[1]. The chief signs of the disorder are vasculitis, cirrhosis of the liver, panniculitis of the skin, and emphysema of the lungs. One of the most widespread genetic illnesses now recognised is AAT deficiency, which is common but clinically underdiagnosed[2]. It is the genetic risk factor for COPD that is most frequently mentioned. Infusion of purified AAT from pooled human plasma, also referred to as "augmentation therapy," is a further treatment for emphysema, COPD, and other respiratory illnesses[2]. It helps to elevate serum levels over the protective threshold and treats AAT insufficiency. When people stay away from things like fumes, particulates, and smoke, the natural history of alpha-1 antitrypsin insufficiency is unquestionably improved[3, 4]. Additionally advised are the influenza and

pneumococcal vaccines. Supportive therapy may involve the use of oxygen, bronchodilators, antibiotics, corticosteroids, and pulmonary rehabilitation[1]. Lung transplantations remain an option for this younger population with advanced chronic obstructive lung disease.[7]

EPIDEMIOLOGY

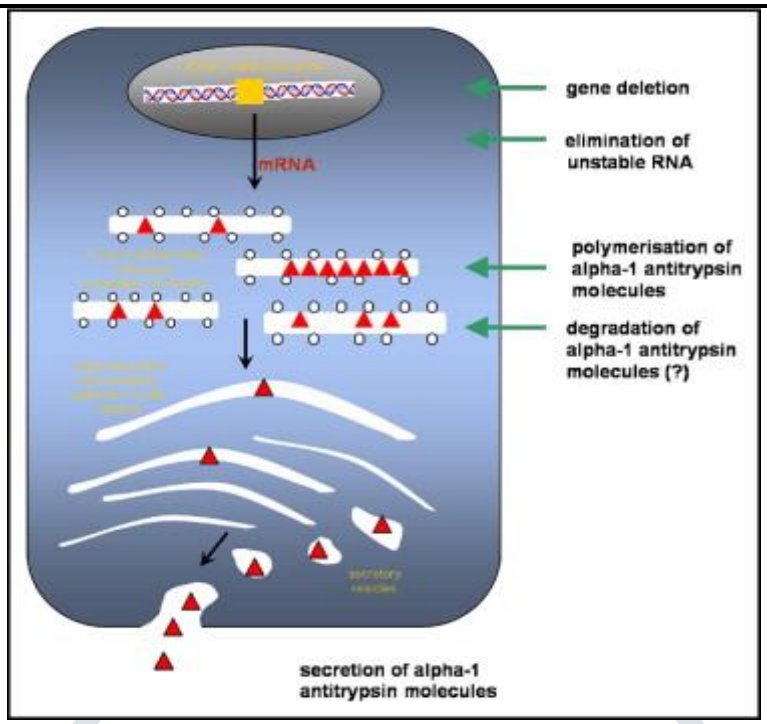
According to studies, the S allele appeared in the Iberian Peninsula between 300 and 450 generations ago, while the Z allele appeared between 66 and 216 generations ago in northern Europe (southern Scandinavia)[5]. Since then, every significant racial group on earth has seen both alleles, with constant north-south and west-east gradients, respectively. However, people of western European ancestry tend to have the highest prevalence of these aberrant genes[9]. According to studies, 90% to 95% of Caucasians have the typical M variation, compared to 2-3% and 1-3% for the PI*SS and PI*ZZ phenotypes, respectively[12]. Both indirect and direct methods have been used to determine the prevalence of AAT deficiency. According to indirect approaches, there may be up to 100,000 people who are significantly AAT deficient and have lung problems, out of the estimated 2-3 million Americans who have emphysema[10]. More specifically, the prevalence of PI*ZZ AAT deficiency has been reported to be 1:1500 to 1:5000 in major population-based newborn screening studies, the largest of which were carried out in Sweden (n = 200,000 infants) and Oregon, USA (n = 107,000 newborns)[6]. These estimations imply that 80,000–100,000 Americans, out of the country's 292,000,000 inhabitants, have significant AAT insufficiency[8]. According to estimates of global prevalence, 2.4 million people have the PI*ZZ, SZ, or SS phenotype, while 116 million people are heterozygotes for the Z or S gene[16].

