

Augmentation Therapy

The Specific Therapy for Alpha-1
Lung Disease



INTRODUCTION

The FDA-approved therapy for the treatment of Alpha-1-related lung disease, specifically emphysema, is generally referred to as augmentation therapy. As currently available, augmentation therapy describes the use of human plasma-derived alpha-1 antitrypsin (AAT) from healthy donors to supplement or augment the AAT levels circulating in the blood and lungs of Alphas diagnosed with emphysema. The therapy is administered via a weekly intravenous infusion and, until other therapies become available, is considered ongoing and lifelong.

While augmentation therapy is considered the only specific therapy for Alpha-1 related lung disease, the treatment plan for lung-affected individuals with Alpha-1 should also include a variety of approaches such as the appropriate use of therapeutic antibiotics, an immunization program including viral hepatitis and influenza strains, reduction or elimination of environmental risks factors, appropriate inhaled medications, an exercise program, and oxygen, if needed.



CROSS REFERENCE: For more information about ways to avoid the risk of disease see “Staying Healthy” another AlphaNet specialty brochure, or refer to “Management of Environmental Risk Factors” in the Big Fat Reference Guide™ at www.alphanet.org.

WHAT ARE THE GOALS OF THERAPY?

The basic goal of augmentation therapy is to increase the level of AAT protein in the lungs. Alpha-1 antitrypsin protects the lungs from the destructive effects of neutrophil elastase, an enzyme released by our body’s white blood cells as they respond to inflammation or infection.

The ultimate goal is that by replacing the deficient protein, the progression of lung destruction will be slowed or stopped. The therapy cannot restore lost lung function — nor is it considered a cure. There is also evidence that augmentation therapy can reduce the frequency and severity of pulmonary exacerbations and it appears to be an effective treatment for the Alpha-1 related skin disease, Necrotizing Panniculitis.



KEY LEARNING: Therapy cannot restore lost lung function nor is it considered a cure. The hope is that by replacing the deficient AAT protein, the progression of lung destruction will be slowed or stopped.

CURRENTLY AVAILABLE THERAPY

There are four FDA-approved products for augmentation therapy currently available in the United States, and additional potential therapies are on the horizon. The four approved products are Prolastin®-C Liquid, Aralast NP®, Zemaira®, and Glassia®. Each of these product versions were introduced to the marketplace since the 1987 approval of the original Prolastin product and each was approved on the basis of demonstrating that they were comparable to Prolastin in their safety and in augmenting blood and lung alpha-1 antitrypsin levels.



CROSS REFERENCE: To learn how augmentation therapy products were approved by the FDA for use in the United States, please refer to the Augmentation Therapy section in the Big Fat Reference Guide™ at www.alphanet.org

Each of the currently available augmentation therapy drugs requires specific preparation prior to their infusion. For this reason, augmentation therapy infusions are typically given by health care professionals in the home, at a physician's office, outpatient infusion center or other medical facility. Sometimes Alphas choose to self-infuse after receiving appropriate instruction from a health care professional and upon receiving approval from their physician. Most frequently, healthcare insurance issues dictate the place of infusion.

As a quick reference, a comprehensive chart describing the three currently available products is available at the end of this brochure.



CROSS REFERENCE: Information about Prolastin, Aralast, Glassia, and Zemaira including the package inserts can be found in the Big Fat Reference Guide at www.alphanet.org

WHO SHOULD RECEIVE ALPHA-1 AUGMENTATION THERAPY AND WHEN SHOULD THEY START?

Augmentation therapy should be given to individuals with documented Alpha-1 and documented emphysema. There has been some controversy, however, about giving augmentation therapy to individuals whose lung disease is very mild or very severe. In some of the research studies conducted since the introduction of augmentation therapy, the benefits identified were primarily seen in certain segments of people with lung disease due to Alpha-1. In these studies, the most dramatic effects were seen in those people whose lung function fell in the mid-range of severity. This is not surprising in view of the fact that it is difficult to improve the lung function of someone who is only mildly affected to begin with. Furthermore, people with the most severe lung disease tend to have a very slow rate of decline, and the subtle differences in this decline among individuals who receive different forms of treatment are not easily detected.

