Subject: Alpha-1 Antitrypsin (AAT) Deficiency Enzyme Replacement Therapy: Alpha-1 proteinase inhibitors

- Prolastin®
- Glassia®
- Aralast NP™
- Zemaira®

Original Effective Date: 12/6/2007

Policy Number: MCP-042

Review Date: 12/16/2015, 6/15/2016, 3/21/2017, 9/13/2018

MCPC Approval Date: 9/13/2018

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

FDA INDICATIONS

All 4 commercially available alpha₁-proteinase inhibitor products [Prolastin®, Glassia®, Aralast NP™, Zemaira®] are indicated for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of alpha₁-proteinase inhibitor (alpha₁-antitrypsin).¹ ² ³ ⁴

Aralast NP™

Aralast and Aralast NP are indicated for chronic augmentation therapy in patients having congenital deficiency of alpha₁-proteinase inhibitor (alpha₁-PI) with clinically evident emphysema. Clinical and biochemical studies have demonstrated that with such therapy, Aralast and Aralast NP is effective in maintaining target serum alpha₁-PI trough levels and increasing alpha₁-PI levels in epithelial lining fluid (ELF). Clinical data demonstrating the long-term effects of chronic augmentation or replacement therapy of individuals with Aralast and Aralast NP are not available. Safety and effectiveness in pediatric patients have not been established. Aralast and Aralast NP are not indicated as therapy for lung disease patients in whom congenital alpha₁-PI deficiency has not been established.

Available as: 0.5 gm (25 ml diluent) and 1 gm (50 ml diluent) lyophilized powder for injection

Approved by the FDA:

Aralast NP™: May 4, 2007
Aralast™: Discontinued

Prolastin®
Prolastin is indicated for chronic replacement therapy of individuals having congenital deficiency of alpha\textsubscript{1}-PI (alpha\textsubscript{1}-antitrypsin deficiency) with clinically demonstrable panacinar emphysema.

**Available as:** 500 mg vial (20 ml diluent) and 1,000 mg vial (40 ml diluent)

**Approved by the FDA:** December 1987

**Zemaira\textsuperscript{®}**
Zemaira is indicated for chronic augmentation and maintenance therapy in individuals with alpha\textsubscript{1}-PI deficiency and clinical evidence of emphysema. Zemaira increases antigenic and functional (ANEC) serum levels and lung epithelial lining fluid levels of alpha\textsubscript{1}-PI. Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira are not available. Safety and effectiveness in pediatric patients have not been established. Zemaira is not indicated as therapy for lung disease patients in whom severe congenital alpha\textsubscript{1}-PI deficiency has not been established.

**Available as:** Individual labeled amount of functionally active A1-PI in mg (20 ml diluent) lyophilized powder for injection

**Approved by the FDA:** July 8, 2003

**Glassia\textsuperscript{®}**
Glassia is an alpha\textsubscript{1}-proteinase inhibitor that is indicated for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of alpha\textsubscript{1}-proteinase inhibitor (Alpha1-PI), also known as alpha\textsubscript{1}antitrypsin deficiency. Glassia is not indicated as therapy for lung disease in patients in whom severe Alpha1-PI deficiency has not been established.

**Available as:** 1 gm in 50 ml of solution

**Approved by the FDA:** July 1, 2010

**RECOMMENDATIONS/COVERAGE CRITERIA**

**ARALAST NPTM**, **GLASSIA\textsuperscript{®}, PROLASTIN\textsuperscript{®}, ZEMAIRA\textsuperscript{®}**
Initiation of **alpha\textsubscript{1}-proteinase inhibitor (human)** [Aralast NPTM, Glassia\textsuperscript{®}, Prolastin\textsuperscript{®}, Zemaira\textsuperscript{®}] therapy may be authorized for members who meet **ALL** of the following criteria **[ALL]**

**Alpha-1 Antitrypsin (AAT) Deficiency**

1. **Prescriber specialty [ONE]**
   - Prescribed by, or in consultation with, a board-certified Pulmonologist, Thoracic Surgeon, or physician experienced in the treatment of alpha-1 antitrypsin (AAT) deficiency. Submit consultation notes if applicable. **NOTE:** Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. **Diagnosis/Indication [ALL]**
Diagnosis of congenital deficiency of alpha1 antitrypsin (ATT) deficiency

- Alpha-1 Proteinase Inhibitors are not indicated as treatment for patients with lung disease in whom congenital alpha-1 proteinase inhibitor deficiency has not been established.

Severe AAT deficiency is confirmed by demonstrating a serum level below 11 micromol/L [which corresponds to 50 mg/dl (nephelometry) or 80 mg/dl (radial immunodiffusion)]\(^A,E\)

- Patients with plasma AAT levels <11 micromol/L have inadequate protection against inflammatory lung disease. Serum Alpha-1-Antitrypsin levels ≥11 µM are protective against accelerated lung destruction. Augmentation therapy is indicated for patients with ATT a serum level of <11 µM.\(^A\) Augmentation therapy is not recommended for patients with heterozygous phenotypes whose plasma AAT level exceeds 11 µmol/L.\(^E,F\)
- Per AMR Reviewers (2012), “Review of the coverage guidelines is in accordance with current ATS/ERS position papers. Some physicians will request coverage for heterozygous phenotypes with alpha-1 levels above 11 micromol/L, which is specifically not recommended by the current ATS practice parameters.” \(^*\) AMR 2012