GENETIC FEATURES OF AATD

The protease inhibitor (PI) locus on chromosome 14's long arm is where the gene for alpha-1 antitrypsin (AAT), which has six introns and seven exons, is located[11]. The protein under discussion, together with the corticosteroid binding globulin (CBG), protein C inhibitor (PCI), and alpha-1 antichymotrypsin, is a member of the superfamily known as serpin (serine protease inhibitor)[14]. The names of the alleles are assigned using the isoelectric focusing method based on the protein's rate of migration through gel electrophoresis. The protein with the quickest movement is labelled A, and the protein with the slowest movement is labelled Z. The symbol M stands for the typical molecule, which has a medium (middle) rate of motion[13]. Extremely low serum levels of AAT of 10% are associated with the defective mutation Z allele. A defective form known as the Z allele, which is characterised by a single amino acid substitution of glutamic acid for lysine at position 342 (Lys! Glu342 substitution), is linked to abnormally low serum levels of AAT (less than 10% of normal)[19]. The Z variation accounts for 95% of cases of severe AAT insufficiency when expressed in a homozygous manner[15]. Allelic variations are categorised based on the associated serum AAT levels because, as will be discussed below, it is crucial to include the serum level of AAT when stratifying the risk of developing lung sickness[18]. There are several different phenotypic groups: Normal: Alleles with typical AAT plasma levels and performance. Alleles that are deficient have plasma concentrations that are sub 35% of the average[20].