Some members of the healthcare community have used these results to suggest that only those individuals with moderate lung disease should receive augmentation therapy. However, because augmentation therapy is considered preventative rather than curative; that is to say, it puts the brakes on lung destruction rather than reversing it, it seems logical to begin therapy as soon as possible after lung disease due to Alpha-1 has been detected.



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Since we do not know which individuals with Alpha-1 will get lung disease, and because the current methods for detection of early lung disease are poor, it could be argued that everyone with Alpha-1 should receive augmentation therapy to keep their lungs as healthy as possible. If augmentation therapy were perfectly safe, easy to administer, inexpensive, proven to be effective, and available in unlimited supply all Alphas probably would be taking it. Unfortunately, none of these conditions are true.





KEY LEARNING: It is the current recommendation of AlphaNet that all individuals with emphysema due to Alpha-1, regardless of severity, consider the use of augmentation therapy.

CONSIDERATIONS BEFORE INITIATION OF AUGMENTATION THERAPY

Prior to commencing augmentation therapy, individuals should be tested for IgA deficiency, a hereditary condition that makes potentially severe allergic-type reaction to plasma products more likely.

It is the recommendation of AlphaNet that immunization against both Hepatitis A and B be considered for all Alphas to reduce the risk of liver injury. Vaccination entails a series of three injections generally administered over a period of six months.



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ARE THERE ANY SIDE EFFECTS ASSOCIATED WITH AUGMENTATION THERAPY?

Individuals receiving all three currently available augmentation therapies have reported a variety of side effects, although the vast majority of individuals receiving these drugs never have any significant problems. The most common side effect is a sense of feeling drained or having flu-like symptoms that typically lasts for up to 24 hours following an infusion. These types of symptoms can often be reduced or eliminated by slowing the rate of infusion. Some patients have symptoms that are suggestive of mild allergic reactions consisting of hives, itching, tightness in the chest, dyspnea, and/or wheezing. Many of these patients can continue receiving augmentation therapy if they are pretreated with an antihistamine, such as Benadryl, prior to their infusions. On rare occasions, side effects are severe enough to cause individuals to change brand of therapy or stop augmentation therapy entirely.

Some individuals have found that switching to a different brand of augmentation therapy eliminates persistent side effects. Individuals who develop severe systemic reactions to one brand of augmentation therapy should be monitored extremely closely if they are to be switched to another augmentation therapy. In clinical trials, all three products demonstrate similar rates of side effects.



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DETERMINING THE PROPER DOSE FOR AUGMENTATION THERAPY

The FDA has approved a dose of 60 mg/kg of body weight administered once weekly via intravenous infusion, for each of the currently available augmentation products. Therefore, the recommended dose for an individual weighing approximately 165 lbs (or 75 kg) would be 4,500 mg per week. Some physician's feel they should monitor AAT levels in the blood and then adjust the dosage of augmentation therapy to achieve some particular level they feel will protect the patient from experiencing lung damage. This approach to dosing is not recommended at the present time.



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The potential fallacy of such an approach lies in the fact that the levels of AAT found in the lungs following prolonged augmentation therapy tend to be much more stable and consistent than the levels found in the blood. Therefore, routine dose adjustments based on blood levels may not produce the desired effect within the lungs. The dosing recommendations approved by the FDA are based on this understanding for the need to achieve a consistent protective level of AAT within the lungs.



In addition, no study has determined the dose of augmentation therapy that will halt the progression of lung disease in all patients. Therefore, we suggest the recommended dose of 60 mg/kg of body weight weekly should be administered without blood level testing.

Many individuals and their physicians have used alternative dosing regimens outside those recommended by the FDA. These include biweekly dosing at 120 mg/kg, dosing every third week at 180 mg/kg, and monthly dosing at 250 mg/kg. While these regimens have been used for years, some evidence suggests that weekly dosing at 60 mg/kg is the most effective. Most Alpha-1 aware physicians limit the use of more extended dosing intervals to individuals with significant logistical problems that make weekly dosing a hardship. Even in these individuals, if lung function decline seems to remain accelerated or if side effects become a problem, it is wise to consider switching to the weekly dosing regimen to determine if this helps to alleviate the individual's problems.