OR

Confirmation of a severe, increased-risk alpha 1-antitrypsin deficient homozygous phenotype as determined by a isoelectric focusing lab test\(^A,E\) [ONE]

- PiZZ
- PiZ(null)
- Pi(null)(null)

- Serum phenotyping by isoelectric focusing performed by a reliable laboratory is the accepted “gold standard” for diagnosing AAT deficiency.\(^A\)
- PiZZ, PiZ(null), Pi(null)(null) or PiSZ phenotypes of alpha 1-antitrypsin deficiency are at the greatest risk for developing panacinar emphysema
- Normal alleles are associated with normal levels of AAT and normal function. The family of normal alleles is referred to as M and the normal phenotype is MM. PiMZ or PiMS phenotypes of alpha 1-antitrypsin deficiency are not covered because these individuals appear to be at small risk of developing panacinar emphysema.\(^E\)
- Per AMR Reviewers (2012), “Review of the coverage guidelines is in accordance with current ATS/ERS position papers. Some physicians will request coverage for heterozygous phenotypes with alpha-1 levels above 11 micromol/L, which is specifically not recommended by the current ATS practice parameters.” \(^*\) AMR 2012

3. Age/Gender/Other restrictions [ALL]

- 18 years of age or older\(^E\)
  - Safety and effectiveness in the pediatric population have not been established with alpha 1-proteinase inhibitor therapy (eg, Prolastin\(^E\), Aralast\(^TM\), Aralast NP\(^TM\), Glassia\(^TM\), Zemaira\(^TM\)).\(^1,2,3,4\)

- Non-smoker or ex-smoker who has not smoked in the past 6 months\(^E\) confirmed by a nicotine test
  - Cessation of cigarette smoking is of key importance for individuals with AAT deficiency who smoke.\(^E\)

- Obstructive lung disease as defined by one of the following: [ONE]
  - If patients have low plasma AAT but normal lung function, they are not treated with augmentation therapy as they have no manifestation of the disease.

- A forced expiratory volume in one second (FEV\(_1\)) of 35% to 65% of predicted value\(^A\)
  - For treatment of lung disease, the ATS/ERS Statement recommends intravenous alpha-1-antitrypsin augmentation therapy for Pi ZZ individuals with FEV\(_1\) between 35 and 65% of predicted.\(^A\)

- A rapid decline in lung function defined as a change in FEV\(_1\) of > 120 mL/year\(^A,I\)

- Symptomatic panacinar emphysema as evidenced by\(^E\): [ONE OR MORE]
● chronic productive cough
● unusual frequency of lower respiratory infection
● airflow obstruction
● accelerated decline of FEV1
● chest radiograph
● CT scan evidence of emphysema

➢ While no firm guidelines have been developed for initiating or continuing augmentation therapy, most pulmonary physicians require the serum level to be below the threshold protective value and that the patient have one or more of the following: signs of significant lung disease: chronic productive cough or unusual frequency of lower respiratory infection, airflow obstruction, accelerated decline of FEV1, or chest radiographic or CT evidence of emphysema.

☐ Member is on optimal supportive therapy for obstructive lung disease, including one of the following [AT LEAST ONE]

- Inhaled bronchodilators, inhaled steroids
- Oral corticosteroids (for asthmatic components or acute exacerbations)
- Early treatment with antibiotics if there is evidence of purulent exacerbations, bronchitis, or respiratory infections
- Preventive vaccines (influenza, pneumococcus)
- Supplemental oxygen, as indicated and during air travel
- Pulmonary rehabilitation (cardiovascular fitness, self-confidence, and stress control)
- Treatment, when necessary, of depression, panic disorder, weight loss, and malnutrition

☐ For post-lung transplant and lung volume reduction patients ONLY: Re-evaluation and re-qualification for treatment post-surgery is required as FEV may increase following surgery.

➢ Evidence for the use of alpha1-antitrypsin augmentation in patients after lung transplantation for alpha1-antitrypsin deficiency is insufficient. However, observational studies do show that inflammation from acute rejection or infection allows for free elastase activity in the epithelial lining fluid of individuals who have undergone lung transplantation. Therefore, the ATS/ERS Task Force favors the use of augmentation therapy for lung transplant recipients during episodes that provoke inflammation.

4. Step/Conservative Therapy/Other condition Requirements [ALL]

☐ Members without anti-HBV antibodies are immunized to hepatitis B immune globulin (0.06 mL/kg)

➢ It has been recommended that patients without anti-HBV antibodies should be immunized, though fewer clinicians appear to be offering such vaccination before initiating augmentation therapy without reported adverse sequelae. If it becomes necessary to treat a patient with intravenous augmentation therapy before an adequate antibody response to vaccination can be achieved, a single dose of hepatitis B immune globulin (0.06 mL/kg) can be given with the first dose of hepatitis B vaccine.

☐ Baseline HIV titers

➢ A general recommendation from the authors of UpToDate is to obtain HIV testing in addition to HepB prior to initiating replacement therapy. Refer to ‘UpToDate’ discussion in the ‘General Information’ section.