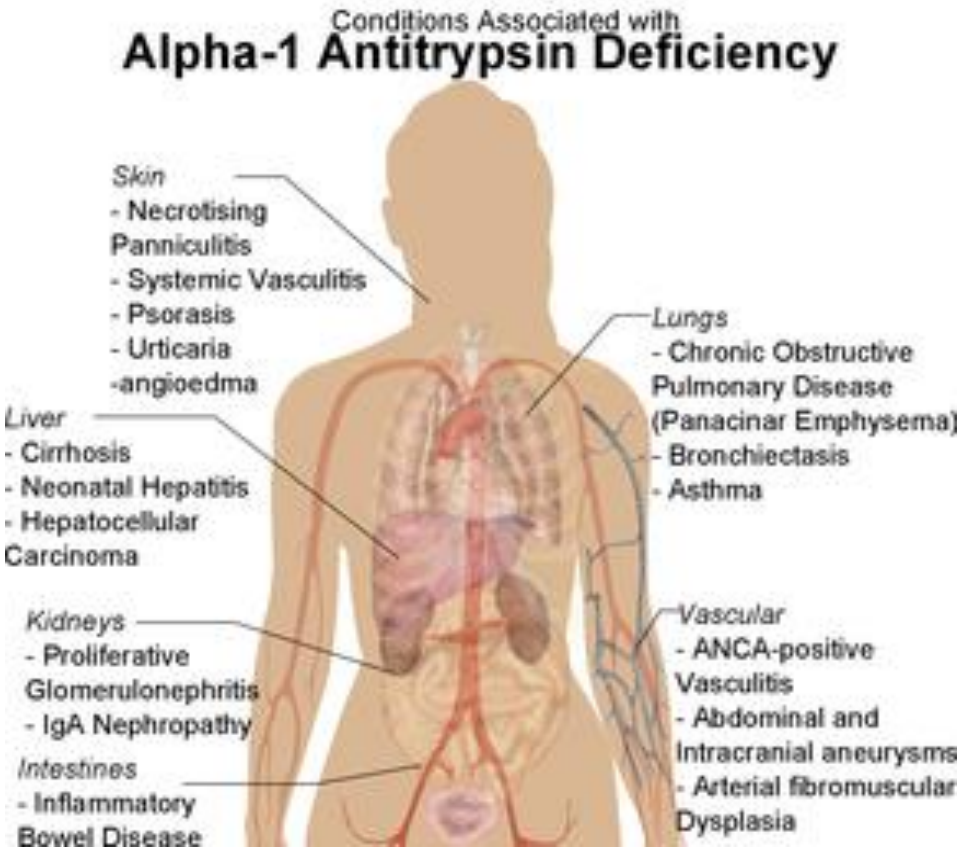
PATHOPHYSIOLOGY

AAT is the representative member of the protein superfamily known as the serine protease inhibitor (serpin), which also contains the enzymes a-1 antichymotrypsin, C1 inhibitor, antithrombin, and neuroserpin[17]. The b-sheet structure of serpins' conformational instability is what makes them vulnerable to mutations and polymerization, which causes serpinopathies[21]. These disorders could be a result of a gain-of-toxic-function defect (i.e., protein accumulation-related), such as liver cirrhosis or dementia (with AAT and neuroserpin, respectively), or they could be a result of a loss-of-function defect, such emphysema, angioedema, or thrombosis[28] .When it comes to PI*ZZ AATD, polymerization causes AAT aggregates to be retained in hepatocytes, which causes liver cirrhosis. The natural antiprotease screen against neutrophil elastase has also been lost, as well as the AAT's inflammatory actions make emphysema more likely[15].



CLINICAL FEATURES

Emphysema, liver failure, panniculitis, and cANCA-positive vasculitis (Wegener's granulomatosis) are the main clinical manifestations of AAT deficiency[31]. There have also been descriptions of aneurysmal diseases, glomerulonephritis, celiac disease, bronchiectasis, asthma, and bronchiectasis. Panacinar emphysema is the most prevalent and frequently most severe symptom of severe AAT insufficiency[26]. Affected individuals may exhibit dyspnea, cough, sputum production, wheezing, and objective indications of airflow obstruction, just like AAT-replete COPD patients. Emphysema frequently develops earlier (i.e., in the fourth or fifth decade) in AAT deficient persons than in "normal" COPD (i.e., in AAT-replete individuals), and radiographic alterations frequently affect the lung bases disproportionately[35]. Patients with alpha-1 antitrypsin deficiencies frequently exhibit obstructive ventilatory illness. Important COPD risk factors include cigarette smoking, environmental pollution, kerosene exposure, working in agriculture, and having parents who have the disease[33].



DISEASES ASSOSIATED WITH AATD

AATD predisposes primarily to liver disease and pulmonary emphysema, but people with AATD may also experience panniculitis, granulomatosis with polyangiitis, and other chronic respiratory conditions[13].

- Pulmonary emphysema and COPD

In contrast to COPD patients, those with pulmonary emphysema experience its beginning earlier, and it frequently seems out of proportion to a patient's history of smoking. Symptomatic patients' lung function tests may reveal signs of enlarged lung volumes, air trapping, and decreased gas transfer[37]. On a computed tomography (CT) scan, patients with significant airway blockage and obvious emphysema may yet have normal gas transport. Patients with AATD may exhibit substantial airflow restriction at presentation, which is frequently unproportional to their history of smoking, but without apparent airways obstruction[30]. Additionally, they don't necessarily cause parenchymal damage and airflow restriction at the same time. Since airflow limitation is frequently not resolved, these individuals' responses to bronchodilators can vary greatly[32]. Patients with the same AATD phenotype might have significantly varying levels of lung function impairment, as can siblings who share the same phenotype[19]. Similar risk variables identified for COPD can also influence how quickly lung function changes in AATD (smoking, exacerbations, environmental exposures, bronchodilator reversibility, age and basal lung function). The signs and symptoms of AATD can resemble those of asthma. Even nonsmokers have a chronic sputum expectoration rate of > 40%. Patients with chronic bronchitis are more likely to develop extensive emphysema and more severe airflow obstruction[34].