An interesting note. It is interesting to note that individuals on augmentation therapy who have their phenotype re-tested will return a result of PiMZ if they were PiZZ prior to therapy. This is because phenotyping looks at the types of AAT protein in the blood and augmentation therapy delivers normal, PiMM protein to individuals who are PiZZ. Thus phenotype testing will reveal both the Alpha's own AAT phenotype, as well as the augmentation-delivered normal phenotype. Genotyping, rather than phenotyping, would be required to determine an individual's underlying AAT genetics while receiving augmentation therapy.

IV ACCESS FOR AUGMENTATION THERAPY

The overwhelming majority of Alphas receiving augmentation therapy choose to have a simple IV catheter or needle placed in the hand or arm at the time of each infusion. These catheters are well-tolerated, remain in place for a brief period of time, and the complications are minimal. There are a variety of devices available, all designed to provide for ease of placement and patient comfort.

Some Alphas, often directed by their health care providers, choose a longer-use indwelling IV access device for their infusions. These devices include the Implanted Vascular Access Device (IVAD), also called a port, and various types of tunneled central catheters or Peripherally Inserted Central Catheters (PICC)



CROSS- REFERENCE: A comparative listing of indwelling IV catheter devices can be found in the Big Fat Reference Guide section on "Specific Therapy for Alpha-1 Lung Disease" at www.alphanet.org

The decision to choose one method of IV access over another should be a well-researched and informed decision. Having such a device in place may make obtaining IV access easier, but it may pose some additional risk to you. Be sure that you clearly understand the procedures involved in the insertion of each of these devices when making your decision. It is important to discuss the risks and benefits of any type of IV access thoroughly with your health care provider and then choose the IV device that makes the most sense for your particular situation.

WHAT TO CONSIDER WHEN CHOOSING AN IMPLANTED VASCULAR ACCESS DEVICE (IVAD) OR CENTRAL CATHETER

- What is the general condition of your peripheral veins? Are they visible on the back of the hands and forearms?
- Are they accessible?
- What is your infusion schedule?
- Have you had previous difficulties with peripheral IV insertions?
- Have you had good experience with certain nurses and bad experiences with others?
- Have you been informed of the risks and benefits of the particular device and do the benefits outweigh the risks?
- Do you understand the procedures for insertion?
- Have you talked with others who have had an implanted device?
- Do you plan on doing your own infusions, or having a spouse or significant other do them for you?
- Whose need is being met? The doctor, nurse, or yours?
- Do you understand the special care and maintenance required of the device?



PORT AND CENTRAL CATHETER INFECTIONS

Infection of the port or central catheter can pose an important challenge for healthcare providers and individuals receiving augmentation therapy because the signs and symptoms of an infection often mimic the signs and symptoms of a reaction to augmentation therapy.

An infection can be external, located at the site where the port or central catheter is implanted, under the skin in the "pouch," or along the tunneled area of the catheter. An infection also can occur within the reservoir of a port, or along the walls of the central catheter in the vein. Bacteria can be inadvertently introduced into the device through lapses in sterile technique, inadequate skin preparation, or contaminated equipment. The device may attract bacteria from other infectious processes in the body and flourish in the port or central catheter. If an infection is present, when the device is accessed and flushed, a shower of bacteria can be sent into the bloodstream. Important signs of infection include:

- Localized site redness, swelling, tenderness, drainage
- Body aches
- Weakness
- Shaking, chills, and/or fever over 101° F
- Abdominal pain
- Nausea and vomiting
- Increased difficulty breathing

Many individuals mistakenly presume these symptoms are related to their augmentation therapy infusion and report a reaction to their medication. Both situations have similar symptoms, and one can mimic the other. Though some patients do have side effects from their therapy, a patient with an indwelling port or a central catheter must first consider an infection, and this should be ruled out before assuming that a medication reaction has occurred.



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WHAT TO DO IF YOU HAVE SYMPTOMS RELATED TO AN INFUSION AND HAVE A PORT OR CENTRAL CATHETER

If you have an implanted device and you experience problems during or shortly after your infusion, report this immediately to your nurse and physician. Check your temperature, especially if you experience shaking or chills. Call your doctor promptly if you have a fever over 101°. If symptoms are severe, seek immediate medical attention.