☐ Member has demonstrated an ability to comply with the prescribed treatment plan or protocol
5. **Contraindications/Exclusions to Alpha-1 Antitrypsin (AAT) Deficiency therapy [ANY]**

Authorization will not be granted if ANY of the following conditions apply [ANY]

- Non-FDA approved indications
- Known hypersensitivity to alpha-1 proteinase inhibitors or any ingredient in the formulation
- IgA deficient patients (IgA level less than 15mg/dL) with known antibody against IgA: due to possible severe reactions, including anaphylaxis to IgA, which may be present in small quantities in the final drug product.
- 18 years of age or younger
- PiMZ or PiMS phenotypes
  - PiMZ or PiMS phenotypes of alpha 1-antitrypsin deficiency are not covered because these individuals appear to be at small risk of developing panacinar emphysema.
- Emphysema not due to AAT deficiency
- Active smokers
- Treatment of cystic fibrosis
- Current non-smokers who start smoking after initial approval can be denied further treatment
- PiMZ heterozygotes or other AAT deficiencies (i.e. PiMM)
- Dosing exceeding package labeling
- Frequency exceeding once weekly infusions
- Non-compliance with therapy

6. **Labs/Reports/Documentation required [ALL]**

- Nicotine test confirming that member has not smoked within the past 6 months
- Baseline hepatitis B virus (HBV) titer obtained before initiating AAT augmentation and members without anti-HBV antibodies are immunized to HBV.
- Baseline HIV Titer\textsuperscript{AMR 2012, AMR Reference #1}

**PER AMR REVIEWER:** One suggestion is to add that there is a general recommendation from the authors of UpToDate to obtain HIV testing in addition to HepB prior to initiating replacement therapy (1). Consider adding testing for HIV in #6 under "Coverage Criteria."

**ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD**

7. **Recommended Dosing Regimen [ALL]**

Dosage prescribed is within the FDA-approved labeling based on member’s confirmed diagnosis: alpha1-proteinase inhibitor: 60 mg/kg by intravenous infusion once weekly

- **Aralast NP:** 60 mg/kg by intravenous infusion once weekly over 40 minutes
  
  \textit{Aralast should be administered at a rate not exceeding 0.08 mL/kg body weight/minute. If adverse events occur, the rate should be reduced or the infusion interrupted until the symptoms subside. The infusion may then be resumed at a rate tolerated by the subject.}

- **Glassia:** 60 mg/kg by intravenous infusion once weekly over 60 minutes
  
  \textit{For intravenous use only, dose = 60 mg/kg body weight once weekly. The infusion rate should not exceed 0.04 mL/kg body weight per minute.}

- **Prolastin:** 60 mg/kg IV once weekly over 30 minutes
This dose is intended to increase and maintain a level of functional alpha₁-PI in the epithelial lining of the lower respiratory tract, providing adequate anti-elastase activity in the lung of individuals with alpha₁-antitrypsin deficiency. Alpha₁-Proteinase Inhibitor (Human), Prolastin may be given at a rate of 0.08 mL/kg/min or greater and must be administered intravenously. The recommended dosage of 60 mg/kg takes approximately 30 minutes to infuse.

- **Zemaira**: 60 mg/kg IV once weekly over 15 minutes
  When reconstituted as directed, Zemaira may be administered intravenously at a rate of approximately 0.08 mL/kg/min as determined by the response and comfort of the patient. The recommended dosage of 60 mg/kg body weight will take approximately 15 minutes to infuse.

8. **Authorization Limit**

- **Initial Authorization**: May authorize **up to 3 months** of initial therapy for a quantity

9. **Route of Administration**

- Molina Healthcare will **not** authorize the inhalation form of alpha₁-proteinase inhibitor (human) since it is considered experimental, investigational, or unproven.
  - There are limited data available regarding the inhalation of alpha₁-PI (human) products. Brand et al. (2003) demonstrated that nebulizer systems varied in their ability to deposit product consistently. A nebulizer that is individualized to use an optimized breathing pattern provides the best product disposition. There are no data regarding the efficacy of inhalation therapy in patients with AATD.

- Medication is considered to be **provider-administered** per information from the manufacturer

- Alpha-1 Proteinase Inhibitors [human] should be administered by clinicians with experience the management of Alpha-1 Antitrypsin (AAT) Deficiency.
**CONTINUATION OF THERAPY**

**ARALAST NPTM, GLASSIA®, PROLASTIN®, ZEMAIRA®**

Continuation of therapy may be authorized for members who meet ALL of the following criteria [ALL]

1. **Initial Coverage Criteria [ALL]**
   - Member currently meets ALL initial coverage criteria
   - Prescribed by, or in consultation with, a board-certified Pulmonologist, Thoracic Surgeon, or physician experienced in the treatment of alpha-1 antitrypsin (AAT) deficiency. Submit recent consultation notes if applicable. **NOTE:** Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. **Condition Requirements [ALL]**
   - Positive clinical and therapeutic response in slowing progression of lung function decline
   - Compliance with therapy as verified by Prescriber and member’s medication fill history (review drug fill history for compliance).
     **NOTE:** Therapy may be discontinued due to compliance issues or poor adherence with agreement between treating physician, member, and Medical Director.
   - No severe adverse reactions or severe drug toxicity