- Asthma

  Asthma may develop as a result of AATD , and those who have both conditions are more likely to experience an accelerated and progressive loss of lung function as a result of some unregulated inflammations. Patients with AATD may initially present with asthma-like symptoms[11]. Airway hyper responsiveness is an important component for reversible airflow obstruction, and participation in asthma pathogenesis may be caused by AATD itself. The extracellular matrix, particularly elastin, will degrade during asthmatic airway inflammation and remodelling, it is characterised by an imbalance between elastase and AAT[23]. Asthma patients produce sputum which contains more neutrophil elastase than do control subjects, and that a decrease in FEV1 is connected with higher neutrophil elastase levels in asthmatic patients[36]. Elastase disrupts signalling pathways controlled by integrin-associated adhesion complex, which causes an inflammatory phenotype and enhanced sensitivity to acetylcholine in airway smooth muscle tissues.
- Bronchiectasis

Incompletely opposing neutrophil elastase activity is the mechanistic connection that connects bronchiectasis to AATD[8]. Neutrophil elastase has been shown to have a direct effect on the advancement of bronchiectasis through its effects on the ciliated epithelium, mucus production, the development of emphysema, and immune system inactivation. It is still unclear, however, whether bronchiectasis results from a fundamental disease mechanism or from recurring respiratory infections[17].

- Liver dysfunction

The second most frequent sign of AAT deficiency, liver disease, affects 12-34% of PI*ZZ people. As previously indicated, people with phenotypes linked to intra-hepatocyte AAT polymerization and sequestration (e.g., Z, MMalton, Siiyama) do not develop liver disease from AAT deficiency[25]. The most typical symptom of hepatitis is jaundice, which is often self-limited but can occasionally proceed to cirrhosis and liver failure[2].

DIAGNOSIS

- Pulmonary function testing in those with AATD

The US Alpha-1 Foundation advises adults be followed up annually with at least a spirometry test and undergo initial examination with comprehensive lung function testing[20]. More thorough pulmonary function tests, which may include measurements of diffusing capacity, may be taken into consideration because the lung illness associated with AATD frequently begins as simply parenchymal damage[5]. The annual assessment of lung function, including post-bronchodilator FEV1 and gas transfer, offers data on disease development, according to the ERS statement[29].

- Chest CT scanning in those with AATD

A baseline chest CT scan is advised in newly diagnosed individuals who are symptomatic and/or have abnormal pulmonary function testing, according to the US Alpha-1 Foundation, but serial chest CT scanning to track the course of the disease is not recommended[30]. Lung densitometry, used in observational cohort studies and randomised clinical trials, is the most accurate indicator of emphysema progression, according to the ERS statement. In the long run, CT lung density drop correlates with a decline in FEV1 and health status, even if there is a limited link between change in lung density and any short-term change in measures of pulmonary function[22]. Further research is necessary to confirm the role of CT in routine clinical practise patient follow-up[4].

- Screening of blood test

screening blood test to determine your body's alpha-1 antitrypsin concentration. If your levels are low, a different blood test may be utilised to identify any faulty genes through genetic testing[9].

TREATMENT

Current therapy of AAT deficiency consists of 3 general components:

1. Common COPD interventions (e.g., smoking cessation, bronchodilators, inhaled or systemic anti-inflammatory agents, pulmonary rehabilitation, preventive vaccinations, antibiotics, oxygen, etc.)[12]

2. AAT augmentation therapy, which is the current infusion of purified pooled human plasma AAT, is a form of treatment that particularly addresses AAT insufficiency[15].

3. Surgical treatment, such as volume reduction surgery and lung/liver transplantation.[24]

Alpha-1 antitrypsin deficiency is incurable. The lung conditions it causes, however, can be treated. Emphysema, a form of COPD, is treated initially in a manner akin to that of emphysema[12].