Your physician will want you to have laboratory tests to check for the presence of an infection. The diagnosis of an infection is based on results from blood cultures often drawn from a vein in your arm, as well as from the device. If you are due for an infusion while undergoing a work-up for infection, you still may receive your infusion if approved by your physician. It is recommended, however, you DO NOT USE the device for the infusion. The infusion should be administered through an IV catheter placed in your hand or arm. Observing for the absence or presence of symptoms during this peripheral infusion will help to determine if a medication side effect is the source of the problems, or if the symptoms are related to the port or central catheter.

If an infection has been confirmed, depending on the severity or the bacteria involved, IV antibiotics may be required to treat the infection. In some instances, the device will need to be removed.

If all blood cultures are negative, further monitoring is required, and investigation into a reaction to the medication should be pursued.

THE BEST INTERVENTION IS PREVENTION

The best intervention for a port or other central catheter infection is prevention. Preventing infection should be the priority of all individuals who have a port or other central device, as well as a top priority for those care providers who access these devices. Because these devices provide a direct connection from the outside environment into the large blood vessels of the body, excellent hand washing and the maintenance of sterile technique while performing all device related procedures is essential in the prevention of infection. It is helpful to limit the number of individuals who handle the port or central line and to avoid allowing anyone who is ill to handle the device. It is generally recommended that anyone caring for these devices wear a mask and a mask is provided in most central device access kits for just this purpose.



TABLE OF SPECIFIC THERAPIES FOR ALPHA-1 LUNG DISEASE (U.S.)

	PROLASTIN[®]-C LIQUID	ARALAST NP[®]	ZEMAIRA[®]	GLASSIA[®]
Current version entered market	2018	2007	2003	2010
Marketed by	Grifols	Shire	CSL Behring	Shire
Recommended dose	60mg/kg IV weekly	60mg/kg IV weekly	60mg/kg IV weekly	60mg/kg IV weekly
Storage (Do not use after expiration date printed on label)	Refrigerate at 2-8°C (36-46°F) [May be stored at room temperatures up to 25°C (77°F) but must be used within one month] Do not freeze	Temperatures not to exceed 25°C (77°F) Do not freeze	Temperature not to exceed 25°C (77°F) Do not freeze	Refrigerate at 2-8°C (36-46°F) [May be stored at room temperatures up to 25°C (77°F) but must be used within one month] Do not freeze
Diluent (sterile water) or volume of product for liquid formulations	20ml for 1000mg vial Liquid formulation	50ml for 1,000mg vial Freeze-dried powder	20ml for 1,000mg vial Freeze-dried powder	50ml for 1,000mg vial Liquid formulation
Infusion rate (average)	0.08 ml/kg per min	0.2 ml/kg per min	0.08 ml/kg per min	0.2 ml/kg per min
Infusion time (approximate)	15 minutes	Not listed	15 minutes	15 minutes
Contraindications	IgA deficiency with antibodies against IgA; history of severe reaction to augmentation therapy	IgA deficiency with antibodies against IgA; history of severe reaction to augmentation therapy	IgA deficiency with antibodies against IgA; history of severe reaction to augmentation therapy	IgA deficiency with antibodies against IgA; history of severe reaction to augmentation therapy
Common side effects	Diarrhea and fatigue	Headache, somnolence, chills, fever, vasodilation, pruritus, (itching) rash, abnormal vision, chest pain, increased cough, dyspnea	Headache, sinusitis, respiratory infection, bronchitis, asthenia, cough, fever, injection site hemorrhage, rhinitis, sore throat, and vasodilation	Headache, respiratory infections, cough, sinus infection, chest discomfort, dizziness, increased liver enzymes, shortness of breath, nausea, and fatigue
Viral inactivation processes	Solvent detergent and Nanofiltration	Solvent detergent and Nanofiltration	Heat Treatment and Nanofiltration	Solvent detergent and Nanofiltration
Number for reporting adverse events	800-520-2807	800-828-2088	800-504-5434	800-828-2088





This brochure is produced by AlphaNet as part of its Alpha-1 Disease Management and Prevention (ADMAP) program.

AlphaNet is a not-for-profit organization providing disease management services and support to individuals affected by Alpha-1 through a staff of medical professionals and specially trained AlphaNet Patient Services Coordinators, available 24 hours a day, 7 days a week. To learn more about ADMAP or to find the AlphaNet Coordinator nearest you, visit our website (www.alphanet.org).