3. **Labs/Reports/Documentation required [ALL]**
   - Positive clinical and therapeutic response in slowing progression of lung function indicated by ALL of the following documentation [ALL]
     - Assessment of therapeutic efficacy: Follow-up evaluations from specialist indicating disease stability or improvement
     - Positive response to treatment as evidenced by:
       - elevation of AAT levels
       - reduction in rate of deterioration of lung function: reduction in FEV1 rate of decline
     - Pulmonary function test to evaluate the member’s pulmonary function status—required every 6 months
   - Nicotine test confirming that member has not smoked within the past 3 months

4. **Discontinuation of Treatment**
   Member should be assessed for discontinuation of therapy if ANY of the following are applicable: [ANY]
   - Starts or resumes smoking
   - Intolerance or unacceptable toxicity from the drug
   - Progression of disease or no improvement
   - FEV1 improves to > 50% of predicted
ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

5. Recommended Dosing Regimen [ALL]
Dosage prescribed is within the FDA-approved labeling based on member’s confirmed diagnosis:

- **Aralast NP**: 60 mg/kg by intravenous infusion once weekly over 40 minutes
  - Aralast should be administered at a rate not exceeding 0.08 mL/kg body weight/minute. If adverse events occur, the rate should be reduced or the infusion interrupted until the symptoms subside. The infusion may then be resumed at a rate tolerated by the subject.

- **Glassia**: 60 mg/kg by intravenous infusion once weekly over 60 minutes
  - For intravenous use only. dose = 60 mg/kg body weight once weekly. The infusion rate should not exceed 0.04 mL/kg body weight per minute.

- **Prolastin**: 60 mg/kg IV once weekly over 30 minutes
  - This dose is intended to increase and maintain a level of functional alpha₁-PI in the epithelial lining of the lower respiratory tract, providing adequate anti-elastase activity in the lung of individuals with alpha₁-antitrypsin deficiency. Alpha₁-Proteinase Inhibitor (Human), Prolastin may be given at a rate of 0.08 mL/kg/min or greater and must be administered intravenously. The recommended dosage of 60 mg/kg takes approximately 30 minutes to infuse.

- **Zemaira**: 60 mg/kg IV once weekly over 15 minutes
  - When reconstituted as directed, Zemaira may be administered intravenously at a rate of approximately 0.08 mL/kg/min as determined by the response and comfort of the patient. The recommended dosage of 60 mg/kg body weight will take approximately 15 minutes to infuse.

6. Authorization Limit [ALL]

- Continuation of Therapy authorization: May authorize **up to 6 months** of continuation of therapy for a quantity

10. Route of Administration [ALL]

- Molina Healthcare will not authorize the **inhalation** form of alpha₁-proteinase inhibitor (human) since it is considered experimental, investigational, or unproven.
  - There are limited data available regarding the inhalation of alpha₁-PI (human) products. Brand et al. (2003) demonstrated that nebulizer systems varied in their ability to deposit product consistently. A nebulizer that is individualized to use an optimized breathing pattern provides the best product disposition. There are no data regarding the efficacy of inhalation therapy in patients with AATD.

- Medication is considered to be **provider-administered** per information from the manufacturer

- Alpha-1 Proteinase Inhibitors [human] should be administered by clinicians with experience in the management of Alpha-1 Antitrypsin (AAT) Deficiency. These agents should be given in the **physician’s office**. Home Care administration may be authorized only under unique circumstances.
**Coverage Exclusions**

All other uses of the mentioned drugs [Prolastin®, Glassia®, Aralast NP™, Zemaira®] that are not an FDA-approved indication or included in ‘Coverage Criteria’ section above are considered experimental/investigational and is not a covered benefit. The following list may not be all-inclusive and is subject to change based on research and medical literature.

- **Cystic fibrosis**
  - Per AMR Reviewers (2012): “Most of the peer reviewed literature centers around use of inhaled alpha-1 replacement therapy in cystic fibrosis (CF). Although reduction in airways inflammation is demonstrated, beneficial effects on lung function have not been demonstrated. AMR Reference #4 At this time, I would consider replacement therapy in CF a coverage exclusion as opposed to an "absolute" coverage exclusion.”

- **COPD** [Chronic Obstructive Pulmonary Disease] without alpha1-antitrypsin deficiency

- **Alpha1-antitrypsin deficiency without lung disease** (even if deficiency-induced hepatic disease is present)

- **Bronchiectasis** (without alpha1-antitrypsin deficiency)

- **Liver disease associated with alpha1 globulin deficiency**

- **Systemic vascular diseases**

- **Glomerulonephritis**

**Description of Procedure/Service/Pharmaceutical**

Alpha1-proteinase inhibitor deficiency is a chronic, autosomal, codominant hereditary disorder characterized by reduced levels of alpha1-proteinase inhibitor in the blood and lungs. Emphysema affects individuals with some severe genetic variants of alpha1-proteinase inhibitor deficiency. Augmentation therapy with an alpha1-proteinase inhibitor is indicated only in patients with severe alpha1-proteinase deficiencies who have clinically evident emphysema. Other therapies include lung volume reduction and lung transplantation.a,b,c

Alpha1-proteinase inhibitor (also known as alpha1-antitrypsin), is approved by the Food and Drug Administration (FDA) for use as a chronic replacement or augmentation therapy for individuals with a congenital deficiency of alpha1-antitrypsin with clinically demonstrable emphysema. All 4 commercially available alpha1-proteinase inhibitor products [Prolastin®, Glassia®, Aralast NP™, Zemaira®] are indicated for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of alpha1-proteinase inhibitor (alpha1-antitrypsin).1,2,3,4 Each alpha1-proteinase inhibitor product was approved by demonstrating that they were comparable to Prolastin in their safety and in augmenting blood and lung alpha-1 levels.