The treatment includes:

• Bronchodilators

By relaxing the muscles surrounding the airways, bronchodilators facilitate easier breathing. They might have either a quick or slow effect. Depending on the disease state, short-acting bronchodilators might be administered for 4-6 hours. Daily use of 12-hour or longer long-acting bronchodilators is common[14].

• Inhaled corticosteroid inhaled

It facilitates breathing and can lessen airway discomfort. The main side effects are hoarseness, oral infections, and bruising[23].

- **Antibiotics**

For episodes of bronchitis and COPD exacerbation, should be administered promptly.[31]

- **Flu and pneumococcal vaccines**

Additionally advised are pneumococcal vaccinations every three to five years and annual flu shots[26].

- **Surgery and other treatments**

Operations options for advanced illness include bullectomy and lung volume reduction surgery. In an effort to reduce the size of the emphysematous portions and enhance the function of the less afflicted areas of the lung, experimental treatments such the implantation of coils and valves into segmental bronchi are also used[11]. Patients with extremely advanced emphysema can eventually need lung transplant surgery. A diseased lung is removed during a lung transplant, and a healthy lung from a deceased donor is substituted. Although lung transplants have a number of dangers, such as infection and rejection, they can greatly enhance lung function and quality of life[15,18].

Augmentation therapy

A protein deficiency must be treated with augmentation therapy in order to stop the condition from progressing. The only kind of augmentation therapy currently accessible is the infusion of pooled human plasma AAT, despite the fact that various methods (such as gene therapy to restore normal blood levels of AAT, inhalation of synthetic AAT, etc.) have been studied[35]. The U.S. Food and Drug Administration has currently approved 3 medications that use pooled human plasma for AAT (FDA). Both biochemical and clinical criteria have been covered in studies on the effectiveness of intravenous augmentation therapy. Particular biochemical efficacy standards include:

1. Support for the claim that augmentation therapy elevates serum levels over the protective threshold and does so for the duration of the inter-dose interval[36].

2. Proof that following delivery, pooled human plasma AAT retains its ability to function as an HNE antagonist[31].

Criteria of clinical efficacy include :

1. Proof that the intravenous infusion decreases emphysema progression or has other therapeutic advantages (e.g., decreased morbidity, enhanced survival)[30]

2. Support for the safety of using augmentation treatment.

Serum levels were consistently above the protective threshold following a once-weekly intravenous infusion of pooled human plasma AAT at a dosage of 60 mg/kg. Additionally, successive infusions increased the trough serum AAT levels while preserving the functional anti-elastase activity of the serum and epithelium lining fluid[35].

CONCLUSION

Alpha-1 antitrypsin (AAT) insufficiency is a widespread yet poorly understood condition. Low levels of AAT, early onset of panniculitis, vasculitis, and panniculitis, as well as elevated risks of liver disease and panniculitis are the main features of this genetic condition. Augmentation therapy is the specialised treatment for alpha-1 antitrypsin deficiency (AATD).

REFERENCE

1. Ignacio Blanco, F. J. de Serres, E. Fernández-Bustillo, et al. Estimated prevalence and number of individuals with the PI*S and PI*Z alleles of the 1-antitrypsin deficiency in Europe. 2006; Eur Respir J 27: 77-84.
2. Bergin DA, Hurley K, McElvaney NG, and co. A powerful anti-inflammatory and prospective new therapeutic drug is alpha-1 antitrypsin. 2012; 60: 81–97 (Arch Immunol Ther Exp).
3. Studies on alpha 1-antitrypsin insufficiency by Eriksson S.Acta Med Scand, Supplement 1965; 432:1–85.5
4. Alpha 1-antitrypsin deficiency: lessons learnt from the bedside to the gene and back again. Eriksson S. Historical viewpoints Chest 1989; 95:181-189.
5. Alpha-1 antitrypsin deficiency: the European experience. Stockley RA, Dirksen A, Stolk J. 2013; 10 Suppl. 1, 50–53.
6. Needham, M., and Stockley, R.A. 3: Clinical symptoms and natural history of antitrypsin deficiency. 2004; 59: 441-445 Thorax
7. Eden E. The role of alpha-1 antitrypsin deficiency in asthma and COPD. Support for the Dutch theory. COPD 2010; 7: 366–374
8.1-Antitrypsin insufficiency. Greene CM, Marciniak SJ, Teckman J, et al. 2016; 2: 16051. Nat Rev Dis Primers