Zemaira, Aralast, Prolastin, and Glassia are derived from human plasma, and therefore the risk of transmission of infectious agents, including viruses and the Creutzfeldt-Jakob disease (CJD) agent.1,2,3,4 Alpha1-proteinase inhibitor (A1PI) products should not be administered in patients with selective IgA deficiencies who have known antibodies against IgA due to the possibility of severe allergic reactions, including anaphylaxis. These agents have similar safety profiles with adverse effects (fever, light-headedness, dizziness, cough, infusion site reactions, headache, somnolence) generally occurring in less than 2% of patients. Due to the similar safety profile and efficacy data among the A1PI human products, determination of appropriate therapy may be based on patient specific factors (i.e. physician determination, availability, infusion duration).
GENERAL INFORMATION

ALPHA-1 ANTITRypsin deficiency

Alpha 1 antitrypsin deficiency-related (AAT) emphysema is caused by the inherited deficiency of a protein called alpha 1 antitrypsin (AAT) or alpha 1-protease inhibitor. ATT deficiency is a chronic, hereditary, usually fatal, autosomal recessive disorder in which a low concentration of A1-PI (or ATT) is associated with slow progressive, severe panacinar emphysema that most often manifests itself in the third to fourth decades of life. AAT, produced by the liver, is a "lung protector." In the absence of AAT, emphysema is almost inevitable. It is responsible for only 2-3% of the emphysema in the United States. An unknown percentage of patients with severe A1-PI deficiency apparently never develop clinically evident emphysema during their lifetime.

AAT deficiency is an autosomal recessive genetic disorder that results in decreased levels of the protease inhibitor alpha 1 antitrypsin. The genetic defect in alpha 1-antitrypsin (AAT) deficiency alters the configuration of the alpha 1-antitrypsin molecule and prevents its release from hepatocytes. As a result, serum levels of alpha 1-antitrypsin are decreased, leading to low alveolar concentrations, where the alpha 1-antitrypsin molecule normally would serve as protection against antiproteases. The resulting protease excess in alveoli destroys alveolar walls and causes emphysema. The accumulation of excess alpha 1-antitrypsin in hepatocytes can also lead to destruction of these cells and ultimately, clinical liver disease.

Although replacement therapies have not been shown to prevent or reverse emphysema in AAT deficiency, population studies suggest a minimum plasma threshold of 11 micromoles/L, below which there is insufficient AAT to protect the lung leading to emphysema.

Alpha 1-proteinase inhibitors are indicated for chronic augmentation and maintenance therapy in individuals with A1-PI deficiency (also referred to as alpha 1-antitrypsin deficiency) and clinical evidence of emphysema. Alpha 1-proteinase inhibitor deficiency is an autosomal, co-dominant, hereditary disorder characterized by low serum and lung levels of A1-PI. There are many genetic variants of A1-PI deficiency, only some of which result in very low levels of A1-PI. The more severe types are the PiZZ, PiZ(null) and Pi(null)(null) phenotypes.

DISEASE MANAGEMENT

Treatment of alpha 1 antitrypsin deficiency (AATD) is based on an individual’s symptoms. There is currently no cure. The major goal of AATD management is preventing or slowing the progression of lung disease.

Treatment involves smoking cessation, bronchodilation, and physical rehabilitation in a program similar to that designed for patients with smoking-related COPD. Organ transplantation is another option for patients with end-stage lung or liver disease. Lung transplantation is reserved for patients with advanced emphysema due to severe AAT deficiency. Similarly, liver transplantation is reserved for patients with end-stage hepatic disease. After liver transplantation, the AAT deficiency is corrected, because the normal phenotype donor liver produces and secretes AAT.

At present, intravenous augmentation therapy is the only FDA-approved treatment specific for alpha 1-antitrypsin deficiency. It is most clearly indicated for patients with moderate degrees of airflow obstruction (FEV<sub>1</sub> 35-65% of predicted). Currently available alpha 1 proteinase inhibitor products include Aralast NP, Glassia, Prolastin C and Zemaira.

According to the American Thoracic Society Standards (2003) Disease management for stable individuals with AAT deficiency coincide with the recommended interventions for AAT replete individuals with emphysema, these include:

- Preventive vaccinations against pneumococcus and influenza
- Inhaled bronchodilators
- Supplemental oxygen as indicated and during air travel
- Pulmonary Rehabilitation for members with functional impairment
- Exacerbations of COPD therapeutic management include systematic corticosteroids and ventilatory support if indicated. Acute infections that increase the threat of elastolytic burden early antibiotic therapy for all purulent exacerbations
AEROSOLIZED AAT

There is limited information regarding the efficacy of aerosolized inhalation of AAT. There are no data regarding the efficacy of inhalation therapy in patients with AATD.