9. Alpha1-antitrypsin deficiency. Stoller JK, Aboussouan LS. 2005; 365: 2225–2236 in Lancet.

10. Carroll TP, Fee LT, O'Brien ME, et al. Lack of alpha-1 antitrypsin: A COPD treatment opportunity lost? COPD Clinical Perspectives, Panos R, ed. 2014, IntechOpen, London.

11.Dawkins PA, Dawkins CL, Wood AM, Nightingale PG, Stockley JA, Stockley RA: Rate of progression of lung function impairment in alpha-1 antitrypsin deficiency. Eur Respir J 2009, 33:1338–1344

12. Alpha1-antitrypsin deficiency, emphysema, necrotizing angiitis, and glomerulonephritis. Miller F, Kuschner M. Am J Med 46:615–623 (1969).

13. Membranoproliferative glomerulonephritis in childhood cirrhosis associated with alpha1-antitrypsin deficiency. Moroz SP, Cutz E, Balfe JW, Sass-Kortsak A. Pediatrics 57:232-238 (1976).

14. Meyers A, Baynes R, King P, Lurie D, Kallenbach J, Zaltzman M, Levy H severe alpha 1-antitrypsin insufficiency accompanied by colitis, quickly progressing glomerulonephritis, and cutaneous vasculitis. Am J Med 79:489–494 (1985).

15. Watts CS, Esdaile JM, Fraser RS, and Fortin PR. a lack of alpha-1 antitrypsin and widespread necrotizing vasculitis. 1991; 18:1613–1616 in J. Rheumatol.

16. Henoch-Schonlein purpura with alpha 1-antitrypsin deficiency. Elzouki AN, Sterner G, Eriksson S. 1995; 10:1454–1457 for Nephrol Dial Transplant.

17. Guickian M, Blundell G, Winney RJ, O'Donoghue DJ Pulmonary haemorrhage and alpha-1 proteinase inhibitor in systemic vasculitis. 1993; 336:331-335 in Adv Exp Med Biol.

18. Testa A, Audrain M, Roge C, Hamidou M, Barrier JH, Sesboue R, Martin JP, and Lesavre P. Systemic vasculitis associated with ANCA positivity: genetic variation of alpha 1-antitrypsin. Kidney Int 1993; 43:1329–1332.

19. Elzouki AN, Wieslander J, Segelmark M, and Eriksson S. Strong association between Wegener's granulomatosis and the alpha 1-antitrypsin PiZ genotype. 1994; 236:543-548 in J Intern Med.

20. Lhotta K, Vogel W, Meisl T, Buxbaum M, Neyer U, Sandholzer C, and Konig P . Patients with vasculitis who have antineutrophil cytoplasmic antibodies have alpha 1-antitrypsin characteristics. 1994; Clin Sci (Lond) 87:693-695.

21. Griffith ME, Lovegrove JU, Gaskin G, Whitehouse DB, and Pusey CD . Alpha-1-antitrypsin Z allele and S allele are related to C-antineutrophil cytoplasmic antibody positivity and P-antineutrophil cytoplasmic antibody positivity, respectively, in vasculitis patients. 1996; 11:438–443. Nephrol Dial Transplant.