- Brand et. al. (2003) outlined the variability in the ability of a nebulizer system to consistently deposit the product.
- Vogelmeier et al. (1997) established safety of inhalation therapy from studying healthy volunteers. The protective concentration qualities were provided for only approximately 50 hours following inhalation by way of a nebulizer. No randomized control trials or clinical studies have been performed and this mechanism of administration is still under investigation.
- According to a review in UpToDate, direct delivery of AAT to the lung by inhalation has been an attractive alternative to intravenous infusion due to a number of potential advantages:
  - The site of clinical damage is directly targeted.
  - Less drug is required than with intravenous therapy (in which only 2 percent of the drug reaches the lung); as a result, aerosolized therapy is much less expensive.
  - Intravenous access is not required.
  - Recombinant AAT, whose short half-life (minutes) when administered systemically precludes intravenous infusion, may be effective when delivered as an aerosol (see below).
  - Inhaling aerosolized medications is more familiar to patients with emphysema and to many clinicians.
  - Patients can self-administer the drug.

AUGMENTATION THERAPY FOLLOWING LUNG TRANSPLANTATION

There is lack of proven efficacy for augmentation therapy post lung transplantation. AAT treatment for this indication is generally not used or recommended.

- A small volume study (19 participants) conducted by King et. al. (1994) was conducted to determine benefit from intravenous augmentation therapy. Bronchoalveolar lavage fluid from 11 A1PI deficient lung transplant recipients and eight control subjects was assayed for free neutrophil elastase activity, immunoreactive alpha 1PI, and elastase inhibitor activity. Samples were taken while the individuals were healthy and during respiratory illness. The AAT deficient recipient did not have detectable free elastase activity noted during clinical stability nor did the control subjects. The fluid tested during illness had measurable free elastase activity. All but one of the A1PI had the ability to inhibit exogenous elastase. Three of the seven A1PI had measurable elastase activity during respiratory illness. This study provided the only potential benefit for augmentation post transplantation.

- One prospective study of 12 patients with advanced AAT deficiency and 18 patients with smoker’s emphysema underwent lung volume reduction surgery (LVRS). There was no statistically significant difference between the groups in dyspnea score, 6-minute walking difference, respiratory mechanics, or lung function data. The FEV1 in the AAT deficient group was lower (24 versus 31% predicted, p < 0.05). Bilateral LVRS showed significant improvements in 6-minute walk, dyspnea, respiratory mechanics and lung function in both groups. The functional measurements returned to baseline at 6 to 12 months post-operatively in the AAT group with the exception of the 6-minute walk test. Further deterioration was noted at 24 months. Caughey (1993) identified a treatment approach for treating post-lung transplantation patients. This approach was to resume augmentation therapy only if characteristic changes of emphysema develop in the newly transplanted lung.
GUIDELINES, GOVERNMENT AGENCY, MEDICAL SOCIETY, AND OTHER AUTHORITATIVE PUBLICATIONS

COCHRANE REVIEW
A review by the Cochrane Collaboration combining the results of 2 small, randomized, placebo-controlled studies revealed no advantage to augmentation therapy.

The authors found two randomized trials (total 140 patients) comparing this treatment with placebo for two to three years. All patients were ex-smokers or had never smoked but had the genetic problem that carried a high risk of developing lung problems. Neither trial reported on the number of lung infections, hospital admissions or death from the disease.

The studies found no difference between the two groups in quality of life or in number of exacerbations of the disease. The lung function deteriorated slightly less measured by CT scan, but slightly more measured by forced expiratory volume in one second.

The review concluded that therapy with alpha-1 antitrypsin cannot be recommended, in view of the lack of evidence of clinical benefit and the high cost of treatment.

META-ANALYSIS
A recent meta-analysis that combined results from high-quality studies with data from the Canadian Alpha-1 International Registry concluded that augmentation therapy significantly slows the progression of airflow obstruction caused by AATD. A meta-analysis including 5 studies enrolling a total of 1,509 patients suggested augmentation therapy slowed the rate of forced expiratory volume at 1 second decline.

SUMMARY OF CLINICAL EVIDENCE REVIEWS
- Alpha-1 proteinase inhibitor therapy is indicated for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of alpha1-proteinase inhibitor.
- Numerous clinical studies have evaluated augmentation therapy in patients with AATD, including cohort and randomized studies. These studies showed that AAT slowed the rate of decline of lung function in patients with AATD and moderate airflow obstruction.
- There is no randomized controlled trial that has definitively demonstrated the clinical efficacy of treatment with alpha1 proteinase inhibitor.
- Although no randomized, controlled clinical trials have established the benefits of augmentation therapy in patients with emphysema associated with alpha 1-proteinase inhibitor deficiency, joint guidelines from the American Thoracic Society and the European Respiratory Society recommend augmentation therapy in carefully selected patients.
- The effect of augmentation therapy on pulmonary exacerbations and on the progression of emphysema in alpha1-deficiency has not been demonstrated in randomized, controlled clinical trials.
- Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals is not available. It is not indicated as therapy for lung disease in patients in whom severe alpha1-proteinase deficiency has not been established.
- Long term clinical data on effects of chronic augmentation and maintenance therapy are not available.
HAYES


Hayes, Inc published a ‘Health Technology Brief” discussing ‘Alpha-1 Antitrypsin (AAT) Replacement Therapy for AAT Deficiency Lung Emphysema.” This brief was published in November 2007 and archived in December 2010. A summary of the brief is as follows

- Hayes, Inc evaluated the limited evidence available which included one small randomized, double-blind, placebo-controlled study (RCT) and one retrospective case series, one retrospective cohort analyses, two registry studies (one with only abstract available), one patient survey, and one meta-analysis (abstract only available) were retrieved for analysis.
- The small number of observational studies suggested a similar quantitative decrease in the rate of decline in lung function (FEV1) in patients treated with alpha-1-PI augmentation therapy limited primarily to emphysema patients with moderate airflow obstruction, however it was noted that these studies had weak designs. While the results of the observational trials for patients with moderate airflow obstruction was consistent in suggesting that alpha1-PI may be appropriate for these patients, the current evidence base is not definitive of the benefits.
- The single randomized controlled trial (RCT) demonstrated no significant effect of therapy which may have been a result of the small number of patients studied and the fact that the recommended dosing regimen was not used. The brief mentioned RCTs are difficult to perform for AAT as a result of the low incidence of the disease, which limits the ability to accrue a sufficient patient sample, and due to its slowly progressive nature, which would require follow-up over many years. Larger RCTs are underway that may provide more definitive evidence.
- There were no studies that demonstrated that systematically evaluated outcomes such as the impact of alpha1-PI on other therapeutic interventions (e.g., oxygen supplementation), quality of life, etc.
- Hayes Rating: C [Potential but unproven benefit. Some published evidence suggests that safety and impact on health outcomes are at least comparable to standard treatment/testing. However, substantial uncertainty remains about safety and/or impact on health outcomes because of poor-quality studies, sparse data, conflicting study results, and/or other concerns.]

UPTODATE AMR 2012 AMR Reference #1

A general recommendation from the authors of UpToDate is to obtain HIV testing in addition to Hepatitis B prior to initiating replacement therapy: “Baseline HIV and hepatitis B virus (HBV) titers are typically obtained before initiating AAT augmentation; patients without anti-HBV antibodies are immunized to HBV.”

This recommendation is due to alpha1-proteinase inhibitors being products made from human plasma and may contain infectious agents, such as viruses. Despite measures of screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Therefore the risk of transmission of infectious agents can not be totally eliminated.

AMERICAN THORACIC SOCIETY (ATS)/EUROPEAN RESPIRATORY SOCIETY (ERS) (2003)A

- Recognizing that the supportive evidence of efficacy comes from concordant observational studies but not from randomized clinical trials, the Task Force recommends intravenous augmentation therapy for individuals with established airflow obstruction from AAT deficiency. Evidence that augmentation confers benefit (e.g., slowed rate of FEV1 decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (e.g., FEV1 35-60% predicted) than those with severe airflow obstruction.
- Augmentation therapy is currently not recommended for individuals without emphysema, and benefits in severe (e.g., FEV1 ≤ 35% predicted) or mild (e.g., FEV1 ≥ 50-60% predicted) airflow obstruction are less clear. Subjects with normal or nearly normal function can be treated, if they experience a rapid decline in lung function (ΔFEV1 >120 ml/year). Patients with very poor lung function, already treated, should be kept on treatment.
- Indication for treatment is independent of the phenotype and based on level (ATT level <11.0 μM) and presence of obstructive lung disease.

Clinical Recognition of AAT DeficiencyA
According to the American Thoracic Society (2003) “Available evidence suggests that PI*ZZ AAT deficiency is frequently under recognized or misdiagnosed by clinicians. The following features should prompt suspicion by physicians that their patient may be more likely to have ATT deficiency:

Early onset emphysema (age 45 years or less)
- Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Anti-proteinase 3-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis)
- Family history of any of the following: emphysema, bronchiectasis, liver disease, or panniculitis
- Bronchiectasis without evident etiology

Patient Selection

The American Thoracic Society in conjunction with the European Respiratory Society has published recommendations for patient selection. These recommendations include:

- Supportive evidence from concordant observational studies but not from randomized controlled clinical trials, the Task Force recommends intravenous augmentation therapy for individuals with established airflow obstruction from AAT deficiency.
- Evidence that augmentation therapy confers benefit (e.g., slowed rate of FEV1 decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (e.g., FEV1 35-60% predicted) than for those with severe (e.g., FEV1 ≤ 35% predicted) or mild (e.g., FEV1 ≥ 50-60% predicted) airflow obstruction are less clear.
- Insufficient evidence regarding the benefits of augmentation therapy in patients who have undergone lung transplantation for AAT deficiency precludes a firm recommendation. However, it has been observed that inflammation results in free elastase activity in epithelial lining fluid in individuals who have undergone lung transplantation (e.g., during acute rejection and infection). In the context of available data regarding this issue, this observation leads the task force to favor augmentation therapy for lung transplant recipients during such episodes.”

The American Thoracic Society (ATS) and European Respiratory Society (ERS) statement on the diagnosis and management of AAT deficiency, as well as other ATS guidelines, can be accessed through the ATS web site at www.thoracic.org/statements.

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD)H

GOLD recommends “…young patients with severe hereditary AAT deficiency and established emphysema may be candidates for AAT augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for COPD that is unrelated to AAT.”

MEDICAL AND SCIENTIFIC ADVISORY COMMITTEE OF THE ALPHA-1 FOUNDATIONf

A 2008 commentary by the authors of the Medical and Scientific Advisory Committee of the Alpha-1 Foundation

“A Cautionary Note” was recently published (Sandhaus, et al., 2008) citing a lack of definitive evidence for efficacy and the unwise use of scarce resources for augmentation therapy for PiMZ heterozygotes. In this advisory, The Medical and Scientific Advisory Committee of the Alpha-1 Foundation strongly advised against augmentation therapy for other than PiZZ homozygotes. In their note, they urged insurance companies to observe for this practice and the Federal Drug Administration to provide labeling to this effect.