22. Baslund, B., Szpirt, W., Eriksson, S., A. Elzouki, A. Wiik, J. Wieslander, and J. Petersen Alpha 1-antitrypsin PiZ allele carriers and non-carriers with Wegener's granulomatosis were compared to learn more about the complexes between proteinase 3, alpha 1-antitrypsin, and proteinase 3 anti-neutrophil cytoplasm autoantibodies. 1996; 26:786-792 in Eur J Clin Investigig.

23. Chang L, Cook L, Burdon J, Daskalakis M, and Doery J. Savige JA. Anti-proteinase 3 antibodies and alpha 1-antitrypsin deficiency in systemic vasculitis caused by anti-neutrophil cytoplasmic antibodies (ANCA). 1995; Clin Exp Immunol 100:194–197.

24. Segelmark, M., Elzouki, A., Wieslander, and S. 24. The PiZ gene of alpha 1-antitrypsin is a predictor of outcome in vasculitis with PR3-ANCA positivity. 1995; Kidney Int 48:844-850.

25. Fernandez-Bustillo E, Blanco I, and De Serres FJ. A review of the global prevalence of PI S and PI Z alpha-1 antitrypsin deficiency a review of existing genetic epidemiological data. Monaldi Arch Chest Dis 2007;67:184–208.

26. Estimates of PI*S and PI*Z alpha-1 antitrypsin deficiency allele prevalence in the Caribbean and North, Central, and South America. De Serres FJ, Blanco I, Fernandez-Bustillo E. 71:96-105 Monaldi Arch Chest Dis 2009

27. What we owe to Carl-Bertil Laurell and alpha-1 antitrypsin, by Carrell R.W. COPD 2004;1:71–84.

28. C-B Laurell and A Eriksson Alpha-1 antitrypsin deficiency's electrophoretic alpha-1 globulin pattern of serum. 1963;15:132–140 in Scand J Clin Lab Invest.

29. Gildea TR, Stoller JK, Singer ME, and Shermock KM. Analysis of the cost-effectiveness of augmentation therapy for severe alpha1-antitrypsin insufficiency 2003;167(10):1387-1392 in Am J Respir Crit Care Med.
30.Hubbard RC, Sellers S, Czerski D, Stephens L, and Crystal RG were the authors. Alpha 1-antitrypsin deficient monthly augmentation therapy: biochemical efficacy and safety. JAMA 1988;260(9):1259-1264
31. Alpha-1 antitrypsin augmentation therapy administered intravenously helps patients with lung illness and alpha-1 antitrypsin deficiency, according to Gtzsche PC and Johansen HK (Review). CD007851, Cochrane Database Syst Rev 2010, 7.

32. Stoller JK, Fallat R, Schluchter MD, O'Brien RG, Connor JT, Gross N, O'Neil K, Sandhaus R, and Crystal RG are the authors of this study. Alpha1-antitrypsin augmentation therapy: patterns of use and adverse effects. Chest 2003; 123:1425-1434.

33. Mullins CD, Wang J, and Stoller JK were 33. Alpha1-antitrypsin deficiency's direct medical costs primarily consist of these elements. Chest 2003; 124:826-831.

34. Mullins CD, Huang X, Merchant S, and Stoller JK were 34. the direct medical costs associated with a lack of alpha(1)-antitrypsin. Chest 2001; 119:745-752.

35.Corda L, Bertella E, La Piana GE, Boni E, Redolfi S, Tantucci C: Inhaled corticosteroids as additional treatment in alpha-1 antitrypsindeficiency-related COPD. Respiration 2008, 76:61–68.

36. DeMeo D, Sandhaus RA, Barker AF, Brantly ML, Eden E, Gerard N, et al: Determinants of airflow obstruction in severe alpha-1 antitrypsin deficiency. Thorax 2007, 62:805–812.

37. Castaldi PJ, DeMeo DL, Kent DM, Campbell EJ, Barker AF, Brantly ML, et al: Development of predictive models for airflow obstruction in alpha-1 antitrypsin deficiency. Am J Epidemiol 2009, 170:1005–1013.