The commentary advised that until supportive data in the subset of heterozygotes becomes available, the only approved use for augmentation therapy is for PI*ZZ individuals.

CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH (CADTH) 2007D
The Canadian Agency for Drugs and Technologies in Health conducted a Health Technology Assessment in 2007 (Chen et al, 2007). A systematic review of the literature was performed. One randomized control trial, four retrospective cohort studies and eight case series reports were used for evidence evaluation. The assessment by the Canadian Agency for Drugs and Technologies in Health concluded the following:

- Evidence showing health improvement from alpha-1 antitrypsin inhibitor therapy is inconclusive.
- In controlled trials, augmentation therapy has not shown reduced lung function impairment in patients with AAT deficiency and chronic obstructive pulmonary disease (COPD), compared with normal care.
- In observational studies, alpha-1 antitrypsin inhibitor therapy is associated with outcomes suggestive of therapeutic benefit in patients with severe AAT deficiency and moderate airflow obstruction.
- Severe adverse events from treatment have been reported in approximately 1 percent of study populations.
- Use of alpha-1 antitrypsin inhibitor therapy in patients without COPD is experimental. The assessment found no evidence evaluating the use of alpha-1 antitrypsin inhibitor therapy in patients with AAT deficiency and no lung function impairment.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE OF THE NATIONAL INSTITUTES OF HEALTH (NHLBI)

The National Registry of Patients with Severe Deficiency of Alpha 1-Antitrypsin

A large cohort study of 1,129 patients was queried using a standardized symptom questionnaire conducted by the National Heart, Lung, and Blood Institute (NHLBI) Registry of Individuals with severe deficiency of AAT. These individuals had a serum AAT level of < 80mg/dl. The most frequently documented symptom was dyspnea on exertion in 84% of the participants. Wheezing with respiratory infection (76%) and without infection (65%) was also commonly reported. Coughing was identified by 50% of the individuals. A chronic productive cough has also been reported in 8-40% of AAT deficient patients. Chest illness that is often recurring was reported in 68% of the participants. This study also showed that FEV$_1$ decline rate was slower among augmentation therapy versus non-recipients. The decline rate for the overall group did not achieve statistical significance (p=0.40). Analysis showed a significantly slower FEV$_1$ decline rate in recipients with moderate, FEV$_1$ 35-49% of predicted airflow obstruction (-66.4 vs. -p3.2mL/y, p=0.03).

The NHLBI registry data also supported clinical efficacy of augmentation therapy by identifying lower mortality rates among augmentation therapy recipients. The risk ratio for death in augmentation therapy recipients was 0.64 (CI 0.43-0.95, p=0.02) and for individuals with Stage II COPD, the risk ratio for death among augmentation therapy recipients was 0.21 (CI 0.09-0.50, p=0.001).

- Survival was enhanced in recipients of augmentation therapy compared with non-recipients.
- In the subset of patients with FEV1 35 to 49 percent predicted, the rate of FEV1 decline was also slowed in recipients of augmentation therapy.

ALPHA-1 ASSOCIATION GENETIC COUNSELING PROGRAM AMR 2012 AMR Reference #3

The Alpha-1 Association Genetic Counseling Program (1-800-785-3177) was established in September 2007 and specializes in confidential toll-free genetic counseling provided by a certified genetic counselor for Alpha-1 Antitrypsin deficiency. The program offers free phone-based confidential information and resources to patients, family members and medical professionals on the genetics of Alpha-1 and provides information on testing options.

DEFINITIONS

Alpha1-antitrypsin: a plasma α1-globulin produced primarily in the liver; it inhibits the activity of elastase, cathepsin G, trypsin, and other proteolytic enzymes. Deficiency is associated with development of emphysema.
Alpha-1 protease inhibitor deficiency may also be referred to as:

- AAT
- AATD
- alpha-1 related emphysema
- genetic emphysema
- hereditary pulmonary emphysema
- inherited emphysema

**Forced Expiratory Volume in One Second (FEV1):** Represents the volume of air forcibly exhaled from the lungs in the first second of a forced expiratory effort. This important measure of obstruction is measured by spirometry during pulmonary function testing.

**Panacinar emphysema** destroys the entire alveolus uniformly and is predominant in the lower half of the lungs. Panacinar emphysema generally is observed in patients with homozygous alpha-1-antitrypsin (AAT) deficiency. In people who smoke, focal panacinar emphysema at the lung bases may accompany centriacinar emphysema

**SPECIAL ALERTS**

N/A at the time of this writing

**CODING INFORMATION**

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**REFERENCES**


**Peer-Reviewed Publications**


**Government Agencies, Professional Societies, and Other Authoritative Publications**


**AMR Peer Review Networks (March 2012)**

AMR Peer Review Network. Board certified in Internal Medicine, Critical Care, Pulmonary Disease. Date completed: 3/23/2012

AND


**AMR References:**

1. *UpToDate Version 19.3 Section on Treatment of alpha-1-antitrypsin deficiency.*

